Research evaluation

EVALUATION REPORT OF THE UNIT

IGBMC - Institut de génétique et de biologie moléculaire et cellulaire

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université de Strasbourg
Centre national de la recherche scientifique - CNRS
Institut national de la santé et de la recherche médicale - Inserm

EVALUATION CAMPAIGN 2022-2023
GROUP C

Rapport publié le 17/05/2023

In the name of the expert committee[1] :

Mr Alfonso Martinez-Arias, Chair

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: Mr Alfonso Martinez-Arias, Universidad Pompeu Fabra, Spain

Experts:

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Mr Frederic Boccard, Institut de Biologie Intégrative de la Cellule, Gif sur Yvette

Mr Frederic Checler, Institut de Pharmacologie Moléculaire et Cellulaire, Valbonne

Mr Alan Dobson, University College Cork, Irlande

Mr Eric Durand, Laboratoire d'ingénierie des Systèmes Macromoléculaires, Marseille (representative of CoNRS)

Ms Catherine Etchebest, université Paris Cité (representative of CNU)

Mr James Hombría Castelli-Gair, Consejo Superior de Investigaciones Científicas, Madrid, Spain

Mr Philippe Huber, Commissariat à l'énergie atomique et aux énergies alternatives, CEA

Mr Jean-Michel Jault, Molecular Microbiology and Structural Biochemistry, Lyon

Mr Ludger Johannes, Institut Curie, Cellular and Chemical Biology, Paris

Ms Isabelle Landrieu, université de Lille

Mr Clément Carré, Sorbonne université (representative of CoNRS)

Mr Christophe Leclainche, Institut de Biologie Intégrative de la Cellule, Paris

Mr Alfonso Martinez-Arias, Universidad Pompeu Fabra, Barcelona, Spain

Mr Antonin Morillon, Institut Curie, Paris

Mr Celio Pouponnot, Institut Curie, Paris (representative of Inserm CSS)

Mr Claus, Storgaard Sorensen University of Copenhagen, Danemark

Mr Didier Stainier, Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany

Ms Gerlind Sulzenbacher, Laboratoire Architecture et Fonction des Macromolécules Biologiques, Marseille (representative of supporting personnel)

Ms Laurence Vandel, Institut de Génétique Reproduction et Développement, Clermont-Ferrand (representative of Inserm CSS)

HCÉRES REPRESENTATIVES

Mr Yacine Graba

Ms Ina Attrée

Ms Marie José Stasia

CHARACTERISATION OF THE UNIT

- Name: Institut de génétique et de biologie moléculaire et cellulaire
- Acronym: IGBMC
- Label and number: UMR 7104
- Number of teams: 43
- Composition of the executive team: Frédéric Dardel

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

Research at the IGBMC is focused on the regulation of gene expression and cell fate decisions which they explore at several levels, from the structural to the organismal and into pathological situations. They use a wide spectrum of model systems and have excellent state of the art technical platforms to carry out their research. Structural studies, supported by an excellent technical platform, provide a central axis for the work in the unit.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The IGBMC is a pioneering centre for the study of gene expression and cell fate decision in eukaryotes, established in 1994 by Pierre Chambon and Dino Moras with affiliations to the CNRS, Inserm and University of Strasbourg. It is placed in a building within the Illkirch-Graffenstaden innovation campus which sets it up in a position to exploit the basic research at the core of its mission for commercial purposes and the creation of spin-offs. The management of the institute is mixed with an in house organisation and an external agency. Over the last ten years, five directors have been at the head of the unit. The private structure, Groupement d'Interet Economique (GIE) CERBM, provides administrative support and, significantly, hires all staff members with fixed term contracts (about 50% of the staff).

RESEARCH ENVIRONMENT OF THE UNIT

The IGBMC is associated with the Faculties of Medicine and Life Sciences of the University of Strasbourg. Significantly until 2020 it has been the centre of activity of the Labex INRT (Biologie Intégrative - Dynamique nucléaire, Médecine régénérative et translationnelle) which has provided funding for a number of initiatives and support for some of the platforms. It has also been associated, at the level of a graduate school, EUR IMCBio, with other Labex programs: NetRNA and MitoCross. Labex INRT ended in 2020 but IGBMC has been associated with NetRNA, MitoCross and HepSYS Labexes and IMCbio to form the Interdisciplinary Thematic Institute (ITI) with the University of Strasbourg. The proposal was funded and represents an extension of LabEx for eight further years until 2028. The Institute has well-endowed technical support on a number of platforms, particularly in structural biology as well as genomics and light microscopy. Some of these provide a service outside the institute, locally or nationally and, some even, Europe-wide. Additionally, IGBMC is a partner of the University of Strasbourg Tech Transfer Office, SATT Connectus that has led to a number of startup companies. Its location within the Illkirch-Graffenstaden innovation campus being an excellent placement for these developments.

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

Permanent personnel in active employment	
Professors and associate professors	19
Lecturer and associate lecturer	18
Senior scientist (Directeur de recherche, DR) and associate	43
Scientist (Chargé de recherche, CR) and associate	43
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	371
Subtotal permanent personnel in active employment	494
Non-permanent teacher-researchers, researchers and associates	153
Non-permanent research supporting personnel (PAR)	11
Post-docs	59
PhD Students	134
Subtotal non-permanent personnel	357
Total	851

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

Employer	**EC**	**C**	**PAR**
CNRS	0	50	66
Université de Strasbourg	35	0	55
Inserm	0	34	51
CHU Strasbourg	1	0	0
Others	1	0	199
Total	37	86	371

UNIT BUDGET

Recurrent budget excluding wage bill allocated by parent institutions (total over 6 years)	27 000.0
Own resources obtained from regional, national calls for projects (total over 6 years of sums obtained on AAP ONR, PIA, ANR, FRM, INCa, etc.)	69 600.0
Own resources obtained from international call for projects (total over 6 years of sums obtained)	6 600.0
Own resources issued from the valorisation, transfer and industrial collaboration (total over 6 years of sums obtained through contracts, patents, service activities, services, etc.)	22 200.0
Total in euros (k€)	125 400.0

GLOBAL ASSESSMENT

The IGBMC is an institute with a distinguished history that, in the past, has been at the forefront of research on the mechanisms of gene expression, cell fate decision and its regulation. It is one of the biggest Life science research entities in France, with over 800 staff and an annual budget over the reporting period of about 21M€. A private entity, GIE CERBM, handles most of this budget. IGBMC has 43 research teams distributed into four departments: Functional Genomics and Cancer (FGC), Translational Medicine and Neurogenetics (TMN), Development and Stem Cells (DSC) and integrated structural biology (ISB)).

The visibility and attractiveness of the IGBMC are excellent to outstanding. Overall IGBMC retains an outstanding scientific reputation in France. This is well illustrated by its leadership and embedding in multiple programs and networks: The PIA LabExes INRT, IMCbio Interdisciplinary Thematic Institute (ITI) within the University of Strasbourg Excellence Initiative and IMCbio graduate school and the FRISBI, Cryo-EM Equipex, Phenomin, Celphedia, and France Génomique programs. The technical platforms, including three major services (Institut Clinique de la Souris (ICS), Centre de Biology Integrative (CBI) and GenomEast, for genome exploration) are excellent, catering for, not only the unit but also other areas in France and, in some cases, Europe. IGBMC unit members are highly involved in meeting organisations (>100 scientific events including eleven Embo workshops and conferences) is the recipient of numerous scientific prizes (10 including Pincus Medal, Loundsbery price, prix Lacassagne du Collège de France, CNRS Silver and Bronze medals, Fondation Bettencourt and Schmumberger prizes), are members of numerous scientific academies (academy of science, of medicine or academy of dental surgery), learned societies (12) and editorial boards (~ 40). IGBMC also holds influential positions in French bodies (Advisor to the Inserm Executive director Inserm, participation to CNRS-INSB Scientific Council) and at the European level (2 ERC panels, 1 Academia Europaea, and 10 Embo members).

Located in between many French and German institutions, notably EMBL, IGBMC is an attractive place for researchers most significantly because of the range of its technical support platforms that enable and motivate excellent research. The excellent attractivitiy of the unit is sustained by PhD and postdoc (~ 300) and team recruitment (9 teams, including 6 international teams, with the support of 3 ATIP-Avenir, Idex /Labex and FRM starting grants) over the reporting period. Visibility, attractiveness and scientific excellence are also corroborated by a high level of success to grant applications at the National (including 145 ANRs, 40% of which are coordinated by IGBMC) and European levels (10 ERC, 1 H2020).

The international visibility of IGBMC is still excellent, although it has been decreasing in the recent years, likely as a result of difficulties in appointing a sound and stable management following the step-down of the historical mentor and manager of the institute. One noticeable exception is the ISB department which is strong and very well known in Europe. Of particular interest, in the context of services and visibility, is the structural biology platform which, given the strength of the ISB department and the interest in related topics in the FGC department, is heavily used and very important. Attractiveness of late mid-career scientists with panache who would act as catalysts to move the unit forward has failed in the last contract. This may result from the local turbulence the unit has experienced over the last few years while facing the aforementioned difficulties. Given the size of the unit, IGBMC could be more represented in national and international bodies. In addition, the number of ERC grants in the unit has dropped over the last few years, though this might be on the mend with the arrival of young group leaders (10 joining at the moment) and the opportunities created by the replacements of a number of senior staff scientists (about 12 in the next few years). The leading and participation to national and European networks and infrastructure (Labex INRT, FRISBI, PHENOMIN, Celphedia, IMCbio, Infrafrontier, France Génomique) are helping regain some of the needed visibility.

The overall level of scientific production is excellent, outstanding for over 20% of the teams. The volume of publication is commensurate with the unit's size: 1200 publications since 2016 with over 60 articles in prestigious multidisciplinary journals (e.g.: Science, Nature, Cell, Molecular Cell and PNAS), and 92 in other highly visible

Nature group journals (including >60 in Nature Comm). The level of productive internal collaboration is also excellent (>140 co-publications). The main areas covered by these articles are structural biology, biochemistry and genetics.

IGBMC develops scientific and technological resources with economic value. The unit is located within an environment that encourages interactions with industry and entrepreneurs and there are excellent activities in both areas with discoveries often leading to patents (22)and spin-offs (3 successful start-ups: Dynacure, Ribostruct and Cascade launched shortly before the current evaluation period). Partnership and interactions were established with tens of private companies including large companies such as Janssen, Sanofi, Merck, Roche, Moderna and Pfizer. This is done through SATT Conectus, a platform that helps researchers take their discovery to market. A highlight of the evaluation period is the partnership agreement with Lysogene to develop a therapy for X Fragile mental retardation syndrome. It is also worth emphasising the entrepreneurial activities fostered by studies on the treatment of neuromuscular disease that have led to Dynacure, a company aiming to tackle rare neuromuscular diseases. The members of the unit take part in scientific outreach activities, according to their scientific skills. Unit members are also highly engaged in communication towards the society (>200 press release, TV, radio broadcasts and public debates).

Over the last ten years, IGBMC has gone through a challenging period due to changes at the helm after an ill-fated attempt to reignite its reputation with the appointment of a director recruited from abroad. This development was not successful and the director departed in 2012. Since then, the unit has had five directors. This has resulted in a lack of stable scientific leadership and direction and, overall, the risk of disintegration. However, over the last two years, the current director has done much by way of steering the unit out of trouble, identifying and addressing the most prescient issues at stake and providing a basis for a much-needed relaunch of high calibre scientific programs. The director has established an inclusive management structure, paid attention to the issues and needs of the technical staff and engaged in the writing of a set of by-laws, a charter, which will establish the rules for the functioning of the unit and the rights and obligations of its members. While appearing technical, this work is of the highest importance considering the previous negative impact that the lack of detailed by-laws has had in the unit. Everybody we met during our visit made clear a strong positive appreciation for the work that the director has done and his engagement with all aspects of the unit. This has resulted in the re-emergence of an attractive unit with potential for the future and good operational practices in place. Notwithstanding these efforts, further improvement of department scientific coherence remains a necessary achievement to facilitate the appointment of a new director.

A DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Most recommendations from the previous reports were centred on the unit governance and management. The unit has responded positively. In particular, under the leadership of the current director, it has responded to the existing governance challenges by setting up a new hierarchically nested structure that takes into consideration the size and thematic content of the unit, the stimulus of internal collaborations and the support and development of the technical platforms. The new governing structure is also representative of the unit as it includes the heads of department and chosen representatives in a scientific committee that will monitor the scientific vision of the IGBMC. The fact that there have been multiple successive directors in the period under review has created a feeling of uncertainty and a lack of long-term vision that has paused under the current direction. The committee feels that the ongoing administrative and organisational restructuring is a prerequisite for the development of a strong scientific vision.

The unit has also responded to the loss of significant figures with the hiring of new, young, group leaders (9 in the period under review) in areas at the forefront of modern research that will contribute to taking the unit into a new era. The unit remains an attractive destination where young scientists can develop the early stages of their careers before moving on, which has been the case in the recent past.

Overall, the response of the unit to the previous recommendations has been good and the unit begins to have the stability it had lost over the last ten years. Also, it should be stated that the progress in the response to the last evaluation has been done despite the challenges created by the Covid crisis, something that should be commended.

B – EVALUATION AREAS

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

Assessment on the unit's resources

The unit has important financial resources (21M€/year excluding permanent staff salaries) and occupies 40 000 m2 in modern buildings. Human resources include over 800 personnel whose scientific activity is organised around 4 departments, 43 research teams, and multiple major platforms often embedded in national networks, providing services locally, nationally and Europe-wide. A particularly important piece of equipment within the unit is the cryo-EM (a second one is being acquired) hosted by the integrated structural biology (ISB) department, part of the Centre de Biologie Integrative (CBI) which acts as a general facility for structural biology.

Assessment on the scientific objectives of the unit

While the committee failed to identify the overall remit, mission or even objectives of the unit before the visit, at the opening session the current director gave a clear exposition of the vision and scientific content of the unit as an internationally recognised centre in the study of gene expression and cell fate decisions from structure to function and translational medicine. Importantly, there was a general acknowledgement that the unit has undergone a period of turbulence which has come to an end with the arrival of the current director. His leadership has calmed many of the difficulties that arose from internal conflicts and weak leadership. He has set in place a new governance structure and, significantly, has given confidence to the different levels of personal in the unit. Everybody acknowledges this and values the stability from which all can work effectively with common objectives.

Assessment on the functioning of the unit

At the moment the unit is functional and complies with all current legal expectations. By-laws are currently being written by the current director, in concertation with all parties involved in IGBMC, to outline proper management and functioning procedures that will be beneficial in solving current malaises with the unit technical staff.

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

Strengths and possibilities linked to the context

The unit is one of the largest research entities in France. The unit occupies 40 000 m^2 and hosts over 800 people. The unit is organised in four departments (Development and Stem cells (DSC), Integrative Structural Biology (ISB), Functional Genomics and Cancer (FGC) and Translational Medicine and Neurodevelopment (TMN)) totalising 43 research teams.

The unit has set up efficient research and technical support, with three major platforms part of national infrastructure: the "clinique de la souris (ICS, Phenomin/Infrafrontier); a FRISBI structural biology platform (CBI); and a genomic platform (Genomeast) part of France Genomique. This is complemented by excellent imaging and proteomic platforms, facilities for multiple models (fly, mouse, zebrafish), and a number of smaller platforms (flow cytometry, screening, monoclonal antibodies…).

The unit has significant financial resources. Part of these originate from its 3 supervising bodies (CNRS, Inserm and Unistra, 4.5 M€/year, excluding salaries) and are largely complemented by project-based incomes, support from

the Plan d'Investissememnt Avenir (PIA, Labex, EUR IMCBio+, Equipex+)) and platform fees, reaching a total of 21 M€/year.

Overall, the unit uses well the resources it has.

Weaknesses and risks linked to the context

A most important issue that came up in discussions concerned the technical staff and relates to the fact that over the last few years a significant number of departures and retirements have resulted in a decrease of the workforce without replacement. The result is an increase of the workload of the remaining staff which creates pressure and stress. This is compounded by a lack of clarity in the individual responsibilities and, importantly, in the rules for promotion. The situation has led to a number of resignations due to poor working conditions. Despite the malaise summarised here, there is satisfaction with the work the director is doing.

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

Strengths and possibilities linked to the context

The strength of the institute lies in the range of research areas covered by the different teams and their scientific quality.

The unit has promoted internal collaborations as illustrated by over 140 internal co-publications.

It cannot be emphasised enough the positive influence that the current director has had and is having on all aspects of the institute. In addition to all the work that he has put on the administration as well as in the scientific and technical organisation of the unit, he has undertaken the writing of by-laws for the functioning of all aspects of the unit something that, surprisingly, was missing. All this has made the unit stronger and more stable and a place where scientists can do what they do best: science.

Weaknesses and risks linked to the context

There was no clear remit of the mission or scientific vision of the institute in the document we received preceding the arrival to the Institute but during the visit, the director provided a coherent and forward-looking vision based on the current strengths and it was clear that there is a theme that runs through the institute and vertebrates it (see above).

There is a fragility to the situation associated with the concern that the current director is planning to leave in 2024 and this will create a leadership vacuum that will need to be filled. It is good news that the director is already working, together with the SAB, on a search strategy for the new director. The appointment of a new director is a critical decision as the wrong person might send the IGBMC to the "pre-Dardel" situation with severe consequences foot the long-term survival and visibility of the unit.

The economic model sustaining the GIE that administers a large fraction of the human resources is outdated and may rapidly run into even more severe structural difficulties.

With one exception, Integrated Structural Biology (ISB), departments do not seem to be organised in terms of science but rather as comfort niches for groups. This applies in particular to two departments: Functional Genomics and Cancer (FGC) and development and stem cells (DSC). There is too much overlap and heterogeneity within each of these departments, with teams in one that could equally well be in another. It appears that the groupings represent where people feel more comfortable rather than where their science fits best. The current groupings might work but each team needs to be assessed in terms of their science and the departments, realigned on this basis.

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

The unifying focus of the unit is the regulation of gene expression and cell fate decisions which is pursued at the levels of structure, function and health. This leads to an organisation into departments which serve as an umbrella for different teams with related interests.

The unit complies with principles of human resources management that respect gender equality and are non-discriminatory, in matters of training, internal mobility and careers development for its staff.

The unit is attentive to the working conditions of its staff, their health, safety and the prevention of psycho-social risks.

The unit applies all the necessary provisions for the protection of its scientific assets and computer systems.

It is also commendable that the unit applies the recommendations on environmental risk prevention and the pursuit of sustainable development goals and regularly updates a business continuity plan (BCP) to enable it to cope with any emergency situations.

The by-laws that are being worked on will fill an important gap in the previous/current functioning of the unit. The by-laws will cover a broad range of matters, including policies for career development (in particular transparent policies for engineer and technician promotions), for internal mobilities, for platform accessibilities, for internal communication and decision making, and for team recruitment at the interface with departments. This will be key to the good management, functioning and performance of the unit.

Weaknesses and risks linked to the context

No identified weaknesses.
The current absence of clear and accepted by-laws is a difficulty in the current unit management (see above).

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The visibility and attractiveness of the unit is excellent to outstanding. IGBMC is an attractive place for researchers because of its location in between many French and German institutions, notably EMBL, and most significantly because of the range of its technical support platforms that enable and motivate excellent research. IGBMC has been very successful in recruiting PhDs (over 300) and young group leader (9 new teams). Attractiveness of late mid-career scientist with panache that would act as catalysts to move the institute forward is, however, lacking. IGBMC also benefits from an excellent visibility, with unit members highly involved in meeting organisations, recipient of numerous scientific prizes, and involved in numerous scientific academies, learned societies and editorial boards. The scientific visibility is also attested by a high level of success to grant applications at the National (145 ANR, INCAs and charities) and European levels (10 ERC, 1 H2020).

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 is proactive in hosting national and international meetings (over 100 scientific events organised) acting as a hub for research in the area of basic and applied aspects of gene expression and cell fate decision. The 11 Embo conferences as well as Jaques Monod amongst others bear witness to this. IGBMC members are invited to present their work in academic institutions or at international and European congresses, which speaks of the quality of the researchers and PIs.

IGBMC members hold positions of influence in European (2 ERC panels, 1 Academia Europaea, 10 Embo members) and French bodies (Advisor to the CEA of Inserm, Scientific Council of CNRS INSB, CNU and CSS Inserm, Academy of sciences (4 members), Academy of medicine (1 member), academy of dental surgery (1 member) and 12 seats in 8 distinct learned academies.

IGBMC members also largely contribute to editorial boards (~ 40 , including eLife, Embo Journal, NAR…) and 10 scientific prizes (including Pincus Medal, Loundsbery price, prix Lacassagne du Collège de France, CNRS silver and Bronz medals, Fondation Bettencourt and Schmumberger prizes).

Weaknesses and risks linked to the context

Leaving aside the ISB department, which is strong, coherent and attractive, an important weakness of the unit is the identified difficulty of attracting mid- late career scientist with panache that would act as catalysts to move the institute forward. There have been significant losses at this level over the last few years without a clear move to replace them. These issues were explored during the visit and remain an important challenge for the immediate future of the unit.

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

Strengths and possibilities linked to the context

The unit has recruited nine teams during the evaluation period, including 6 international teams, with the support of 3 ATIP-Avenir, Idex /Labex and FRM starting grants.

The unit has recruited over 300 PhD students, 180 having defended during the period of evaluation. PhDs student that have defended their PhDs have on average published two original articles. Out of the 180 young doctors, 77 are currently postdoctoral fellows, 42 work in the private sector and 37 already obtained academic positions.

The unit regularly attracts junior and senior researchers who apply for tenured/permanent positions and for whom it offers a favourable environment for the development of their research activities.

The unit implements the operational strategy of its supervisory authorities on research integrity and open science (75% of the unit-led articles are in open access).

Weaknesses and risks linked to the context

After the visit it is obvious that the main weakness in this area is the difficulty of attracting top level scientists to the position of Director and, in general, the equal challenge to bring in high level medium or medium late career scientists. There is also a clear loss of international visibility (with the potential exception of ISB) that needs to be addressed.

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 unit and the teams successfully respond to international and European calls for projects. Ten ERC grants were running during the period of evaluation, and 145 ANR projects were held (4.8M€/year, >40% coordinated by IGBMC). Grants were also obtained from other French agencies including INCA (1.6M€/year) and charities (3.1 M€/year, ARC, Ligue contre le cancer, FRM…).

IGBMC is also involved in structures and projects funded by the Future Investments Programmes (PIA): Labex INRT and the Interdiscilpinary Thematic Institute (ITI) from 2021, the IMCBio graduate school and the CryoEM Equipex program.

Weaknesses and risks linked to the context

Despite all the success in grant applications during the reporting period, there seems to be a recent problem of competitiveness as reflected in the loss of ERC awards and European grants (a single H2020 grant during the reporting period). While some of this can be ascribed to Covid, there might be other reasons here. The point

raised above of the difficulty of attracting mid career 'high flyers' is something that fits these issues and will need to be addressed.

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

Strengths and possibilities linked to the context

Equipment and technological support are major strengths of the unit. In addition to excellent imaging and proteomic platforms, facilities for multiple models (fly, mouse, zebrafish), and a number of smaller platforms (flow cytometry, screening, monoclonal antibodies…) the unit has three major platforms part of national infrastructure: the "clinique de la souris (ICS, Phenomin/Infrafrontier); a FRISBI structural biology platform (CBI); a genomic platform (Genomeast) part of the France Genomique.

The ICS platform provides Europe-wide services, and handles a large number of projects (> 4000 in the evaluation period).

The structural biology platform (CBI) handles a broad set of technologies (X ray crystallography, EM&super resolution, computing, optomechanics…) including cryo-EM which is particularly cutting edge. Soon they will have 2 Titan machines that will make it a very special place in Europe for this kind of increasingly necessary piece of equipment.

The unit has a development, maintenance and renewal strategy, and a strategy to open up its platforms, major equipment and demonstrators to industrialists.

Weaknesses and risks linked to the context

The major weaknes is the need to assure the maintenance contract for the large equipment.

The CBI platform displays a relative lack of opening, with only 10% of the project being of external origin.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

Overall the scientific production is excellent to outstanding. The unit has been very successful, publishing over 1200 manuscripts during the period under review. 65 of these are in prestigious multidisciplinary journals such as Nature, Science, Cell, Molecular cell and PNAS. The publications exhibit a bias towards biochemistry and genetics which speaks for the strengths of the unit.

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

Strengths and possibilities linked to the context

The overall level of scientific production is excellent, outstanding for over 20% of the teams. The volume of publication is commensurate with the unit's size: 1200 publications since 2016 with 65 articles in prestigious multidisciplinary journals such as Science, Nature, Cell, Molecular Cell and PNAS, and 92 in other Nature group journals (including >60 in Nature Commun).

The level of productive internal collaboration is also excellent (>140 co-publications). The main areas covered by these articles are molecular and structural biology, biochemistry and genetics.

All areas of IGBMC interest are well represented, in particular molecular and structural biology, biochemistry and genetics.

The biggest strengths of the unit rely on its long-standing focus on structural biology and transcriptional regulation that are pursued from different perspectives, building on the tradition laid out by its founders. The work produced, particularly in the area of protein structure, has international standards. IGBMC also has strong

technical platforms that support the work, particularly in structural biology, light microscopy and patho-physiological investigations carried out on genetically optimized preclinical models.

Over the last few years, biological sciences have seen technical developments that are influencing progress in the areas of strength in the IGBMC. In particular, in the area of structural biology where the advent of cryo-EM has led to a revolution in methods and results. IGBMC has been successful to jump onto this revolution and, through the acquisition of modern equipment, specifically a *Titan* Krios cryo-EM has placed itself in a pole position to make significant contributions to the field. They have also secured funding for a second machine that will expand their ability to serve the different teams in the unit.

Weaknesses and risks linked to the context

An area that has transformed the biomedical sciences is computational biology. This is an area that has developed very quickly involving genomics, proteomics and statistical methods. IGBMC is making an effort to catch up by introducing young groups, which while adequate remains a few.

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 scientific production is excellent to outstanding for a unit with 43 teams and 15 strong technical platforms, both regarding quantity and quality.

Weaknesses and risks linked to the context

No weakness identified.

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

IGBMC complies with research integrity, ethics and open science. This is illustrated by internal committees (Cometh, SBEA) and several actions including OpenLink, an integrated platform for data management, sharing and publication repository, supported by an ANR call for Open Science and the IFB (Institut Francais de Bioinformatique).

Weaknesses and risks linked to the context

Preprints are becoming an essential element in the dissemination of science. The preprint culture is not widely adopted amidst the teams.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The unit has a number of mechanisms and activities in place that allow it to make excellent to outstanding (for some teams) contributions to the local community beyond its scientific productivity. Members of the unit are at the origin of 62 invention declarations, 22 patents, and three startups launched shortly before the start of the current contract, and that developed successfully during this contract. Members of the unit are also heavily involved in outreach activities.

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

Strengths and possibilities linked to the context

The unit has well-established interactions with non-academic agents. Activities in this area are mediated by Société d'Accélération du Transfert de Technologies (SATT) Conectus that promotes partnerships with industry and helps scientists take their innovations into the marketplace. Partnership and interactions were established with tens of private companies including large companies such as Janssen, Sanofi, Merck, Roche, Moderna and Pfizer.

A dozen of medical professors with clinical positions at the "Hôpitaux universitaires de Strasbourg (PUPH and MCUPH) are part of IGBMC, promoting translational research and providing an interface with the clinic.

Weaknesses and risks linked to the context

A synthetic overview of non-academic interaction was not provided at the unit level, and could only be inferred from team activities.

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

Strengths and possibilities linked to the context

The unit develops scientific and technological resources with economic value. It conducts an active policy to protect intellectual property and in particular fills Invention declarations (62) and patents (22). It is also a source of three successful start-ups (Dynacure, Ribostruct and Cascade launched shortly before the current evaluation period) and clinical trials (4).

A highlight of the evaluation period is the partnership agreement with Lysogene to develop a therapy for Fragile X mental retardation syndrome. It is also worth emphasising the entrepreneurial activities fostered by studies on the treatment of neuromuscular disease that have led to Dynacure, a company aiming to tackle rare neuromuscular diseases.

Weaknesses and risks linked to the context

A synthetic overview of products for the socio economic was not provided at the unit level, and could only be inferred from team activities.

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 members of the unit take part in scientific outreach activities, according to their scientific skills. They are present in the media (>182 press release, TV and radio broadcasts), on the internet or on social media, in compliance with research integrity and ethical requirements. They also organise awareness-raising actions for young people involving school pupils, and are engaged in broad audience public debates (>20).

Weaknesses and risks linked to the context

No weakness identified.

C – RECOMMENDATIONS TO THE UNIT

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

A most important goal should be to find a new director who will take over and reap the benefits of the current director excellent stewardship. The ideal person should be someone with an international visibility, a female if possible, with scientific vision aligned with the activities of the IGBMC who will command respect from the team leaders, the administration and the technical staff and with an understanding of the French scientific

administrative system. The committee acknowledges that this is a high order task and there should be a plan B. One possibility would be on a rotating basis, by the heads of the departments who would become scientific directors every other contract. This would separate science from the administration and might result in an attractive situation for new appointments.

Departments, with the exception of ISB, do not seem to be organised in terms of science but rather as comfort niches for groups. It is possible that lack of department scientific coherence is an inheritance of the turbulence of the last few years but perhaps, taking advantage of the present situation, the unit could consider a realignement and, perhaps, even a renaming. For example, the DSC has vey little developmental biology and very little by way of stem cell research but some solid cell biology. So, perhaps a change of name (together with a regrouping) would be beneficial and also attract new PIs more aligned with the content of the departments. The weaknesses of DSC were also highlighted in the Directors presentation as high turn over, difficulty in attracting postdocs (perhaps due to the instability of the department and the youth of the teams) and the fact that they lag behind in the use and application of organoid technology. The FGC, although more consolidated, also faces some challenges due to the retirement and departures of many PIs (7 in the next 10 years). Some of its groups could easily be located to ISB or TMN, without loss of identity. So perhaps FGC, TMN and a newly named cell biology department with a reshuffling of the teams to where their scientific activity fits best will improve the situation.

The ISB department hosts the cryo-EM facility of the CBI which is of very difficult access to the members of the unit (or anybody else for that matter) that are not under the umbrella of or in collaboration with the ISB. This issue of a broader accessibility to the structural biology equipment, including within IGBMC by members of the unit that are not in CBI needs to be looked into and resolved.

The unit has a good group of PIs with an increasing representation of young PIs that will be bolstered by the opportunities for new appointments opened by the retirement of older PIs. A plan should be developed for the stepwise filling of these positions in the context of the future scientific direction of the IGBMC

The economic model sustaining the GIE that administers a large fraction of the human resources is outdated and may rapidly run into even more severe structural difficulties. The outsourcing of some of these matters, in particular the hiring of personnel to GIE is in need of revision.

The by-laws that are being written at the moment are a very important element for the future of the unit. It will be important that the by laws will consider matters linked to the management of the technical staff human resources.

Recommendations regarding the Evaluation Area 2: Attractiveness

The unit has lost some of its international visibility and needs to work to recover it. While it remains an attractive home for young PIs and students and is seen as a reference in France, internationally it is still perceived as the institute of Pierre Chambon with a recent troubled history. This needs to change. The current director has made great strides to create harmony and a fertile ground that now needs to be worked on with the opportunities afforded by the possibility of new appointments.

Another important element should be increasing the scientific cohesiveness of the departments within the current strengths of the unit as a whole; this should make it even more attractive to young PIs. The unit should look into the future and not its past history and should make efforts to make sure that this is the case.

IGBMC should increase the number of ERCs, and therefore encourage its members to apply, and also, liaise with other European institutions in Marie Curie training programs centred at IGBMC.

Recommendations regarding Evaluation Area 3: Scientific Production

The committee encourages the posting of preprints (e.g in bioRxiv) which have become a major currency in the emerging arena of scientific publishing and are being considered in all major fellowships and grant applications.

Computational biology is essential for biomedical sciences. IGBMC is somewhat behind in that field. This is an area that the unit needs to reinforce.

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

No specific recommendations considering the lack of synthetic overview for that item at the unit level, which hampers providing relevant recommendation.

RESPONSES TO SUPERVISING BODIES CONCERNS (IF ANY)

No concerns were expressed by the supervising bodies.

TEAM-BY-TEAM ASSESSMENT

Department of Integrated structural biology (ISB)

Team 1: Structural biology of epigenetic targets

Name of the supervisor: Mr. Jean Cavarelli

THEMES OF THE TEAM

The team is interested in analysing the structure/function relationships of epigenetic enzymes focusing on protein arginine methyltransferases (PRMTs). For this, it aims at understanding the regulation of methylation by PRMTs using X-ray crystallography and single-particle cryo-electron-microscopy. It also studies PRMT inhibitors and is involved in early drug discovery.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) Projects should be selected with the potential to provide high quality publications where the team has played a leading role.
All researchers are fully involved in the PRMT project, being part of the molecular biology/biochemistry, biophysics aspects and structure determination by X-ray and Cryo-EM.
2) PhD students should be given the opportunity to develop leading roles in projects.
Unfortunately, no PhD student has joined the team since (the last PhD student left in 2018).
3) The experts committee recommends to build international recognition with high quality publications focusing on the team's core strength in PRMTs.
The team has built a strong collaboration on CARM1 structure/function with a lab in the Netherlands.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	2
Lecturer and associate lecturer	2
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)	1
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

The overall assessment of the team

This is a very good to excellent team that is extremely well established in the structural biology ecosystem nationwide. It has produced original work and the team members are involved in teaching.

Strengths and possibilities linked to the context

Altogether, the team has excellent visibility in the structural biology field. The team leader is the deputy director of the French Infrastructure for Integrated Structural biology (FRISBI) and is in charge of the "bio-crystallography" module of the Integrated Structural Biology (ISB) platform. He is thus involved in the European Infrastructure Instruct-Eric project. Besides, the team leader coordinates two BAG groups (Soleil, ESRF). The team members (4 professors/assistant professors) have strong teaching activities at the bachelor/master's levels. The team leader and another member of the team administrate and manage the Structural Biology Master of Strasbourg University. The team leader has been involved in the creation of a French National Training network in Integrated Structural Biology (ReNaFoBiS) which has increased the visibility of structural biology for academics and industry.

Overall, the scientific production of the team is very good to excellent. The team has developed an original approach using peptide-based transition state mimics to reveal the conformation of peptide substrates upon binding of a given PRMT. For the design and synthesis of new PRMTs modulators, the team has established collaborations with chemists. During the evaluation period, the production of the team includes five publications as leader or co-leader: Sci. Rep (2016), PNAS (2017), FEBS J (2017), Philos. Trans R Soc Lond B Biol Sci (2018), ChemBiochem (2021) and four publications in collaboration: NAR (2017), Proteins (2017), Bioorg. Chem (2020) and Embo J. (2020). During the same period, the team is co-author of 65 PDB depositions (55 related to PRMTs, 10 for other projects).

The non-academic activity of the team is excellent. The team leader and another member of the team are cofounders of a start-up. The team has deposited an invention disclosure (2016) on PRMTs inhibitors.

Weaknesses and risks linked to the context

The team is relatively small (5 people) and gathers 4 university professors/assistant professors with full teaching activities and one engineer.

Unfortunately, no PhD student has been hosted in the team since 2018 (the last one was in the team from 2014-2018) nor has any postdoc.

The last funding contract has been obtained in 2019.

RECOMMENDATIONS TO THE TEAM

There is no recommendation from the expert committee as the team won't be renewed upon the retirement of the team leader.

Team 2: Chemical biophysics of transcriptional signalling

Name of the supervisor: Ms. Annick Dejaegere

THEMES OF THE TEAM

The team studies nuclear receptor proteins, hormone activated transcription factors involved in very broad physiological processes. The complementary expertises of the team in computational, biophysical and structural biology allow adressing 1) molecular modelling and dynamics simulations, 2) experimental structural and biophysical studies and 3) nuclear hormone receptor proteins and their co-activators from structural dynamics to allostery.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report was that "to optimise the collaboration between both groups should be moved into the same lab". This has not been achieved.

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)	2
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	1
Subtotal non-permanent personnel	1
Total	**7**

EVALUATION

The overall assessment of the team

The team has a very good to excellent publication track record over the period (54 publications) exemplified by a collaborative publication in Nature Com (2019). The visibility is excellent in the field with several international collaborations and with a high attractiveness (3 PhD and several masters students).

Strengths and possibilities linked to the context

The visibility of the team is excellent and members are invited to national and international meetings. They list several different collaborations with groups in France (mostly within IGBMC and Unistra), Spain, Norway and the USA. The computation-oriented members of the team participate to the Elixir consortium in structural bioinformatics. The quality of these collaborations is high with 45 collaborative publications within the period. They obtained several contracts on public and charitable funding, with 4 ANR funding (2 as coordinator). The team writes software for protein structural analysis which they distribute to the wider scientific community. The main contribution of the team to activities of collective interest is through mentoring of young researchers (permanent members of the team), teaching at the undergraduate and master levels (1 Professor; 1/2 ATER position), developing new teaching programs and administration, participation in different recruitment committees, evaluation committees, animation of scientific societies, editorial activities, review of publications (15 publications per year), review of grants (11/year), participating in thesis and HDR committees (5/year).

The team has a very good to excellent scientific productions. Among 52 publications within the period, nineteen present a member of the team as the main author, including a Nature Commun. (2019). The published work (including collaborative papers) with manuscripts in Nat. Comm. (4), in NAR (4), Angew. Chem Int Ed Engl (2), Chem Sci (2), J Med Chem (3), Biophys J (1), Scientific Reports (3), as well as in various journals in (bio)chemistry, biophysics, endocrinology was cited 534 times.

Weaknesses and risks linked to the context

The team is located in 2 distinct buildings separating the experimental members from the computational ones and thus complicating communications and efficiency of research work.

RECOMMENDATIONS TO THE TEAM

The recommendation is mainly to identify a solution to reunite the team in one single space to improve communication between the experimental and computational parts of the team.

Team 3: Biomolecular condensation in nuclear organisation and function

Name of the supervisor: Mr. Mikhail Eltsov

THEMES OF THE TEAM

The team aims at determining nuclear organisation at different scales. A focus is given to non-membrane-bounded domains (termed biomolecular condensates) and their roles in the organisation of heterochromatin (nature of the condensed silent state), the shaping of defined domains on mitotic chromosomes using condensins, DNA damage responses, nucleoli and transcriptional factories. The team notably uses cryogenic microscopy methods, correlative light and electron microscopy, computational image processing (enhanced with artificial intelligence tools) to explore these structures.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was established in 2019. It therefore does not appear in the previous Hcéres report.

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	2
Non-permanent research supporting personnel (PAR)	0
Post-docs	1
PhD Students	2
Subtotal non-permanent personnel	**5**
Total	**6**

EVALUATION

Overall assessment of the team

The team created in 2019 conducts excellent research. It is still quite small with one PI, one postdoc and two PhD students. Since its creation, the team has made remarkable progress that is documented in corresponding publications in international journals, the obtaining of an ANR grant, and industrial collaboration. Opportunities for truly groundbreaking discoveries clearly appear on the basis of its forefront technological expertise and carefully chosen experimental systems. The team should be strongly encouraged and supported such as to be put in an optimal position to compete for international funding.

Strengths and possibilities linked to the context

The team is currently building its visibility. A remarkable strength of the team is the interdisciplinary work at the interface between biophysics and molecular and structural cell biology. A highly competitive network of collaborators has been assembled that includes specialists of chromatin biophysics, conformational variability, and modelling. The team has also embarked in the development of novel computational tools for the tomographic reconstitutions. For this, the choice of Charles Kervrann at INRIA, Rennes, as a collaborator for deep learning-based tools appears highly appropriate. The team clearly draws on the outstanding environment at IGBMC, notably within the Integrated Structural Biology Department. The team leader has already secured substantial funding from ANR (163,506 Euros via the ANR-20-CE11-0020-02 program), and from the Idex Eltsov (95,000 Euros).

The team conducts excellent research. The project concerns nuclear gene regulation processes that impact wide areas of physiopathology, such as embryogenesis, stem cells, aging, and genome reprogramming during cancer. The team has for the first time observed conformational transitions of nucleosomes in situ in the nucleus. These striking findings were published in 2018 in Nucleic Acids Research, a leader journal in the domain. Another enabling strength of the team is the use of cryo-electron tomography to characterise condensing complexes on isolated chromosomes and thereby, to understand how potential biomolecular condensates made from mitotic chromatin are modelled into particular shapes. Furthermore, evidence was provided that ionising radiation-induced foci have reduced RNA density (published in 2020 in the International Journal of Molecular Sciences), which changes the current dogma. The rare capacity of the team to perform computational work in relation to their high-end experimental explorations (published in 2021 in Frontiers in Molecular Bioscience) has allowed them to obtain an unmatched quantitative visualization of chromatin states.

Besides its fundamental program, the team also interacts with companies (i.e., Leica microsystem GmbH, Diatome Ltd.). This permits to improve the methodology to reach better Clem resolution and to improve sample preparation for in situ cryo-ET imaging, and ultimately for the scientific community to benefit.

Weaknesses and risks linked to the context

As a junior team leader who has just been recruited to IGBMC, the PI is rather exposed to threats rather than to weaknesses. One of these threats is the competition for funding. The PI has already obtained substantial local and national funding. He is strongly encouraged to reach out for international funding sources once corresponding opportunities arise.

Another threat is linked to the size of the team. The attribution of technical and scientific personnel with permanent work contracts to the team would be a key asset. With increasing funding, the recruitment of experienced personnel on temporary contracts will also help to further speed up operations.

RECOMMENDATIONS TO THE TEAM

The team leader and his team members are strongly encouraged to continue their excellent and exciting research. Future publications of the emerging team's own original work will be a strong asset for strengthening its position in competitive funding.

Team 4: Biomolecular Nuclear Magnetic Resonance

Name of the supervisor: Mr. Bruno Kieffer

THEMES OF THE TEAM

The team is focused on deciphering molecular mechanisms linked to protein-protein interactions and structural transitions due to binding to biomolecules or to post-translational modifications. Their interests concern gene expression with a biomedical orientation to understand prostate cancer resistance to current therapies through androgen receptor studies. In addition, methodology development benefitting the community is part of their activities. The team is multidisciplinary in nature, combining biophysics, cancer biology and analysis of multi-scale data.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) An effort has to be made to make the group more visible internationally.
Despite an excellent national visibility, international collaborations and projects remain weak and incoming international mobility is rare. The team has, however, participated in an EU-wide infrastructure network that shows a promising step in that direction.
2) Promote higher number of young scientists in the group.
The group has supervised a very good number of young scientists and welcomed an excellent number of internships. The team defends a position of quality instead of quantity, testified by very close supervision of post-docs and PhD students and reflected in the excellent career prospects of the former PhDs.
3) Include the different projects of the team in a consistent, global, perspective.
Although multidisciplinary is an excellent opportunity for the team, dispersion of the projects remains an issue. However, the team leader has presented a common project concerning the androgen receptor role in prostate cancer resistance to treatment, starting from clinical data and going to molecular basis of the disease, which is an interesting research line to gather the team strengths.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	1
Lecturer and associate lecturer	2
Senior scientist (Directeur de recherche, DR) and associate	2
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	**7**
Non-permanent teacher-researchers, researchers and associates	5
Non-permanent research supporting personnel (PAR)	0
Post-docs	0
PhD Students	3
Subtotal non-permanent personnel	8
Total	**15**

EVALUATION

Overall assessment of the team

The team had a very good to excellent production based on a very large panel of expertise. The biomedical and translational side of the research is emerging but still need additional efforts to be fully established. National visibility of the team leader is excellent. An extensive network of collaborations within the IGBMC, and at the national level is deployed based on the team deep expertise in analytical and structural biology. International involvement remains under-exploited. Interaction with the economic world is excellent. The team has embraced open-science practices.

Strengths and possibilities linked to the context

The team has an excellent national visibility. PIs of the team participate to journal editorial boards (Frontiers in Molecular biosciences, European Biophys Journal and ReScience C). The team is also very active in providing data to the community, available in generic (e.g. zenodo) or thematic public repositories (BMRB) or scientific demonstration in Jupyter notebooks. The team has obtained six ANR project during the last period, three as coordinators, in four different CE (6, 11, 29, 44), which shows the competitive interest of the multifaceted expertise developed in the team. The team was a partner in an EU-wide infrastructure project (FT-ICR mass spectrometry). In addition, funding has been obtained from Inserm, the region of Alsace and by local and national anti-cancer charities. The funding of the team is well shared between the PIs. A PI has been involved in the steering of a learned society and three national congresses have been organised by the team. The team leader has interest in developing novel teaching approaches at Unistra and a mooc about "NMR introduction" has been produced. Five PhDs were supervised during the period, with two defences. Two of the PhD students are co-supervised with another local laboratory.

The scientific production of the team is very good to excellent. The team has published 76 original articles during the period with sixteen as first/last or corresponding authors in very good journals for specialised audiences. Notably, 28 of the 76 articles are published together with other IGBMC team members. Contribution to other IGBMC team projects by providing structural biology expertise resulted in publication in high visibility journals (NatCom 2017, Embo J 2017). A consequent part of the collaborative publications (25) is based on the original methodology developed in the team, more specifically in data analysis for FTICR mass spectrometry proteomic approaches. The expertise of the team in Fluor NMR and its application to characterise a proline-rich region in proteins is original and also lead to collaborative publications (4). Results from the team own project relevant to biomedical applications in prostate cancer were published in 2021/22 in Mol Oncology, showing the emergence of biomedical and translational research. The team software development (Spike, Palma) activity is at the service of the community, both for NMR and mass spec data analysis.

The team has very good contacts with the economic world and performed research services for local companies. The team has made four declarations of invention and two patents are in preparation. The team hosts researchers from CASC4DE (a spin-off of the team developing analytical NMR and MS methods) and ALMS-Therapeutics (performing structural analysis of biodrugs) companies. One PhD student of the team benefits from a Cifre contract with CASC4DE. Members of the team are actively involved in steering committees of three charities related to prostate cancer fight, including one at the European level. Recommendations were provided to ISO and Afnor. The team seizes opportunities to have contact with the public and communicates on social media.

Weaknesses and risks linked to the context

International involvement of the team is weak with no international networking or research project funding. Only one postdoc has joined the team during the period.

Publications of the team own research results are mostly in specialised journals.

Maintaining the large equipment infrastructure has become difficult in a general manner that is relevant to the team that manages NMR spectrometers.

RECOMMENDATIONS TO THE TEAM

The PIs of the team are strongly encouraged to promote the visibility of the junior researchers of the team and to increase efforts to establish the biomedical and translational research lines of their project. Efforts have been made to present a clearly defined common research goal involving all researchers of the team around the

androgen receptor role in prostate cancer resistance. This should be pursued to present a clear identity that would benefit the team visibility and attractiveness.

The team contribution to knowledge and know-how is undoubtful but the team needs to find the right balance between efforts to pursue its own research interest and efforts to advance collaborative projects.

The probable departure (retirement) of a very active and respected PI during the next contract will require anticipation to allow proper transfer of his huge expertise.

Given the interest of the team members for innovative training and capacity to supervise early stage researchers, joining an EU doctoral network seems a challenge that would very well fit the team profile of activities.

Team 5: Large complexes involved in gene expression

Name of the supervisor: Mr. Bruno Klaholz

THEMES OF THE TEAM

The team is focused on deciphering molecular mechanisms dictating gene transcription and translation at multi-scale structural level. Research efforts are focused on structural investigations of the human ribosome, chromatin, nuclear receptor and viral complexes.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendation from the previous report was:
The team is in a position to reinforce its national role in structural biology and should take steps to ensure wider access of its microscope to the national community.
The PI has been actively involved in the context of the French Infrastructure for Integrated Structural Biology (FRISBI) to promote access to high-end Cryo-EM instruments to the national community.

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	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)	1
Subtotal permanent personnel in active employment	**5**
Non-permanent teacher-researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	0
Post-docs	3
PhD Students	7
Subtotal non-permanent personnel	12
Total	**17**

EVALUATION

Overall assessment of the team

This is an outstanding research team, highly productive in terms of publications in the very best journals and recognised at the international level. The team is engaged in several collaborations within the unit and beyond. The team leader is strongly involved in the coordination of the IGBMC CBI platform, associated with various national and international infrastructure and the team takes advantage of the CBI infrastructure to develop and promote cutting-edge technology. The team leader contributes significantly to training by research and is involved in industrial partnerships.

Strengths and possibilities linked to the context

The team has an outstanding visibility. The team leader has received several recognitions for his scientific achievements (Richard Lounsbery prize, French and American Academy of Sciences; Raimond Castaing prize, French Society of Microscopies; Fellow of the University of Strasbourg Institute of Advanced Studies (USIAS); Silver Medal Award by the Centre National de la Recherche Scientifique (CNRS)). The team leader has contributed two chapters to teaching books and can forward a very strong involvement in several national and international research infrastructure, either as the main coordinator (National infrastructure for Integrated Structural Biology (FRISBI), or as a participant (European Infrastructure Instruct-ERIC; European Infrastructure iNEXT-Discovery). The PI is also coordinating the Centre for Integrative Biology (CBI), hosting the Cryo-EM platform which is part of the France-Cryo-EM Equipex+ program. He was also a member of the "Conseil National des Universités" until 2018. Funding has been secured by several contracts (ANR, INCA, and regional instances). Four PhD students have defended their thesis and three of them are still active in research. One researcher of the team has obtained the French HDR qualification,

The scientific production of the team is outstanding. The team employs an integrated structural biology approach combining cryo-EM, the major field or expertise, with X-ray crystallography and super-resolution imaging to address issues of gene transcription and translation related to human health at the structural level. To this end the team has a privileged access to high-end instruments and is therefore enabled to maintain leadership in cutting-edge technology. The team also develops cutting-edge software to push forward the resolution limit in the different techniques they master. The team can forward an impressive publication activity, with over 40 peer-reviewed publications, several of them in high-profile journals (Nature, 2017; NAR Cancer, 2020; Nat Commun 2016 and 2019 (2X); Science, 2021; PNAS, 2020,). Among the major results obtained, one can mention the high-resolution 3D structure of the human ribosome allowing the visualization of chemical modifications of the RNA subunits and the 3D structure of MeCP2, involved in Rett syndrome, a neurodegenerative disorder (in coll. with the team of Ali Hamiche within the IGBMC). Three software contributions for data analysis have also been provided.

Several contracts with the company Janssen had been obtained.

Weaknesses and risks linked to the context

The contribution of team members to overall team activities, apart bench work (1 PR assures teaching), appears to be weak.

The team leader assured several communications towards media, but very few general outreach activities by the team are reported.

RECOMMENDATIONS TO THE TEAM

All team members should be encouraged to participate actively in overall team activities (teaching, fund-raising, management …).

Given the high scientific performance, the team should reach out for ERC funding.

The team should be more proactive in science outreach activities.

The team leader should foster access to the cryo-EM facility for all IGBMC teams, beyond the ISB department.

Team 6: Chromatin stability and DNA mobility

Name of the supervisosr: Ms. Valerie Lamour and M. Marc Ruff

THEMES OF THE TEAM

The team studies large, non-covalent transient nucleoprotein complexes involved in DNA stability and mobility. Three main axes are developed: 1) Regulation of DNA topology by the nucleoprotein complexes of DNA topoisomerases. The team has focused on the determination of the architecture of the full-length prokaryotic (Bacterial DNA gyrase) and human Top2 in complex with small molecules and DNA, by combining structural, biophysical and biochemical methods to better link structural information and functional activities; 2) Preintegration complexes of the retroviral nucleoprotein integrate complexes focusing on the integration step and trying to understand the molecular mechanisms of viral DNA integration; 3) A drug design axis for developing new HIV inhibitors and antibiotics against nosocomial bacteria.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) The team has established powerful systems for studying the proteins of interest. Over the next two years, it is important that these are converted into outputs in the form of high-quality research papers. This will help to maintain and boost their international research profiles and to justify future funding.
The team has followed the previous recommendation publishing 27 original papers, thirteen of which in leader and top journals (Nat. Comm. Sci.Adv. JACS, NAR). Several funding has been obtained from ANR (one as coordinator) and ANRS
2) The best way to improve international visibility is by producing high quality publications. Team members should also attend international meetings to promote their research, ensuring that colleagues are aware of their work.
The quality of the publication was improved and the team leaders have been regularly invited to reputed conferences (Gordon conferences and EMBO workshops. Besides national collaborations, international collaborations are starting.
3) The team works on proteins that are potentially drug targets and should consider how this aspect will be pursued in future. .
The presence of the "Drug design axis" partially address this recommendation.
4) Care should be taken to ensure that PhD students have the opportunity to contribute to projects and obtain publications that will launch their careers.
Most of the PhD students first authored publications except one who was simply associated with publication. On average, they published 3 papers during the period, which clearly fulfills the previous recommendation.

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	0
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	1
Research supporting personnel (PAR)	2
Subtotal permanent personnel in active employment	**7**
Non-permanent teacher-researchers, researchers and associates	1
Non-permanent research supporting personnel (PAR)	1
Post-docs	2
PhD Students	5
Subtotal non-permanent personnel	9
Total	**16**

EVALUATION

Overall assessment of the team

Overall, the team is excellent. Considering the size of the team, the scientific production productivity was excellent, with publications in highly visible international journals. The team is engaged in several collaborations within the unit and at the national level. The international visibility is improving with new collaborations. The PIs have significantly contributed to training by research. The team was successful in national grant applications and was also involved in a fruitful industrial partnership.

Strengths and possibilities linked to the context

The quality and team reputation lies on an outstanding expertise in biochemistry combined with a valuable competence in cryo-EM techniques to explore important nucleoprotein complexes. In terms of national reputation, the team is involved in the French integrate network. This reputation has led to obtain ANR grants as Principal Investigator (ANR-19-CE11-0001-01) and as Collaborator (ANR-18-CE45-0010-02). The team was also successfully supported by five ANRS grants. On the period, the team has got ~1.8 M€ of external funding from the regional and national agencies. The team has maintained its attractiveness with three PhD students who defended their thesis during the period with an excellent level of publications (3 on average) and a significant acknowledged recognition. Moreover, one of the team leader is the President of the French National network of MD-PhD programs. The team also benefits from an excellent international visibility, with regular invitations to reputed conferences (Gordon conferences and EMBO workshops).

Overall, the team has published 27 original papers and thirteen of which in leader and top journals (Nat. Comm. Sci.Adv. JACS, NAR) and 2 reviews. The team has a long-standing expertise in studying integrases at the molecular level. This was particularly useful to develop the more recent but highly productive work on topoisomerase. Indeed, they elucidated at the molecular level, even with an atomistic resolution, key mechanisms associated with the catalytic activity for two major systems i.e. e-coli DNA gyrase complex and human Top2 enzyme. This led to major publications (Nat. Comm. 2019, Nat. Comm. 2021, both recommended by F1000) and contributed to develop a productive international collaboration with an expert in the field of

topoisomerase (Sci.Adv. 2019). Besides this recent axis led by an assistant-professor (co-head of the team), the work on integrase led by the other team co-leader focused on the viral DNA integration step using a bottom-up strategy that consists in studying and reconstituting the whole complex piece-by-piece using new production technologies that were detailed into two main publications (Methods Mol. Biol 2018 and Nat. Comm. 2016). The team also contributed to the developments of instrument ("Protein complexes production in mammalian cells using a modified vaccinia virus as an expression vector, Unstable Protein Purification through the Formation of Stable Complexes")

The team also develops a "Drug design axis", with a strong industrial link established with companies, with several contracts for a total amount greater than 1 M €. The team also deposited five invention reports.

Weaknesses and risks linked to the context

The "Drug design axis", which is strongly supported by industrial contracts appears as a side and service group. It would deserve to be better integrated in the whole project and driven by new questions related to topoisomerase project that will become the main axis of the team.

RECOMMENDATIONS TO THE TEAM

The team is strongly encouraged to pursue its productive work. The retirement of the PI leading the integrase axis might weaken the team by loss of a recognised expertise and of a strong collaboration network in the field of nucleoprotein. New recruitments that seem to be planned should be finalised. They will contribute to strengthening the promising "topoisomerase" axis.

Care should be taken not to lose the industrial partnership. The drug design deserves to be better incorporate considering the renewed orientation of the team.

Team 7: Molecular Basis of Chromatin and Transcription Regulation

Name of the supervisor: Mr. Christophe Romier

THEMES OF THE TEAM

The team studies epigenetic mechanisms to understand their involvement in nuclear processes, their dysfunctions in diseases, and how to modulate the activity of epigenetic effectors using drug candidates.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) Strengthen the impact of the team further, taking leading roles in analysis as well as structure resolution:
The 2019-recruited CRCN Inserm researcher, with expertise in crystallisation, X-ray data collection, and structure determination, is clearly an asset toward more independence in structure determination.
2) The team should consider which area offers the best opportunity to establish its research identity. That does not mean they cannot operate on three lines, but choose one, to establish the visibility that will help in getting funding.:
The team has made a tremendous effort to be recognised for its scientific work in epigenetics, notably on histone chaperones, with a main focus on zinc-dependent histone deacetylases (HDACs) from pathogens. This project has been funded by the large EU FP7 project A-ParaDDisE (Anti-Parasitic Drug Discovery in Epigenetics; 2014-2017).
3) The experts committee recommends to visit conferences in the area of epigenetics to become (even) more visible in this field.
Although the team is pro-active at organising scientific events (Forum BioChem, Symposia, Conferences), its participation to international conferences, notably in the field of epigenetics, remains weak.

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)	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	2
Subtotal non-permanent personnel	2
Total	**6**

EVALUATION

Overall assessment of the team

This is an excellent team, which has made several original contributions in the fields of epigenetic mechanisms, notably on histone chaperones and histone deacetylases. The work of the team contributes to the molecular understanding of this process and also participates to the identification of promising therapeutic targets for the treatment of numerous human diseases. While improved over the reporting period, the team will still benefit from a higher international visibility.

Strengths and possibilities linked to the context

The team is internationally recognised for developing the technology of protein complex reconstitution by co-expression in *E. coli* and for its work in epigenetics, notably on histone chaperones and histone deacetylases. The team has made significant contribution notably toward the development of anti-parasitic and anti-cancer drug leads by the resolution of the structure of parasitic zinc-dependent histone deacetylases (HDACs). This has led to numerous collaborative works, notably in the field of medicinal chemistry. The team has been efficient in fund raising (1,270 k€), with several national and charity grants (ANR, FRM, ARC) and the participation to a EU FP7 project A-ParaDDisE (Anti-Parasitic Drug Discovery in Epigenetics). The team has hosted eight PhD students/postdoctoral fellows, and recruited an Inserm CRCN researcher, to work on Cohesin and cohesinopathies and for developing the use of the zebrafish preclinical model to address the team translational medicine analyses. In the next reporting period, a CNRS CRCN researcher, with expertise in chemistry and crystallography, will join to further develop the HDACs projects, including in medicinal chemistry. These recruitments will strengthen integrated structural biology studies.

The scientific production is excellent with 27 publications issued during the reporting period, including team leading publications in well recognised scientific journals (Cell Reports, 2021; Nucleic Acids Research, 2021; J. Medical Chemistry, 2018; Nature Structural Molecular Biology, 2016). The team employs an elegant and powerful integrated structural biology approach, combining *in vitro*/structural data coupled with *in cellulo* and/or *in vivo* analyses in order to decipher the structure/function relationships of the targets in-depth and to increase the impact of their work. Approaches include structural studies (X-ray crystallography and cryo-EM) accompanied by biochemical and biophysical characterisation of proteins and their complexes. Complementarity is achieved by a strong collaborative network, but also within the team.

Weaknesses and risks linked to the context

The team should continue its effort to be recognised in the field of epigenetics and histone chaperones and apply to competitive national and international grants.

The participation of the team to international conferences, notably in the field of epigenetics remains weak. Efforts should be set up to establish the visibility that will help in getting funds and students.

RECOMMENDATIONS TO THE TEAM

The committee recommends continuing with the chosen research lines.

The committee recommends increasing attendance to international conferences in the area of epigenetics to become more visible in this field.

Team 8: Structural biology of molecular machines

Name of the supervisor: Mr. Helgo Schmidt

THEMES OF THE TEAM

The team is focused on deciphering the molecular mechanisms governing the function of ATPases from the AAA+ family associated with various cellular activities, centring in particular on two major aspects of the vast activities operated by these complex machineries: 1) ribosome maturation and 2) microtubule transport.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has been established in 2017 and therefore does not appear in the previous Hcéres report.

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	0
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	**2**
Non-permanent teacher-researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	0
Post-docs	0
PhD Students	1
Subtotal non-permanent personnel	3
Total	**5**

EVALUATION

Overall assessment of the team

This emerging team has an original and interesting project, supported by excellent infrastructures and know-how. The team is a very good team but suffers from a limited scientific production and primarily still needs to establish itself through its scientific excellence. The team has shown an excellent capacity to attract funding.

Strengths and possibilities linked to the context

The team has emerged in 2017, supported by .an ATIP avenir grant, complemented by an ATIP+ grant, covering the period of 2018 to 2022. In addition, the team has obtained an ANR grant in 2019 coordinated by the PI. Two fundings were obtained from the region Grand Est. The PI defended his HDR in 2019. The team benefits from the

excellent local infrastructures in structural biology (integrated structural biology platform). Two post-doc and two PhD students have joined the team during the contract. One postdoc is the first author on the Rea1 publication and a PhD student graduated and is the first other author in the submitted BicD2 publication. The second postdoc is associated with both publications.

The team masters cryo-electron microscopy, a technique with a bright future in structural biology. The scientific objectives of the team are clearly defined, with one project established in the community, while the project on Rea1 is emerging. The team published in 2018 (in eLife) the first Rea1 structure contributing to a better understanding of its regulation and molecular function regarding the assembly of the ribosome. The results were presented at the French-German Biophysics meeting in 2019 and the French Integrated Structural Biology meeting in 2021. Another manuscript concerning the cargo adaptor to dynein BicD2 has been published in Structure in 2022, in collaboration with team 4.

Weaknesses and risks linked to the context

The scientific production is low, even for a challenging project, with one article published during the reporting period.

The team size is small to sustain its project.

The team has not yet activities outside the fundamental research aspect.

The team has little interactions, particularly in the cell biology area.

RECOMMENDATIONS TO THE TEAM

The team needs to reach a sustainable size to be able to amplify its project and diversify its activities. PhD students should be attracted to join the team. The excellent level of funding needs to be continued to recruit in particular post-docs.

The team would benefit from additional collaborations, both internally and internationally.

Team 9: Transcription co-activators

Name of the supervisor: Mr. Patrick Schultz

THEMES OF THE TEAM

The team aims at understanding the molecular structure, role and mechanisms of action of macromolecular assemblies regulating eukaryotic gene transcription in a chromatin environment. The team combines different and original approaches ranging from production, purification, enzymatic or binding assays, multiresolution structure determination (cryoEM) to explore the regulated transcription in a chromatin environment and benefits from expertise in the cutting-edge methods for the analysis of image data. The team has explored several systems of major importance: the binding of yeast TFIID to promoter DNA, the transcription/DNA repair factor TFIIH, the giant Tra1 subunit, the Saga complex bound to TBP, the NUA4 coactivator and the HAT module of NuA4, the SWI/SNF chromatin remodeller. The team also contributed to significant developments to study their systems of interest in a cellular context.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) *To publish rapidly the outstanding results on the Tra1 subunit of Saga.*
The work was published in Nature in 2020 and Nature Comm. in 2017.
2) *To make efforts to increase the proportion of students/postdocs.*
The team has recruited 7 PhD during the period, with 4 of them having been recently recruited. Two defended their thesis, one abandoned before the defense. IDuring this period, 6 post-docs were recruited.
3) *To focus on those that are feasible in the short term and capitalise on them to attract more grants, and to explore for ways of attracting additional funding to ensure that the various projects proposed will be done.*
The funding rate during this contract was excellent.
4) *To gain more fluent access to Titan microscope.*
No information allows assessing this recommendation.
5) *To continue developing methods to tackle the study of macromolecular assemblies within the nuclei, keeping in mind that this will also require enough grants to remain competitive.*
Instrumental developments have been performed combined with cutting-edge methods in data analysis.

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	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)	3
Subtotal permanent personnel in active employment	**7**
Non-permanent teacher-researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	0
Post-docs	1
PhD Students	6
Subtotal non-permanent personnel	9
Total	**16**

EVALUATION

Overall assessment of the team

The team has an outstanding research level and continued its highly productive work on the fine exploration of transcription co-activators, which has led to gain international recognition. This outstandingly productive team is tackling extremely challenging projects. The continuation of certain projects may be compromised by the absence of tenured team support in molecular biology, a fragility in the cell biology expertise and the absence of high-level funding from European sources.

Strengths and possibilities linked to the context

The team has a high visibility and attractiveness. The team has multiple collaborations within the unit with joint publications (teams 2, 5, 6, 8, 10, 11, 23, 24, 27, 31, 32, 36, 53,). The teams is also engaged in national (G. Zuber (ESBS, Strasbourg; CRMB, Montpellier; Museum National d'Histoire Naturelle) but also international collaborations (Regensburg, Germany). The team organised three international conferences. The team has supervised seven PhD, with two who defended during the period and were co-authors of publications in high reputation journal (Nature and eLife). Attractiveness is confirmed with the hosting of eleven internships and seven post-docs. Team members were awarded by two prizes: the team leader got the USIAS Prize in 2021, and an Inserm researcher got the prize "Les Grandes Avancées Françaises en Biologie" from the Académie des Sciences in 2020. The team has got an extremely high success rate in national grant applications, with twelve ANR (7 as coordinator), two INCA, one Ligue Contre le Cancer, and one European Grant (ended in 2016). Overall, the external funding represents more than 2.3 M€ and projects are supported until 2025.

During the last period, the team had an outstanding scientific production with 41 original papers (plus 5 papers as a contribution to 2 books) with more than half of them in a leading position. Importantly, these papers were regularly published in very high reputation journals (4 Nature Comm, 2016, 2017,2018, 2019, 1 Nature 2020, 2 Mol Cell 2018, 2019, 1 NAR 2020 as last authors; and 2 PNAS 2016, 2020, 1 Sci. Adv 2017 in collaboration with IGBMC teams). By solving with a high resolution, the structure of the full Saga complex bound to TBP that was elegantly completed with biochemical experiments, the team has provided for the first time, a comprehensive view of the interactions between partners of this major complex and more importantly proposed mechanisms in which they are involved. The team has also contributed to the instrumental developments (Microtome-integrated microscope system for high sensitivity tracking of in-resin fluorescence in blocks and ultrathin sections for correlative microscopy).

The team was involved in industrial partnerships with the signature of a contract for a total amount of 336 K€.

Weaknesses and risks linked to the context

The main risks identified are due to the human resources, in particular the absence of a tenured team support in molecular biology might slow down the projects. This is also true for the cell biology axis, which is of major interest.

The two PhD students who defended their thesis during the period published a paper, but not as a first author.

RECOMMENDATIONS TO THE TEAM

The team is strongly encouraged to pursue its outstanding project that combines molecular and cellular aspects for exploring the transcription co-activators. Funding from the EU would be extremely valuable to reach this aim.

Team 10: Viral Oncoproteins and Domain-motif networks

Name of the supervisor: Mr. Gilles Travé

THEMES OF THE TEAM

The team focuses on the molecular mechanisms of viral induced cancers, most notably the structure/function and inhibitory effect of the oncoprotein E6 from the human papillomavirus. The team also started more recently a new research axis on neurodevelopmental syndromes. In addition, the team develops strategies to optimise their purified recombinant proteins for structural purposes (e.g. codon optimisation, fusion proteins, mutations…) and, on top of that, innovative approach for high-throughput quantitative interactomics.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) *The team should rapidly identify and profit from the research environment at IGBMC, to continue its outstanding research.*
The team has developed collaborations with several teams within IGBMC (e.g. teams 36 and 53) leading to seven joint publications (see below), so it seems well positioned within the institute.
2) *The experts committee recommends to continue the current strategy with high profile funding and industrial interaction.*
The team is on the right track regarding the funding of its two research axes (see below).
3) *The experts committee recommends to continue efforts to attract PhD students and obtain funding for them. The IGBMC is a highly attractive environment for PhD students. It is not clear if the other PhD student published a paper during the period of the report; this is however essential.*
The team has currently three PhD students plus two other students so it seems quite attractive.
4) *The research plan should be pursued, and the adequate size of the group reached, essentially through recruitment of post-docs and PhD students.*
This is still a matter of concern regarding the relatively small size of the team, and the development of a new research axis. Yet, the team has been very successful so far in the research it tackles and acquiring fundings, so the committee is confident that the same success will continue.

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	1
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	1
Non-permanent research supporting personnel (PAR)	0
Post-docs	1
PhD Students	3
Subtotal non-permanent personnel	5
Total	**10**

EVALUATION

Overall assessment of the team

This is an excellent team, especially given its relatively small size, which plays a leading role in the field of virus-mediated oncogenesis. They obtained outstanding results on the human papillomavirus E6 oncoprotein and its hijacked cellular partners published in top-journals level (i.e. Nature)., endowing the team with an excellent international visibility. The second axis on neurodevelopmental syndromes recently developed remains fragile and needs to be validated by excellent publications. The team has established a strong network of collaborations, locally, nationally and internationaly.

Strengths and possibilities linked to the context

The team has established a strong network of collaborations, locally (within the unit, e.g. with teams 36 and 53, with ISIS in Strasbourg and ESBS in Illkirch,), nationally (Pasteur Institute in Paris, AFMB in Marseille, CRBM in Montpellier) and internationally (EMBL-Heidelberg, Konstanz University, Bergen University, University of Indiana, University of Virginia, Russian Academy of Sciences in Moscow). A young scientist from the CNRS, (section 20) joined the team in 2020. The team has been particularly successful to obtain, on a regular basis, funds from various sources (ANR, Ligue contre le cancer, European community, NIH, Angelman Syndrome Foundation). In particular, the team has a continuous support from NIH since 2010 and is a "équipe labellisée Ligue" since 2015. It has a lot of contracts/service delivery with the industry, even if the amount of money is often limited.

In total, this team published 31 papers, 9 times as leading authors (Nature, 2016; Nat Comm, 2021; Structure 2020; 2 PLoS One, 2016 and 2020; Anal Biochem, 2020; Microb Cell Fact 2018; IUcrJ 2016 and Viruses-Basel, 2018). Seven of these publications were made in collaboration with other teams from IGBMC including one Embo J (with teams 9, 36 and 53) and one Embo Rep (with teams 1, 36 and 53). The team is at the forefront of research on the oncoprotein E6 from the human papillomavirus (35 X-ray structures have been deposited in the PDB in the past three years) and has therefore an excellent international visibility on this topic. Of particular note is a paper published in Nature (2016; corresponding author) where the structure of the complex between E6, the E6AP ubiquitin ligase, and p53 were solved by shedding the light on the degradation of p53 mediated by HPV. Recently, the interactions between variants of the E6 oncoprotein and the seven human 14-3-3 isoforms revealed a very wide range of binding affinities due to the sequence variation in the PDZ-binding motif of E6 (Nat. Comm, 2021; corresponding author). The team also started a new research axis on neurodevelopmental syndromes, because the gene encoding the E6AP ubiquitin ligase is altered/deleted, or even duplicated, in some pathological disorders such as Angelman mental retardation or Dup15q autism spectrum syndrome. Although very promising results were already obtained, these data have not been published yet. In addition, the team develops strategies to optimise the production of purified recombinant proteins and innovative approach for quantitative interactomics. This later technique allowed so far the determination of about 65 000 affinity constants for the human interactome and viral proteins (coll. AFMB, Marseille, Nat. Comm, 2022). The success of this high-throughput quantitative interactomic approach is very impressive and quite promising for future collaborations.

Weaknesses and risks linked to the context

One IR arrived in 2016 and left the team in 2019.

The team leader mentioned the lack of Bioinformatician to exploit the wealth of data accumulated from quantitative interactomic, especially with the huge increase in the data generated by the interactomic approach.

A second research theme is now emerging in the team (i.e. neurodevelopmental syndromes). As pointed out by the team leader, this second research axis, although quite pertinent to the virus-mediated oncogenesis process, might diverge in the future.

The recurrent fund from the NIH stopped in 2020.

There is no involvement of this team in Congress/colloquium at the National/international level, and little in scientific events to the 'grand public'.

RECOMMENDATIONS TO THE TEAM

The committee recommends maintaining the excellent/outstanding quality of the research.

The team should maintain an equilibrium between the two research axes and the human potential dedicated to these two axes. Given the success of the team so far, and the awareness of the team leader about this possible hurdle, the committee trusts the team leader to ensure a right balance between them.

The team should get more involved in science outreach towards the general public.

Team 11: Regulation of transcription

Name of the supervisor: Mr. Albert Weixlbaumer

THEMES OF THE TEAM

The team studies the macromolecular complexes controlling transcription using biochemical and Cryo-electron microscopy. Their work investigate mechanistically how RNA polymerase interacts with other proteins and RNA to initiate, pause, elongate or terminate transcription. They are also analysing how the polymerase is influenced by its interaction with the ribosomal proteins and how these interactions with ribosomal complexes affect transcription. Their main model is bacteria but they are also finding universal mechanisms active in eukaryotes.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) *Finalize the solving a high-resolution structure of the RNAP/NusA complex.*
This was achieved and published (Mol. Cell, 2018).
2) *Acquire independence in cryo-EM, a major methodology to study macromolecular assemblies.*
By the group's publication record since 2018 it is clear that this has been successfully achieved and the group now masters the technique.
3) *Gain international visibility*.
The group has already been able to publish a number of research papers over the current evaluated period which has helped it to establish itself in the field.

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)	0
Post-docs	2
PhD Students	2
Subtotal non-permanent personnel	6
Total	**9**

EVALUATION

Overall assessment of the team

This is a team that produces outstanding work in a very competitive field. Durlng the evaluated period, the team did not implement international collaborations. We recommend establishing such collaborations that could further reinforce their position and visibility in the field and attract international postdoctoral researchers.

Strengths and possibilities linked to the context

The team has excellent technical skills having been able to transit from X-ray Crystallography to the more useful technique of Cryo-electron microscopy (Cryo-EM). The IGBMC is a perfect environment for this research, given the number of other groups using the same techniques.

Since the group was established in 2016, it has grown considerably, with the recruitment of 5 postdocs, 6 PhD students (two of them are ongoing) and one CNRS researcher (CRCN) that joined the team "as part of a collaboration to study the interplay of human transcription and mRNA processing". It would be a boon to the group if this scientist remained in the team at the end of the collaboration.

The team was initially supported by an ERC Starting grant, and as a result of the outstanding research performed by the PI and his team, more recently by a prestigious Bettencourt Foundation Coup d'Elan Prize in 2021.

This high-quality production is in line with the previous performance of Dr Weixlbaumer before he became an independent researcher and shows he has been able to establish himself as a successful team leader. The team has published outstanding papers in highly regarded international journals like Science 2020, Molecular Cell 2019 and 2018, and three reviews (Transcription 2021, Frontiers in Microbiology 2021, Faculty Reviews 2021) as well as a comment in PNAS in 2021, where the PI was the leader and the first authors were from the laboratory.

The team has numerous collaborations within IGBMC and at the national level.

Weaknesses and risks linked to the context

The low level of international collaborations is suprising.

The team has had an ERC starting grant but failed to obtain a consolidator grant. This may impact on the future production of the team. It is difficult to predict if the same level of publications will be maintained now the ERC funding is over.

The team's output is of exceptional quality, but the number of publications (four research articles) has been inferior to the potential offered by its funding and human resources. Some results obtained in the 2016-2021 period have resulted in additional recent major publications (Nature Commun and Mol. Cell). However if reduced funding will allow the team to produce the same levels of science remains an open question.

RECOMMENDATIONS TO THE TEAM

The committee recommends the team to increase international collaborations to increase the team impact.

The committee also recommends the team leader not get discouraged by ERC grant refusal and reapply for international funding.

The team may consider integrating complementary in silico modelling skills in the team.

The team should aim to have a more informative webpage to attract possible postdoctoral applicants.

Team 12: Molecular Basis for Protein Synthesis by the Ribosome

Name of the supervisor: Mr. Marat Yusupov and Ms. Gulnura Yusupova

THEMES OF THE TEAM

The overall goal of the research of the team is to understand how the atomic structure of the ribosome ultimately determines its function. The team follows a research line established some decades ago centred on deciphering fundamental aspects governing protein synthesis by focusing their research on structural studies by X-ray crystallography and cryo-EM of prokaryotic and eukaryotic ribosome structures.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendation from the previous report was to obtain adequate funding.
The team ensures financing of research activities via national and international contract.

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	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)	1
Subtotal permanent personnel in active employment	**4**
Non-permanent teacher-researchers, researchers and associates	1
Non-permanent research supporting personnel (PAR)	0
Post-docs	0
PhD Students	5
Subtotal non-permanent personnel	6
Total	**10**

EVALUATION

Overall assessment of the team

This is an outstanding research team, highly productive in terms of publications in highly visible journals and recognised at the international level. The team arises from a merge of two teams lead previously independently by the two PIs. This evolution is highly coherent given that research objects and outcomes had been shared for over a decade. Interactions with the social and economic environment are excellent.

Strengths and possibilities linked to the context

The team visibility and recognition are high. Both PIs are Embo members, and one has been awarded the title of "Chevalier de la Légion d'Honneur". A postdoctoral fellow obtained recognition by the Lavrentiev award (award in mathematics and mechanics by the Russian Academy of Sciences). The team coordinated an ERC grant 2012-2017. The team has secured funding via 5 international (4 NIH grants, 1 ERC) and 9 national calls (Inserm-BOD, several ANR, FRM, Sidaction…).

The scientific production is outstanding. The team has published 38 research reports during the period, one in collaboration with an IGBMC team 21 signed as the last author, ten with PhD students as the first author (5 NAR, 1 Embo rep, 3 Nat Comm, 2 PNAS, 1 Embo J, 1 Nat Chem, 1 TIBS and 1 Nature). The team focuses on structural investigation of large ribosomal assemblies by X-ray crystallography and cryo-EM, combined with biochemical, biophysical and molecular genetic approaches, focusing particularly on ribosome inhibition by anticancer and antibacterial drugs and mechanistic aspects of transcriptional fidelity.

The interactions with the social and economic environment are excellent. The two PIs have created the spin-off company Urania Therapeutics, and financial incomes have been secured by industrial contracts (Lilly, Ribostruct). Some communication efforts have been documented (CNRS, Techno-Science).

Weaknesses and risks linked to the context

Human resources appear to be fragile.

RECOMMENDATIONS TO THE TEAM

The committee encourages the continuation of raising funding and be vigilant on human resources.

The team is invited to consider thoroughly the future in terms of scientific outlooks and management thereof.

Development and stem cells (DSC)

Team 43: Biophysics of cell growth and division

Name of the supervisor: Mr. Gilles Charvin

THEMES OF THE TEAM

The team develops quantitative assays combining genetics, single-cell imaging and microfluidics to study the mechanisms underlying cell homoeostasis in budding yeast and *C. elegans*. The main research topics are the mechanisms leading to the entry into replicative senescence, the response to oxidative stress and cell size homoeostasis.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) *The main recommendation would be to reinforce interactions with other teams in the IGBMC and to focus on publishing the studies they completed recently.*
The team established collaborations with the groups of B. Reina San Martin (Plos One, 2019) and N. Molina (eLife, 2018).
2) *More effort should be put into the valorisation and dissemination of the methodological advances and to disseminate this know-how in method papers that could be abundantly cited and raise the profile of the team.*
The team published two methods papers (Methods Cell Biol., 2018; Plos One, 2019) as core papers and one in collaboration (Micromachines, 2019).
3) *It is urgent to secure funding for the next five-years, especially with the introduction of C. elegans as model.*
The team leader obtained one FRM grant as coordinator and four ANR PRC grants as partner during the past term.
4) *It will be important to secure sufficient funding to develop the projects, and to improve interactions with other teams from the IGBMC.*
See above.

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	2
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	1
Subtotal permanent personnel in active employment	**4**
Non-permanent teacher-researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	1
Post-docs	0
PhD Students	0
Subtotal non-permanent personnel	1
Total	**5**

EVALUATION

Overall assessment of the team

The team develops original research and has recognised technical expertise in the development of quantitative approaches. The scientific production is excellent both in terms of the team's own projects (6 original publications over the period, including three in eLife, one in Cell reports and one in Biophysical journal), and in terms of collaborations (5). The visibility is excellent, as shown by the multiple national and international collaborations.

Strengths and possibilities linked to the context

The team visibility is excellent. The team leader has been invited to seven conferences, including three international conferences. The team leader was awarded an "Espoirs de l'Université de Strasbourg" prize in 2017, attesting to the recognition of the quality of the team's work has taken on collective responsibilities as he served as department head from 2018-2020. The visibility of the team leader at national level is also evidenced by its recent appointment to the CoNRS 22 committee. The team has a strong network of collaborations that resulted in seven collaborative articles. Compettitive fundings were obtained, including one as a coordinator (FRM) and four as a partner (ANR PRC). Attractiveness and mentoring are overall very good, with four theses defended in 2020 or 2021, two of which resulted in first author publications. A postdoc who left the team in 2016 also published two first author papers. Two permanent researchers were present over the period evaluated, one of whom published a first-author paper (Cell reports 2019) - the other recently published her work as well (PlosOne 2022).

The scientific production is excellent considering the size of the team, with six articles as corresponding author including multiple publications in highly visible journals (Biophys. J. 2016, eLife 2017, 2018, 2021, Cell reports 2019). The team also published high quality collaborative studies (Genes Dev. 2018, eLife 2019, Molecular Cell 2020, Embo Journal 2012). The research projects are original from a fundamental point of view and involve the development of innovative methodological tools. Among the most important results of the team, they showed by combining quantitative single-cell analysis and mathematical modelling that the formation of a single circular rDNA by excision is sufficient to induce senescence in yeast, demonstrating that it is not aging per se

that triggers senescence (Cell reports 2019). In another study, they analysed the dynamics of the oxidative stress response at the transcriptional level and showed that it is not linear, explaining the phenomenon of stress tolerance acquisition in yeast (eLife 2017). The team developed a fluorescent marker that allows for the precise analysis of the cell cycle in yeast and thus identified a new mechanism controlling cell size (eLife 2018). They also developed an experimental setup to analyse the successive transitions between cell cycle and quiescence at the single cell level (eLife 2021).

Weaknesses and risks linked to the context

The number of grants obtained as coordinator is not commensurate with the scientific production of the team.

Four students have completed their PhD in the team over the period under review, but no new PhD students have started after 2018, which may be the result of a lack of visibility of the team's research topics within the IGBMC.

Contribution of research activities to society was not completed in the report.

RECOMMENDATIONS TO THE TEAM

The team has recently joined the UMR 5176 Génétique Moléculaire, Génomique, Microbiologie (CNRS/Université de Strasbourg) in 2022, of which the team leader will take over the direction. It has undergone a profound reorganisation on this occasion, since the two staff scientists have now joined other teams of the IGBMC. This transition will imply an important effort to relaunch the activity of the team, but could eventually allow the team to be in an environment closer to its scientific themes and help it to solve its problems of recruitment of PhD students. The committee recommends prioritisation of team relaunching including permanent researchers and technical staff, and taking advantage of the novel scientific environment to increase PhD attractiveness.

Team 13: Brain development and physiology

Name of the supervisor: Mr. Pascal Dollé

THEMES OF THE TEAM

The team is studying the pleiotropic contribution of retinoid signalling in dopaminergic neurons and in glial cells (microglia and oligodendrocytes) development and homoeostasis. They investigate both upstream regulators and downstream targets of retinoid receptors to understand the mechanisms underlying retinoid-related regulation, and by studying these processes, propose new treatments to prevent central nervous system disorders. In addition, the team has developed a click-reaction based-method to detect *in vivo* retinoic acid metabolites and studied an endogenous ligand of RXR of nutritional origin.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) *The team needs to validate the very good quality of the research developed within the team by publications in higher impact journals.*
Publications in very reputed international scientific journals were produced based on international collaborations or on collaborations within IGBMC. One PNAS article was published with a team PI as corresponding author. Publications are mostly in well-regarded journals and their real impact needs to be put in perspective of the topics: chemical biology journals might be characterized by lower impact than neurobiology journals but this parameter does not reflect by itself the interest and originality of the research of the team.
2) *Funding needs to be increased.*
Funding was very good but needs to be sustained.
3) *Interaction with the social, economic and cultural environment need to be continued.*
The team succeeded in maintaining its very good interactions with the socio-economic world and the social environment. The team research has strong biomedical interest.

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)	1
Subtotal permanent personnel in active employment	**3**
Non-permanent teacher-researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	0
Post-docs	2
PhD Students	4
Subtotal non-permanent personnel	6
Total	**9**

EVALUATION

Overall assessment of the team

The team had an excellent scientific production based on a project of quality with impact in the biomedical field. Clear lines of research and a focused strategy based on new data are promises of a bright future. The team benefits from a strong interdisciplinary background to develop its project from chemical biology to neurobiology. In addition, the team has an extensive network of national and international collaborators. The team has been very active to communicate to various public including patient organisations, and had excellent valorisation activities.

Strengths and possibilities linked to the context

The team has an excellent visibility. The team has an extensive network of valuable collaborators, in Strasbourg, France and internationally that offer complementary expertise in chemistry or neurobiology. The team has participated to one international network Era-Net project (RAinRARE 2019-2022). On the international level, the team has organised two congresses, participates to the editorial board of two journals (peerJ and Frontiers in molecular neurosciences) and to the International Society for Developmental Neuroscience. On the national level, the team participates to the steering of two national learned societies and has provided its scientific expertise by participating to an ANR panel (CE13) for three years and to the scientific council of Inserm for five years. The team attracted nine PhD students with four still on-going, and four postdoctoral researchers, although mainly for short durations. The team participates to two GDRs in the fields of Chemobiology and Developmental Biology and to the network « Filière Santé Maladies Rares Tetecou". The team was granted four ANR supports during the contract, including two as coordinators. Funding was complemented by three contracts from the association pour la recherche sur la sclérose en plaques (Arsep).

Research conducted by the team is original and interdisciplinary with applications in the biomedical field. The team has produced 28 original articles with fifteen with a member of the team as first/last or corresponding author. Seven of these articles originate from internal collaborations with other IGBMC teams. High-profile research results of broad scientific interest were published in very reputed international scientific journals, based on international collaborations (1 Nature Commun., 1 Science Advances, 1 Cell reports, 1 eLife) or based on internal collaborations (1 Nature Commun. involving contribution of 4 IGBMC team). In addition, one PNAS article was published with a team PI as corresponding author. More specialised results are published in well-regarded journals such as JBC, JMedChem, and Mol NeuroBiol. Publications in Nanoscale Adv. and Biomol. Chem. as corresponding authors show the interdisciplinary capacity of the team in the field of chemical biology.

The team has excellent valorisation and outreach activities. In relation with its expertise, the team has produced 3 patents related to compounds derived from retinoic acid with therapeutic interest. The patents were licensed to the company CisCarex, which was co-founded by a team PI. The team has provided R&D services to a company Syndivia SAS. An agreement letter has been signed with Plexxikon company (USA) for the use of a microglia team model to evaluate compounds that could lead to a research collaborative project. One PI has been very active in communication to the public, through press articles about an original chemistry-based approach to counter secondary effects of drugs (published in Nat Com 2016). In collaboration with Arsep, the team also organised twice an "open laboratory days" to host MS patients and their families. The team welcomes pupils in the lab (one each year) for a vocational week and membres of the team intervene in schools during Science awareness days. One PI is also a lead scientist in a patient organisation advocacy group "Cure MCOPS12".

Weaknesses and risks linked to the context

Most funding contracts have expired or are close to their conclusion: three ANR project are finished, emphasising a need to secure funding for the coming years. New fundings have been obtained in 2021/22, outside the scope of the current evaluation, indicating that the risk of unsufficient funding for the coming years is low.

Two team members, have left the team without on-going compensation.

RECOMMENDATIONS TO THE TEAM

The team should promote its research at the national and international levels to attract high-level post-doc and sustain funding to support its original project.

The team should provide an attractive and supportive environment for its junior members.

The team should continue the excellent interdisciplinary approach.

Team 14: Differentiation and physiopathology of endocrine cells in the pancreas and intestine

Name of the supervisor: Mr. Gérard Gradwohl

THEMES OF THE TEAM

The team aims at understanding the molecular and cellular mechanisms controlling pancreatic and intestinal endocrine cell differentiation and function. It focuses on the identification of the gene regulatory networks that control endocrine cell fate decisions, endocrine subtype specification, and the maintenance of the endocrine phenotype.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations form the previous report were:
1) The team should try to attract foreign post-docs.
Four postdoctoral fellows have been trained during the evaluation period, one was from abroad.
2) The team should increase its interactions with the general public to disseminate science culture".
The team activity with the socio-economic world and the general public is still very limited.
3) *The team leader might consider less ambitious/competitive projects or else side projects for the PhD students in order to allow them to publish faster.*
Some progress has been made in this direction as three out of the five current and past PhD students published either first, co-first, or second authors on the reported scientific production from the team.

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	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)	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	1
PhD Students	2
Subtotal non-permanent personnel	3
Total	**8**

EVALUATION

Overall assessment of the team

The team is very good to excellent. One of its strengths relies on the use of multiple approaches (genetics, physiology, multi-omics and systems biology) and model systems including human organoid to analyse at the molecular level physiological processes. The production and the visibility are excellent while the non-academic activity is relatively limited.

Strengths and possibilities linked to the context

The team's visibility is excellent. It has benefited of excellent fundings with two projects funded by ANR and an international grant from Novo Nordisk Fondation. Currently, the team is composed of the team leader, another DR, one CR, two PhD students, one IE and one technician. The recruitment of two tenured scientists (1 DR + 1CR) is a big asset to the team. Five PhD students and four post-docs are/have been trained in the evaluation period.

Overall, the publication record is very good to excellent and one can expect an increase in the coming years as a result of the recent arrival of two tenured scientists. In the evaluation period, the team published 3 papers as a leader: two Mol Metab (2019 and 2021) and one J Mol Endo (2016), and in collaboration: a Mol Metab (2021), a Cell Mol Gastroenterol Hepatol (2021), two Development (2019, 2020) and a Cell Death and Disease (2016). The research project is excellent, aiming at understanding the molecular and cellular mechanisms controlling pancreatic and intestinal endocrine cell differentiation and function. More specifically, it focuses on the identification of the gene regulatory networks that control endocrine cell fate decisions, endocrine subtype specification, and the maintenance of the endocrine phenotype. For this purpose, they use multiple approaches (genetics, physiology, multi-omics and systems biology) and model systems including human organoid. More recently, they also went into single-cell transcriptomics and the related bio-informatics integration of the data in collaboration with team 18.

Even though the non-academic activity of the team is not relevant, the recent introduction of human organoids and human induced pluripotent stem cells in the laboratory will reinforce the group's research impact on society.

Weaknesses and risks linked to the context

The team's publication record has not yet paralleled their excellent financing nor their research potential.

The team members do not appear to be involved in an editorial activity and their visibility could be improved in this respect.

Not all PhD students have a first author publication at the end of their PhD.

The team's involvement in developing products for the socio-economic world is very limited, as is its knowledge sharing with the general public/ taking part in debates in society.

RECOMMENDATIONS TO THE TEAM

The team should continue to attract PhD students and postdoctoral fellows and secure funding.

The team leader and PhD student supervisors should pay attention to providing projects that allow PhD students to publish faster.

With the arrival of two tenured scientists, one could expect an increase in the publication record in the next years.

The team should increase its interactions with the general public to disseminate science culture.

Team 15: In vivo cellular plasticity and direct reprogramming

Name of the supervisor: Ms. Sophie Jarriault

THEMES OF THE TEAM

The team focuses on the molecular mechanisms of reprogramming and transdifferentiation in vivo, using C. elegans where they have identified a specific event in which a rectal cell is reprogrammed into a motorneuron during the second larval instar. The team has provided a large amount of mechanistic information about this event, including an involvement of the C. elegans homologues of mammalian Sox2 and Oct4 in thus hinting at a universal mechanism underlying reprogramming.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

None

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)	3
Subtotal permanent personnel in active employment	**5**
Non-permanent teacher-researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	1
Post-docs	1
PhD Students	2
Subtotal non-permanent personnel	4
Total	**9**

EVALUATION

Overall assessment of the team

This is a strong active team with an outstanding international visibility and solid fundings. Work during the reporting period however only led to a moderate publication impact, with 3 methodological research articles. An impressive large set of unpublished data sets a solid ground for future publications. The team is strongly engaged in teaching activities, council activities and societal/outreach activities.

Strengths and possibilities linked to the context

The international visibility of the team is outstanding. The team leader has given over 25 invitated talks in national and international meetings and is a co-funder and current chair of Genie, an international network of C. elegans young investigators. Scientific recognition is also attested by an impressive number of reviews invitations (Cur Top Dev Biol, 2021, Genetics, 2019, Int. J. Dev. Biol. 2018, Development, 2017, Genetics 2016, Curr.Op. Genet. & Dev., 2016), by an ERC CoG grant complemented by national competitive granting through the ANR, by participation to Scientific Advisory Borads (including the CNRS Life science advisory board), by its editorial activities (Editor at Genesis) and a strong international collaborative network (Swiss, UK, Spain and Belgium).

The scientific strength of the team is the system (the transdifferentiation of a rectal cell into a motorneuron) with which they work that has been established over the years and provides a solid and useful framework to explore in detail many different questions. This is spelled out in their report with 8 subthemes through which they identify a number of actors and processes that mediate the transdifferentiation event and proof their roles by manipulating their expression. Most striking is the participation of homologues of mammalian Sox2 and Oct4 (ceh-6) in this process and the proof of concept that mouse Oct4 will compensate for the loss of ceh-6 in the process. The team has also identified other similar events that they plan to explore in the future. Solid but unpublished results thus collectively set an impressive ground of high-quality production that are currently in publication process (5 manuscripts in preparation and 2 submitted). This unpublished data is to be considered when evaluating the scientific production of the team during the period of evaluation, where the team has had a moderate publication impact, with three methodological papers (2x micropub Biol, 2020; Genetics, 2020) with a very good balance of authors and contributions which appears well spread over the different publications.

The team has also been strongly engaged in teaching activities (Master of Strasbourg University and Hydra Stem Cell summer school) and responsabilities (IMCbio committee member), and in societal and outreach activities (Woman in science, OpenLab actions, Decllics….).

Weaknesses and risks linked to the context

One issue that should be given consideration is the extreme focus on the implementation of the reprogramming through transcriptional activity and epigenetics. This leaves untouched the triggers of the process. This is particularly important as this is something that happens in vivo. In addition, and not unrelated, is the narrow focus of the research which, though sustainable in the short/medium term, may not be competitive in the longer term.

Over the last few years the scientific productivity of the team has slowed down. Perhaps this was due to the pandemic. However, during the visit it was clear that unpublished will shortly result in a number of papers out and new projects emerging.

RECOMMENDATIONS TO THE TEAM

It would be important for the team leader, when thinking of future projects, to consider diversifying either the questions that they ask or the system they work on. One concrete suggestion is to explore the triggers of the process in an active manner. Perhaps some of these are already in the collection of mutants from their screens.

The committee also recommends to preprint and publish the results that were presented during the visit.

Team 16: Common Mechanisms of Development, Cancer and Aging

Name of the supervisor: Mr. Bill Keyes

THEMES OF THE TEAM

The team studies senescence, a mechanism involved in ageing and protection against cancer, using in vivo and vitro models including organoïds. Focus is on the role of senescence in physiological and pathological conditions, including normal embryonic development, cell plasticity and tissue regeneration.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team joined IGBMC in September 2016 and was not formally evaluated by the prevois Hcéres committee. In the strategy and 5 year plan, the team was asked to prioritize projects on specific aspects not being too broad in developing all aspects at once. This has been followed with most projects being published.

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	0
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	1
Subtotal permanent personnel in active employment	**2**
Non-permanent teacher-researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	1
Post-docs	1
PhD Students	3
Subtotal non-permanent personnel	5
Total	**7**

EVALUATION

Overall assessment of the team

This is an excellent team. The team joined IGBMC in 09/2016. This term allowed to set-up a rather well-structured team 1DR, 1CRCN, 1 Tech, Post-docs and PhD students. The team is well recognised in the field and made important contributions. The team favor publications of quality rather than numbers. The presence of a CRCN with a formation of developmental biologist is an asset to the team. Regarding the balance in publications, some students and Post-docs do not have yet a first author publications although they figure as co-authors. Moreover, the interaction with the society is rather limited.

Strengths and possibilities linked to the context

The team has a very good visibility, with the recruitment of 3 postdoctoral fellows, 3 PhD students, and one CRCN. It has been awarded the Schlumberger Foundation prize in 2018. Attesting scientific recognition, the team leader was recruited to Inserm as Research director. Review and comment invitations (Development, 2019; Genes &Development, 2020) indicates international recognition. The team work was well funded through multiple competitive fundings including a starting team FRM label (300k€), FRM equipe funding (248k€), FRN Luxembourg (129k€), Idex (130k€) and also as partner an ANR (140k€).

The scientific production of this rather small recently settled team at IGBMC is execellent, with 3 peer-reviewed original papers with excellent visibility where the team have major contributions (first and last authors) (Oncogene 2017, Genes&Dev 2017/2020), one article in BioRxiv (2021, now published in 2022 Plos Biol), and one Nat Commun. paper as a collaborative work within the IGBMC. The team made major contributions by uncovering new roles of SASP (senescence-associated secretory phenotype) in promoting regenerative function by inducing cell plasticity and stemness. This may have important implications in tissue regeneration. They also showed that senotherapeutic drugs (ABT-737) can be useful in promoting tissue regeneration in vivo. The team has some interactions with lay audience. This includes a visit by high school student from a local Lycée. The team leader was also interviewed by an editor from a popular science magazine (The scientist) to discuss the research field, which was included in an article. They also recently published a work with a broad interest both at the clinical and society level showing that Valproïd acid induced neurodevelopmental disorder though p19-mediated senescence (BioRxiv, 2021, Plos Biol, 2022).

Weaknesses and risks linked to the context

The current team composed of two staff scientists (PI (DR Inserm) +1xCRCN joined in 2017), one postdoc, two PhD students and one technicians (Inserm) is a bit small.

The team leader spends considerable time as departmental head, which is a position that is not well recognised for example by funding bodies.

Although publications are of quality, their total number is limited (3 peer-reviewed original papers+1 in BioRxiv now published in PLoS Biol.).

The collaborative network of the team is limited. Only one collaborative work (1x Nat Commun) was published with other teams of IGBMC.

While the tenure researchers (CRCN and PI) have published as major authors (first and last co corresponding authors), and beside a former postdoctoral fellow who published as first author, the other PhD and postdoctoral fellows have not yet first author publications.

The interaction of the team to society is rather limited. Only few interactions with the public are mentioned (visits of high school students, interview by an editor for a lay audience journal).

RECOMMENDATIONS TO THE TEAM

The team projects need the development of new models which is time consuming. Since the team is interested in the role in senescence in development, this could be achieved by establishing collaborations within IGMBC but also at the national and international levels. An alternative could be to focus on a given specific model and digging deeply into the senescence mechanisms within this model. This strategy would have the added advantage of increasing the possibility of publications in the very top journals, which could foster top level funding such as an ERC advanced grant.

The size of the team is rather small and should be increased to be more competititve.

Although PhD students and postdoctoral fellows are coauthors of different publications, a better balanced in first author should be achieved.

The interaction with the society should be improved. The team leader has through recent years spent considerable time on the departmental leadership, a position that should be transferred to a colleague. This would allow increased focus on science, grant writing and outreach activities.

Team 17: Nuclear organisation and division

Name of the supervisor: Mr. Manuel Mendoza

THEMES OF THE TEAM

The team is studying how chromosome segregation and cytokinesis are coordinated. In particular, the team seeks to understand how the Aurora-B kinase-dependent checkpoint "NoCut" regulates cytokinesis abscission when chromatin bridges are delayed at the site of cell division. The team is also interested in the differences in nuclear organisation after asymmetric cell division and how nuclear pore complexes control cellular identity.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was recruited in 2017 and was not evaluated in the previous report.

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	0
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	1
Subtotal permanent personnel in active employment	**2**
Non-permanent teacher-researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	0
Post-docs	2
PhD Students	2
Subtotal non-permanent personnel	4
Total	**6**

EVALUATION

Overall assessment of the team

The team is overall excellent. The scientific production is excellent to outstanding, with four published papers with the team leader as senior author in journals that give excellent visibility, including Nature Communications in 2020 and Nature Cell Biology in 2018. The team that settled at IGBMC in 2017 has already succeeded in obtaining several national grants from charities (FRM, ARC, La ligue). Actions towards societal visibility are lacking.

Strengths and possibilities linked to the context

The team is scientifically very visible in successfully linking the two highly competitive fields of nuclear pore and cell division. The level of funding of the team is also excellent with grants from the ARC, the League and a team labeling by the FRM. The team's funding has made it possible to recruit several postdocs and PhD students to effectively launch projects at IGBMC. The writing of a review (Frontiers in Gneteics, 2020) and recent promotion of the team leader as Research Director (DR2) confirms the scientific recognition of the team work.

The team has a scientific production that varies from excellent to outstanding with a total of 8 publications, and 4 publications where the team leader is the senior author in journals that ensure the visibility of the team's work, including a Nature Cell Biology (2018) and a Nature Communications (2020) and a study deposited in bioRxiv (2021), now published in Embo Journal (2022). The major findings over this evaluation period are 1) that replication is not completed in interphase and that the NoCut abscission checkpoint coordinates cell division with the completion of DNA replication, 2) the deacetylation of nuclear pore complexes in daughter cells delays cell cycle entry.

Weaknesses and risks linked to the context

The size of the team is small in relation to its scientific objectives. In addition to not reaching a critical mass to ensure its sustainability, it should be noted for most of the reporting period the absence of permanent technical support which is essential to maintain and transmit the technological developments specific to the team.

The fact that the team depends heavily on funding from charities, and has no funding from the ANR, is surprising, given the very fundamental aspect of the research.

The team is not involved in outreach activities.

The team leader does not seem to be involved in the organisation of scientific events in France, nor in structures of scientific animation or national societies, which could help him to build networks of collaborators to submit collaborative ANR projects for example.

The PhD students and post-docs do not all have first author papers.

RECOMMENDATIONS TO THE TEAM

The team should diversify its funding sources at the national level. The quality of its scientific production should also allow it to target European funding very soon.

The team leader should increase its visibility by getting more involved in outreach activities in France, by organising meetings and by participating in scientific animation in societies for example.

Team 18: Stochastic Systems Biology of Gene Regulation

Name of the supervisor: Mr. Nacho Molina

THEMES OF THE TEAM

The team is a computational team focused on the modelling of transcription at the single cell level with a focus in chromatin and also the interface between cell cycle and cell fate determination. They use principle-based methods rooted in bioinformatics, Bayesian statistics, stochastic processes and statistical mechanics.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team settled at IGBMC in 2016. It has only been evaluated for its prospective strategy and 5 year-plan.

Recommendation from the previous report were:
1) *To regularly evaluate the advances made in the wet part of the projects, and to reconsider doing these experiments by himself.*
This has not been implemented and there is no reference in the report as to the reasons why this has never happened or whether there has been an attempt to do it. However, the pandemic would have made difficult any attempts to do that and more so with someone starting a new lab.
2) To build new collaborations based on its competences in mathematical models. In this perspective, the panel recommends to create new collaborations inside the IGBMC with teams sharing the same interest in transcription regulation and chromatin modifications.
This has been implemented through a number of in house successful collaborations
3) *Not to start too many projects and to focus on high-gain projects. The recruitment of two postdocs should help.*
This has been implemented well.

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	0
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)	2
Subtotal permanent personnel in active employment	**3**
Non-permanent teacher-researchers, researchers and associates	3
Non-permanent research supporting personnel (PAR)	0
Post-docs	2
PhD Students	2
Subtotal non-permanent personnel	7
Total	**10**

EVALUATION

Overall assessment of the team

Overall, the scientific production of the team in the last five years has moved from very good to excellent, with recent publications in leading positions in highly visible journals (Nature Commun., 2021; PLoS Comp. Biol, 2021, iScience, 2021). International visibility and leadership in collaborative work has been moderate, but recent developments set grounds for improvement.

Strengths and possibilities linked to the context

The team leader has a portfolio of methods and interests that address important issues in modern molecular biology. He has an excellent background, experience and very good ideas, which was leverage in multiple local (7 at IGBMC) and European (4) collaborations, as well as in the participation to an EU ITN program. The team recuited 6 PhDs and 3 Post-doctoral fellows and has secured fundings from collaboratives ANR (3) and a Labex Chair. Visibility of the team is reflected by a few oral communications at scientific meetings (5) and the organisation of two summer schools.

The main aim of the team is to develop stochastic and large-scale models of eukaryotic gene regulation using modern methods at the interface between machine learning and biophysics. The team published thirteen papers, five where the team has had a leading role, including publications in higly visible journals (2 Nat Commun. 2021, 1 iScience 2021 and 1 PLoS Comp Biol, 2021). Most of the scientific production is in a collaborative context, mainly within IGBMC.

Weaknesses and risks linked to the context

For a computational lab, the output is low. This might have been a combination of starting a lab and the pandemic but it is clear in the report that the team leader has created a strong and productive network of collaborators at IGBMC and that work is taking off. The last three papers are in this direction but more needs to be done. The team needs some postdocs and engineers that add critical mass to the enterprise.

The team relies on collaborations that provide the data and the questions for them to do the modelling.

International visibility is limited.

The focus of the lab is perhaps too narrow and very limited to the expertise of the team leader.

No socio economic or outreach activities were reported.

RECOMMENDATIONS TO THE TEAM

The team has two urgent needs: to obtain more funding and to hire postdocs. The aim should be to create a critical mass that allows it to develop their potential and to have the ability to attend collaborations that should be looked for intensely.

Then, and in parallel, there is a big need to develop more productive collaborations and not just short term, adding analysis and methods to somebody else's study but as part of the core developments in the lab. One can see that, over the last few years the lab is developing along these lines (the last three publications with the team leader as senior author) but this needs to continue.

Team 19: Molecular biology of B cells

Name of the supervisor: Mr. Bernardo Reina San Martin

THEMES OF THE TEAM

The team works on the elucidation of the molecular mechanisms leading to antibody diversification in B lymphocytes by somatic hypermutation (SHM) and class switch recombination (CSR) to establish highly specific and adapted humoral responses.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) To work at attracting foreign students and fellow.
This is still a matter of concern regarding the relatively small size of the team. Due to successful grant application, the committee is confident that the hiring of excellent candidates will come soon.
2) To improve technology transfer.
The team has developed the Universal Expression System (UES), an innovative and extremely flexible cloning system for which they created a web site open to the community. The UES is now provided as a service by the Molecular Biology platform of IGBMC.
3) To increase the size of the team with more students.
This is not yet achieved.

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	0
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	1
Subtotal permanent personnel in active employment	**2**
Non-permanent teacher-researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	0
Post-docs	1
PhD Students	0
Subtotal non-permanent personnel	1
Total	**3**

EVALUATION

Overall assessment of the team

This is an excellent team of international standard in this field of research, especially given its relatively small size. The team plays a leading role in the elucidation of the molecular mechanisms leading to antibody diversification. They obtained outstanding results on protein complexes involved in the targeting of the "Activation-induced cytidine deaminase" (AID) and in the repair of DNA damage inflicted by AID in vivo.

Strengths and possibilities linked to the context

The team visibility is attested by an impressive and very productive interdisciplinary collaboration network in France (IGBMC, IBMC, Institut Pasteur, Insitut Jacques Monod, ESBS, Rennes University) and abroad (University of Oxford, Leiden University Medical Center Giessen, Oxford, Northwestern University, Chicago, and New York University). This network has contributed to eighteen publications in prestigious journals: Mol Cell, Nat Comm, Nature, Cell Rep, Front Immunol, Embo Mol Med. The Team nineteen has obtained important fundings (1.2 M€ from Fondation ARC, INCA, FRM, ANR and Fondation ARC). The team recruited five PhDs and three Post-docs. All PhD students have defended their thesis with a first-author publication.

The team's long-term scientific objectives are clearly set, with a focus on molecular mechanisms controlling AID function at specific Ig loci, and how the repairing of AID-induced DNA damage promote Ig diversification while preventing genomic instability elsewhere. The team has made numerous excellent and outsanding contributions, with five original publications where the team leader is at coordinator position. The team has notably investigated how the Cohesin and Mediator complexes control immunoglobulin class switch recombination (J Exp Med 2016). They also showed that Parp9 (from the PAR signalling pathway) is dispensable for B cell development and Immunoglobulin Class Switch Recombination (Eur J Immunol. 2017). By studying the mediator complex, they demonstrated that Med1 deficiency affects the second phase of Somatic Hypermutation (SHM), notably by introducing a bias into the mutation frequency at particular residues defined as hotspot motifs (Eur J Immunol. 2018). They then identified a novel regulatory region, enhancer that controls IgH locus transcription and switch recombination in an isotype-specific manner, promoting CSR (Cell Mol Immunol 2019). Lastly, using a very efficient CRISPR/Cas9 genome-wide knockout screen for genes required for CSR, they identified the protein Fam72a that controls the balance between error-free and error-prone DNA repair during antibody diversification (Nature 2021). These findings have potential implications for tumorigenesis.

Weaknesses and risks linked to the context

The team size is rather small, composed of 4-6 people as a mean, with the team leader and a CNRS engineer being the only permanent staff. This may negatively impact on its long- term sustainability. The team has suffered from the departure of Dr. Isabelle Robert (under Sauvadet'' law), a very talented and efficient researcher with a very valuable wide range of expertise, which was able to train and supervise young lab members.

The team suffers from the lack of good applications from young students (Master and PhD).

The team is not active towards valorisation, outreach activities, scientific expertise and editorial activities.

RECOMMENDATIONS TO THE TEAM

The expert committee recommends to increase the team size notably by recruiting new PhD and post doctoral researchers to strengthen the group and help with its long-term sustainability. This could be achieved through Horizon 2020, MCSA Doctoral Networks, and or Postdoctoral Fellowships schemes, which are suited for this type of recruitment. Teaching at the local university and/or in national or European university networks could improve the attractiveness of the team. Applying at competitive postdoctoral fellowships might help attract good candidates. Finally, a strategy should be set to propose early career scientists for permanent academic position (CRCN).

The expert committee recommends that the team attempts to contribute more actively to outreach activities.

The team should collaborate with IGBMC teams working on various tumor models.

Team 20: Actin dynamics and biomechanics of the early embryo

Name of the supervisor: Ms. Anne-Cécile Reymann

THEMES OF THE TEAM

The team studies the role of the actin cytoskeleton in cell differentiation in the early C. elegans embryo. To this end, the team is quantifying the dynamics of actin and its regulators, made fluorescent by CRISPR/Cas9 genome editing, during the differentiation of cells. The team is particularly interested in the study of human actin mutations in C. elegans involved in diseases called actinopathies.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was recruited in 2017 and was not evaluated in the previous report.

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	0
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	**2**
Non-permanent teacher-researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	0
Post-docs	0
PhD Students	3
Subtotal non-permanent personnel	5
Total	**7**

EVALUATION

Overall assessment of the team

The team is overall very good. The scientific objectives are very convincing and well linked to biomedical problems. Some projects contain very high-level experimental developments. The team is well funded by the ANR, a local Idex program and a European Joint Program for Rare Diseases. The PI has a good national and European visibility thanks to outreach activities, organisation of meetings, and participation in national actions of scientific animation. However, the main projects of the team, mainly developed by PhD students, did not lead to publication so far.

Strengths and possibilities linked to the context

This recently established team (2017) has an excellent visibility. The team seems to be perfectly integrated in its field, especially with the teams studying the actin cytoskeleton in the C. elegans embryo. The collaborative articles and the obtaining of European funding with several other teams show that the team has built a solid network of national (5) and international collaborations (4). Visibility is also attested by invitated conferences (6) and meeting organisations in progress (3, including the co-organisation of a Joint meeting of the French Society for Developmental Biology (SFBD) and the Japanese Society for Developmental Biology (JSDB), together with Human Frontier Science Program (HFSP)), and by sitting on the board of the GDR AQV which animates the physics-biology interface in France. The level of funding is excellent for a young team since it is supported by the ANR, the Idex, and a European program for the study of rare diseases. The team has an excellent training activity with three ongoing PhD theses.

The PI participates to outreach events such as the DECLIC program, which consists in bringing science to high schools.

Weaknesses and risks linked to the context

The team does not include experienced postdocs and appears to be overly dependent on PhD students for its scientific output.

Since opening in 2017, the team has only published papers in collaborative projects led by other laboratories. None of the team's PI-led work has been published to date.

RECOMMENDATIONS TO THE TEAM

The preliminary results presented during the visit are extremely promising and should undoubtedly lead to high quality publications. The team must publish its major work quickly to maintain its visibility and its ability to obtain funding.

The recruitment of experienced postdocs in this young team could facilitate the publication of the work in progress.

Team 21: Signal transduction in metabolism and inflammation

Name of the supervisor: Mr. Romeo Ricci

THEMES OF THE TEAM

The team works on protein kinases involved in stress signalling in response to environmental cues, and in particular to nutritional and inflammatory stresses that promote cellular dysfunctions and diseases. It has been involved in deciphering the link between stress kinases of the Mitogen-Activated Protein Kinases (MAPK) family and chronic inflammation thereby leading to type two diabetes (T2D) and atherosclerosis. Lately, its work was focused on the p38 member that senses oxidative stress and its effect on the activity of Protein Kinase D (PKD). It also studies the Calcium/calmodulin-dependent protein kinase ID (CaMK1D) that plays a role in T2D, and the link between PKD, the NLRP3 inflammasome and Enolase 1 an enzyme of the glycolytic pathway.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) *The team needs to better capitalise on their work and make broader contributions to community. The team leader should be involved in conference organisation further afield.*
The team leader has been the main organizer of an Embo Workshop in Naples (Italy) in 2018. He has been invited to several international meetings (e.g. 7th Embo Autophagy, ASCB/Embo Meeting…)
2) *The experts committee recommends to maintain the investment in PhD training. The team should be helped to attract additional students.*
5 PhD students have defended their thesis during the period considered and 4 PhD students are still engaged in their theses, so the team has been quite successful to attract many students.
3) *The team should be given all the space and staff requested, if available; but perhaps they could be encouraged to better articulate their future plans. Based on their record, we anticipate they will be very successful, but a clear delineation of future projects would help them in obtaining additional funding. The committee believes that with the proposed refocused project, with advice from their colleagues, and with strong support from the institute, this team should be able to obtain competitive funding and produce cutting-edge science.*
A MCU-PH, arrived in the team in 2020 and he obtained his Habilitation to Direct Research (HDR) in 2018. A second MCU-PH just arrived in the team. They will develop their own projects. Thus, the risk of dispersion of forces by conducting too many subjects is always present in the team albeit the increased number of permanent researchers.

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	0
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	3
Non-permanent research supporting personnel (PAR)	0
Post-docs	2
PhD Students	4
Subtotal non-permanent personnel	9
Total	**12**

EVALUATION

Overall assessment of the team

This is an excellent team which is leader in the field of stress signalling mediated by protein kinases that leads to metabolic pathologies. The team international recognition extends now to the field of inflammasome and autophagy with outstanding discoveries in these research themes.

Strengths and possibilities linked to the context

The team has acquired a very strong recognition at the international level in the field of stress signalling linked to pathological disorders, with several outstanding discoveries in this research area. The team has been attractive. It hired nine PhD students, two post-docs, one of them being first author on the Nature paper and another postdoc as first author of a JEM paper. Two scientists (MCU-PH) joined the team and one already co-signed with the team leader a joint publication (Gastroenterology 2019). Two scientists were also presented to secure a permanent research position at the CNRS or Inserm. The team has been quite successful to secure funds for their work with three ANR, Ligue contre le Cancer, ARC, European Foundation for the Study of Diabetes, Société francophone du diabète, FRM (team 'labélisée'), USIAS Strasbourg, Ingestem, Labex IGBMC and the Alsace Region – FHU Arrimage. In total, they got almost 2.5 M€.

In total, the team published 20 publications including several as leading authors: J. Exp. Med 2017; Diabetes Obes. Metab. 2018; J Mol Biol 2020; Cell Death Dis. 2016; Cancers 2020; Sci Rep. 2016; Nat Comm 2019 and Cell Rep 2021. Among them, eight were published in collaborations with other IGBMC teams including four with a leading role, notably the Cell Rep paper. This is a major accomplishment and attests of the very good integration of the team within the IGBMC institute. Of special achievements is the finding that the degradation of insulin granules is strongly enhanced in cells of diabetic islets, with a concomitant suppression of autophagy (Nat Comm 2019). Another major result concerns the requirement of the phosphorylation of the mitochondrial fission factor by PKD to allow the mitotic mitochondrial fission to be processed properly (Cell Rep. 2021; work performed in collaboration with another IGBMC team). Still on PKD signalling, the team found that the recruitment of NLRP3 to vesicles prior to the inflammasome assembly is controlled by phosphorylation by this protein-kinase (J. Exp.

Med, 2017). This opened new perspectives on inflammasome leading to major international collaborations with two teams highly recognised in the membrane trafficking field (NIH, Bethesda, USA and, Tigem, Naples, Italy), with already 2 joint publications (Nat. Comm 2021; Embo Rep 2019).

Weaknesses and risks linked to the context

There are four permanent staff in this team and, apart from a technician, the three permanent members have duties at the hospital (teaching plus to run a laboratory).

The team leader mentioned that the recently recruited permanent researchers will develop their own research, in addition to the two main existing research axes. So, there is a risk of dispersion of the research themes.

There are no indications of societal interactions.

RECOMMENDATIONS TO THE TEAM

The team should pursue on the same track and continue to perform research at the same high level that it is doing now.

With the arrival of two MCU/PH in the team, it is important to strengthen the collaborative effort as the number of permanent positions is relatively small and the three researchers have duties at the hospital. It is important to stay focus on the two main axes of research on which the team has been quite successful so far.

Team 22: Cell physics

Name of the supervisor: Mr. Daniel Riveline

THEMES OF THE TEAM

The team studies cellular functions related to motility, polarity, division, morphogenesis, and wound healing. A focus is given on collective effect of interacting cells. The particularity of the team is that it works at the interface between physics and biology. Within the same team, researchers perform cell biology experiments and use theoretical modelling for an in-depth understanding of the molecular mechanisms that underly the above-mentioned cellular functions. A back-and-forth approach has been put in place to go from experiments to modelling, and vice versa. In addition to theoretical physics and quantitative imaging techniques, the team uses microfabrication to shape cells into defined patterns.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) *The reinforcement of the team is recommended. It is recommended to recruit scientist staff or post-docs on longer period.*
Funding is available for post-docs. Recruitment of staff scientists is projected.
2) *Funding is low and outstanding grants are not mentioned.*
Competitive funding has been obtained.
3) *The international visibility has to be improved (invitation to outstanding international conferences are few, only 2).*
The international visibility of the team has been critically strengthened.
4) *The leadership in national and international program or network needs to be improved.*
The team leader is coordinating national and international programs.
5) *The PI should take into account the future of the post-docs.*
By assuring publications, the future of post-docs is best prepared.
6) *The translational potential of the team's findings is not described.*
The team has a prematuration contract with SATT Connectus.
7) *Links and coherence between projects are missing.*
The coherence of projects between physics and biology is clearly apparent now.

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	0
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	1
Subtotal permanent personnel in active employment	**2**
Non-permanent teacher-researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	0
Post-docs	0
PhD Students	4
Subtotal non-permanent personnel	6
Total	**8**

EVALUATION

Overall assessment of the team

The team conducts an excellent research and occupies a special place at IGBMC by proposing a project that is intrinsically interdisciplinary at the interface between physics and biology. The team promotes the dissemination of this original approach through the organisation of conferences and courses at the local, national and international levels. The team has obtained striking results that were published in leading international journals. The team has succeeded to obtain competitive international funding and has strongly increased his international visibility.

Strengths and possibilities linked to the context

The international visibility of the team is excellent. It is documented by the organisation of an international HFSP symposium in 2017 in Lisbon, of an international summer school in 2016 in Strasburg, and of an Israel-Unistra-Académie des Sciences Symposium in 2018. The team has collaborative programs ongoing with leading international institutes, e.g., Max Planck Institute of Molecular Cell Biology and Genetics in Dresden (visiting professor) and the Crick Institute in London. An "International Research Project" (former LIA) was created with CNRS, and importantly, these collaborations have resulted in publications. Very clearly, a critical strength of the team is to reach out for excellence. The team leader shapes his local and regional environment by organising a Biophysics Club at IGBMC and the Cell Physics Master at the University of Strasbourg. Another critical strength results from the implementation of the team in the infrastructural and scientific network at IGBMC. The physics component that is foundational to the team's identity is thereby optimally embedded with forefront cell biology and the instrumentation that is needed to perform truly quantitative studies on living matter. Highly competitive international funding has been obtained from the prestigious Human Frontier Science Program and the Swiss National Foundation. This success clearly highlights the international repute of the team. Other funding comes from Idex and CNRS. Total funding in the evaluation period is 689 k€.

The scientific production is excellent. A major strength and originality of the team lies in the interdisciplinary back-and-forth link between experiment and theoretical modelling. Experiments are quantitatively exploited using

theory, and predictions from theory are then tested in new experiments. The team has coined the term "ratchetaxis" for a specific type of cell migration that they have pioneered and in which collective effects rather than gradients are of critical importance. This novel concept was explored in depth, in parallel with other aspects of cell migration, cell division and morphogenesis. These important findings have been published in highly visible international journals with the team leader as last author: Jove 2016, Nature Communications 2016, Development 2017, Methods in Cell Biology 2018 and 2x 2020, Biophysical Journal 2018 and 2020, Physics Reviews E 2018, European Physics Journal E 2020 and 2022, Cell Systems 2020, eLife 2021 and 2022, and iScience 2022.

The team recently invested into non-academic interactions by obtaining a prematuration contract with the SATT Conectus on 3D modelling of organoids to increase the reproducibility of their formation. The team leader has also participated in three science lectures to the general public (Grandes écoles, Uni. Strasbourg, CNRS) and a scientific discussion with general public (Déclic in 2019).

Weaknesses and risks linked to the context

Permanent staff researchers and engineer are limited.

RECOMMENDATIONS TO THE TEAM

The team is strongly encouraged to keep up the positive dynamics since the last Hcéres evaluation.

The team should be reinforced through the recruitment of staff personnel at engineer and researcher levels. This should help to further stabilize and reinforce the scientific dynamics of the team. To find researcher profiles at the interface between physics and biology, the team has to draw on a worldwide very limited pool of individuals who have the corresponding training and mindset.

Team 23: Cell cycle and ubiquitin signalling

Name of the supervisor: Ms. Izabela Sumara

THEMES OF THE TEAM

The team has a long-standing interest in cell cycle regulation and in particular the role of ubiquitination in this process, including in pathological contexts such as cancer and fragile X syndrome. The first axis concerns the study of the role of de-ubiquitinating enzymes in mitotic progression and the second the role of ubiquitin-binding proteins (or ubiquitin receptors). An emerging project concerns the coupling of mitochondrial fission mechanisms with the cell cycle.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) *The PI should become active in the organisation of meetings outside of Strasbourg.*
This was not commented in the report.
2) *The PI should build additional clinical collaborations to valorise the potent candidate molecules for therapy.*
To date, the team has not developed direct collaborations with clinicians but nevertheless continues its translational work in partnership with the SATT Conectus in the perspective of a patent application.
3) *Teaching could be an opportunity for the team to communicate on its research area and meet students, who might want to join the team for an internship or thesis, in turn providing more manpower.* This was not commented in the report.
4) *This very promising team should be strongly supported by the institute. Mentoring and advice on grant applications would help this team to grow to a size that is commensurate with their scientific achievements to date.*
The team succeeded in obtaining competitive funding (ARC Labellisé, La Ligue Contre le Cancer, Sanofi, Aviesan, ANR, INCA) during the previous timeframe, including 1 INCA funding as coordinator.

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	0
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	1
Subtotal permanent personnel in active employment	**2**
Non-permanent teacher-researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	0
Post-docs	3
PhD Students	3
Subtotal non-permanent personnel	8
Total	**10**

EVALUATION

Overall assessment of the team

The team has achieved excellent work over the past term, with seven research publications as last or corresponding author including three papers in highly quality journals (Developmental Cell, Embo Journal, Cell Reports) and several high-profile collaborative studies. The visibility of the team is excellent, with many collaborations within and outside of the institute. The investment in bio-medical research is also excellent, with an industrial partnership which could lead to a patent registration in the short term. However, the team is small and must be cautious not to multiply research topics.

Strengths and possibilities linked to the context

The excellent scientific reputation of the team is attested by the various editorial activities of the team leader (Associate editor for Frontiers in Cell and Developmental Biology; Editorial board member for Oncotarget; International Advisory Board member of Translational Oncology), the writing of three reviews (including a Nature Review Mol Cell Biol, 2021) and the attractiveness in recruiting 8 PhDs and 7 post-docs. The team also had solid local and international collaborative networks that led to several (5) high-profile collaborative studies (including Nature Commun, 2016; Nature Genetics, 2016; Nature Cell Biology, 2018; Cell reports 2020). The team obtained fundings from the INCA, ARC (programme labelisé), ANR (partner), and ligue contre le cancer for their fundamental work, and from Sanofi ((iAwards) and SATT conectus for their more applied research.

The scientific production of the team is excellent, with seven last author and five collaborative research publications. The team has a recognised expertise in the field of cell cycle and ubiquitination and has produced high quality outputs during the considered period of time. This is reflected in the team publishing its major publications in leading journals (Developmental Cell, Embo Journal, Cell Reports), as well as in high quality national and international collaborations (with publications in Nature Genetics, Nature Biology, Nature communications, Cell reports, Cell death and differentiation) and writing of review articles. Among the notable results, the team showed that an ubiquitin receptor called UBASH3B is essential for mitotic progression by allowing relocation of the major mitotic regulator Aurora B (Developmental Cell, 2016). They also showed that high levels of UBASH3B lead to chromosome segregation defects and are frequently found in aggressive tumors, making UBASH3B a potential new therapeutic target for cancer treatment (Molecular and cellular oncology, 2018). Another major achievement was to show that RNA-binding proteins of the Fragile-X related (FXR) family are required for nuclear pore reformation after mitosis, and that inhibition of these proteins leads to the formation of cytoplasmic inclusions of nuclear pore components, a phenotype also observed in fragile X syndrome models (Embo Journal, 2020). Finally, in collaboration with Romeo Ricci's team (Team 21), the team has identified a pathway that links mitochondrial fission with mitotic progression (Cell Reports, 2021).

The team is very dynamic in valorisation. On the one hand, they have identified a UBASH3B inhibitor for the treatment of cancer, for which two pre-maturation projects have been obtained with SATT Conectus, as well as a Sanofi Innovation Award, with the prospect of an upcoming patent filing. A third pre-maturation project was obtained to develop new therapeutic strategies for Fragile X syndrome. These partnerships have generated significant financial resources for the team, and in particular the recruitment of two postdoctoral researchers. The team is also active in the dissemination of its work in society through regular participation in public events (Fête de la science, Relais pour la vie) or through publications in the press.

Weaknesses and risks linked to the context

The main risk is that the team leader is the only permanent researcher. The team also includes a permanent research engineer, but all other members are students or post-docs.

Partnerships with the private sector offer funding opportunities but also require an increase in the number of research projects, which is potentially destabilizing for this small team.

RECOMMENDATIONS TO THE TEAM

The committee recommends to continue the very high quality basic and translational research carried out in recent years, but with a reflection on the coherence of the basic questions between them.

It will also be important to recruit one or more permanent researchers, particularly if partnerships with the private sector are planned to continue. Therefore, the PI should continue to promote opportunities for recruitment or mobility.

The excellent collaborations, including the local ones, should be pursued.

Team 24: Dynamics of chromatin structure and transcription regulation

Name of the supervisor: Mr. Lazslo Tora

THEMES OF THE TEAM

The team studies the nature and assembly of transcription molecular machineries, with three main research axes. The first one directly led by the team leader investigate how multisubunit transcriptional complexes are assembled from the moment when the proteins are translated, during nuclear import and their final nuclear assembly. The two other axes are each led by an experienced researcher and aims at i) studying how the preinitiation transcriptional complex forms and its variability in different cell types, and ii) exploring the role of coactivator complexes Saga and Atac.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report did not make any remarkable recommendations.

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	1
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	3
Subtotal permanent personnel in active employment	**6**
Non-permanent teacher-researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	0
Post-docs	1
PhD Students	1
Subtotal non-permanent personnel	2
Total	**8**

EVALUATION

Overall assessment of the team

This is an outstanding, large and solid team, with 3 experienced staff scientists including the team leader. The team has numerous publications (37), which are the result of a high number of national and international collaborations, and includes 15 publications where the team appears as last or corresponding author in high quality journals (Mol Cell, 2017, Embo. J, 2017, Journal of Cell Biology, 2018, Nature Commun 2019 and 2020, Cell reports 2021…). The team has received enormous amounts of funding from different sources including from the NIH and NSF, an ERC Advanced and ANR.

Strengths and possibilities linked to the context

This is a leading team in the field of transcriptional regulation, with an outsanding international visibility. This is attested by a strong network of French (7) and international collaborations (8) that has resulted in a high number of quality collaborative papers. The team leader has been chairing the ERC LS1 panel, the ANR CES twelve committee, and is an Embo and Europaea academia member. Scientific recognition is also evidenced by writing five reviews (including a review in Mol Cell, 2018), scientific editorial activities (Embo. J, Embo reports, Transcription, Epigenomes, PLoS one, JBC) and invitated talls (24). The team has trained 10 PhD students (3 ongoing) and 6 Post-doctoral fellows (3 ongoing) and each experienced researcher is teaching at Strasbourg University. The group has raised high level of funding at the national level (4 ANR) and most importantly from international sources (ERC advanced, NIH and NSF). The move to the Development and stem cell Department has offered them a good research environment that has enhanced the number of collaborations with other groups in the institute.

The scientific production of the team is outsanding, considering both collaborative work and team-leaded projects. Work led to a total 37 publications including 15 publications where the team appears as last or corresponding author in high quality journals (Mol Cell, 2017, Embo. J, 2017, Journal of Cell Biology, 2018, Nature Commun 2019 and 2020, Cell reports 2021…).

Weaknesses and risks linked to the context

A minor weakness given the level of funding secured by the team is the limited connections to the socio-economic world.

RECOMMENDATIONS TO THE TEAM

The team should consider if new bio-informatic approaches (AlphaFold and successors) can become a threat to their future and make sure their technological skills can provide additional value to such novel approaches.

The team should try to initiate connections with the socio-economic world, but without weakening their outstanding basic research work.

Functional genomics and cancer (FGC)

Team 25: Structural and functional basis of chromatin remodelling

Name of the supervisor: Ms. Elisa Bergamin

THEMES OF THE TEAM

The team is investigating structure and function of the chromatin remodeller mSWI/SNF, which is frequently mutated or aberrant in cancers. The team lists a long-term goal of designing pharmacological inhibitors for mutant mSWI/SNF complexes. More specifically, they are studying new mSWI/SNF complex subunits as well as the impact of cancer-derived aberrations from a structural point of view. A current focus is on BCL7, a new cancer-relevant subunit. In terms of methods/approaches, the team employs cryo-EM, protein crystallography, biochemistry, proteomics and cell-based approaches.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

This is a new team so there was no recommendation in the previous report.

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	0
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	**2**
Non-permanent teacher-researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	0
Post-docs	1
PhD Students	2
Subtotal non-permanent personnel	3
Total	**5**

EVALUATION

Overall assessment of the team

The team was established in 2018 and has excellent potential for scientific production. . They have developed appropriate technologies to pursue the relevant and tractable questions within the scope of mSWI/SNF research. The team has not published and they have suffered from a number of structural challenges including limited instrument access, Covid-19 based delays, and internal competition. There is potential for excellent visibility and non-academic activities, though this is also too early to judge.

Strengths and possibilities linked to the context

The team is committed to clear research questions, it is technically/experimentally capable and appears reasonably well-funded. They have developed appropriate technologies to pursue the relevant and tractable questions within the scope of a very important chromatin modifier, mSWI/SNF. The strategy of focusing on mSWI/SNF subcomplexes is smart and can (together with focus on the very obvious cancer links) lead to new discoveries with translational potential. The team have now started collaborating when necessary to broaden the scope of their science. Thus, there seems to be good progress in projects. The team leader is in the preparatory stage for writing up 1-2 manuscripts for publication.

Weaknesses and risks linked to the context

Publication as last author are still in progress and this is really an important matter for the future of the team. Further delay in publishing can lead to insufficient funding and team attrition. It is possible that the team should focus even more on one main story to advance for publication.

Furthermore, the team has limitations that are not entirely on the team leader shoulders (beyond Covid-19 delays). These mainly entail issues with access to instruments and internal competition that are challenges to successful and timely completion of first round of independent publications from the team.

RECOMMENDATIONS TO THE TEAM

Prioritise one (max 2) manuscript and push this to high level publications.

The development of strong collaborations is excellent for the team and should be continued.

The team leader and unit/departmentdirectors are strongly recommended to work out agreements that ensures team access to equipment/instruments. The team leader should compile prioritized list of experiments crucial for completion of one-two manuscripts as well as obvious revision requests, these can serve as necessary basis for scheduled instrument access.

Finally, the unit director need to sort out the issue of internal competition, solutions must be based on principles of good governance.

Team 26: Hematopoiesis and Disease

Name of the supervisor: Ms. Susan Chan and Mr. Philippe Kastner

THEMES OF THE TEAM

The team works on the role of the Ikaros transcription factors (TFs) in hematopoiesis and disease by combining in vivo and in vitro observations. Ikaros TFs acts as tumor suppressor genes in leukemia and are involved at different steps in the hematopoietic lineage. In September 2018, a previous team leader of the institute who is now emeritus (H. Gronemeyer) joined the team to continue to develop its own projects which differ from the main focus of the team. He studies regulatory events in cancer and neurogenesis.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has followed the previous recommendations by focusing on projects where they have their best expertise, and not pursuing project on DNA damage and repair during ageing. The team has reinforced its links with the clinics by welcoming an associated-MD in haematology, training 3 MD-PhD student and establishing collaborations with clinicians.

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	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	1
PhD Students	3
Subtotal non-permanent personnel	4
Total	**10**

EVALUATION

Overall assessment of the team

This is an excellent team, well organized and structured. The projects are well focused allowing to share materials including models and tools. The scientific production is well balanced among members of the team and is of excellent quality. The team has limited interactions with non-academic, although involved in science dissemination by hosting regularly middle school students and by actively participating in seminars with broad audience.

Strengths and possibilities linked to the context

The team visibility is excellent. The team benefits from national (>10) and international collaborations (5, USA, Canada, Sweden...). Team members are cofounders of the upper Rhine immunology group (2018) and are part of the European MSCA PhD cofund program. The team has published one invited review (Curr Opin Immunol 2018). One of the team leaders is directors of the IGBMC "Functional Genomics and Cancer" department, and team members are also involved in different IGBMC committees. The team has been attractive, recruiting 11PhDs, 1 Post-doctoral fellow, 2 permanent researchers, and the hosting of a senior emeritus researcher. Scientific recognition is also attested by contributions to scientific committees (Inserm CSS2 and CSS7, and Portugal gant panel). The team (including research associates) obtained competitive national grants (ANR-PRC, INCa ANRJCJC (2021-2025), Ligue contre le Cancer Label (2015-2017), FRM) and is part of a European ITN network (MSCA) for PhD. Altogether, this represents about 200k€/years excluding salaries which represents an excellent amount to develop their projects.

The scientific production of the team is excellent. The team has generated complex mouse models and in vitro systems to study the role of Ikaro TFs in different hematopoietic cell types. They worked on four axis 1/Ikaroas in B cells 2/Ikaros in Th17 cell polarisation 3/in dendritic cells 4/ Helios in stem and progenitor cells 5/ the structural analysis of Ikaros family proteins. The work led to 18 original articles with nine publications as main contributors (last authorship) of excellent quality in journals with broad audiences (PNAS 2021, J Exp med 2021, PloS Genet 2018). Last authorship is well shared with the three research associates, and two of them obtained their HDR. Almost all PhD students published a first-author article during this term.

The team has developed links towards the clinics. It has hosted three MD-PhD students and has collaboration with clinicians at several hospitals: Hôpital Hautepierre (Strasbourg), Hôpital Robert Debré and Hôpital Saint-Louis (Paris) and Institut Paoli-Calmettes (Marseille). The team also obtained a pre-maturation grant with SATT connectus to study potential therapeutic avenue for BCP-ALL. The team regularly participated in the "Relais pour la Vie", organised annually by the Bas-Rhin section of the Ligue Contre le Cancer.

Weaknesses and risks linked to the context

The number of publications could be higher for a group composed on an average of 10-12 people (1 DR, 1 MCU-PH, 3 CR and 1 technical engineer (IE), 1 MD, 1-2 postdoctoral fellows and 3-5 PhD students). In addition, the two team leaders are systematically present on each publication of the team, which could cast a shadow on the self-development of young group leader.

No invitations to international meetings are mentioned.

Outreach activities are restricted to hosting middle school students or presenting their work in lay audience.

The team research is biomedical in nature, which should allow interaction with industry. Although interactions with clinicians are established, the translation of the team key findings into clinics and patenting is not yet achieved.

RECOMMENDATIONS TO THE TEAM

The team should continue its seeding activity by promoting young staff scientists to publish in the last and corresponding author and to obtain their own grants in order to lead them to emerge as future team leaders.

The team have produced and published interesting basic knowledge but should reinforce its link with non-academic world. Its research being in biomedical area, more interactions with clinics and industry should be developed. The training of MD-PhD students as well as new collaborations with clinicians may help the translation

into clinics of the key findings. Interestingly, the team has been awarded a funding to study potential therapeutic avenue for BCP-ALL which may represent a first step into the translation of its research to clinics.

Team 27: Genome expression and repair

Name of the supervisor: Mr. Frederic Coin

THEMES OF THE TEAM

The team investigates the link between gene expression and DNA repair. The work aims to characterise TFIIH, a basal transcription factor involved in two activities (transcription and nucleotide excision repair) and in particular to understand the basis of molecular defects observed in patients carrying mutations in several subunits of the complex. Different lines of research are conducted: the impact of TFIIH mutations on chromatin structure and gene expression, the role of DNA repair factors in transcription, the impact of TFIIH inhibition in melanoma cells, and an analysis of the structure-function of TFIIH.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report indicated the need to increase the international visibility of the PI in order to ensure continued success in recruitment and funding.

The former team leader, now emeritus, has still a high visibility and produced many research and review articles as last author during the period (Sciences Advances 2022, Embo Mol Med 2021, Scientific Reports 2020, Nat Com 2019, Mol Cell 2017, Mol Cancer Ther 2016). The production of the new team leader as last author is very good while less impressive than the former team leader over the same period (last author in Embo Rep 2021, Nat Com 2019, Mol Cell 2017). Eight out of the nine PhD students over the period were under the responsibility of the new team leader suggesting the leadership transition is underway.

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	3
Non-permanent research supporting personnel (PAR)	0
Post-docs	0
PhD Students	3
Subtotal non-permanent personnel	6
Total	**9**

EVALUATION

Overall assessment of the team

Overall the team has an excellent activity and is internationally recognised for its work on TFIIH. The research performed by the group is excellent with remarkable contributions in the different lines of research. The team has produced 30 original and review articles in excellent to outstanding journals including Molecular Cell (2 articles), Nature Comm (2 articles), Embo Rep, Nucleic Acids Research, Nat Chem Biol. The visibility of the new team leader is very good with some international invitations.The team has an excellent non-academic activity with a collaboration with a biotech company elaborating anti-cancer molecules that bind to DNA and disrupt essential mechanisms such as transcription and DNA repair.

Strengths and possibilities linked to the context

The visibility of the team is excellent with a well-established team composed of four permanent members, nine PhD students, ten post-docs and 11 internships during the period. The team has an international reputation in the field of gene expression and DNA repair. The team has established several collaborations, either within IGBMC or elsewhere in France and abroad (Germany). The group will recruit a structural biologist to develop the structure-function analysis of the TFIIH complex.
The team has been successful every year to obtain national fundings (ANR, INCA, ARC, Ligue Contre le Cancer).
The team has the opportunity to attract students interested by the themes of the group as several members are involved in teaching at the Master 1 level.

The scientific production of the team is excellent to outstanding with several key publications in the field (Nature Comm (2 articles), Embo Rep, Nucleic Acids Research, Nat Chem Biol.).

The non-academic activities of the team is excellent with a collaboration with a biotech company for the development of anti-cancer molecules targeting gene expression and DNA repair. An initiative is underway to develop contacts with an association of Xeroderma pigmentosus patients in Mayotte.

Weaknesses and risks linked to the context

The dysfunction of TFIIH has many consequences in gene expression and DNA repair by affecting several processes involved the regulation of chromatin composition. Considering the size of the group and the many possible projects, it will be important to limit the number of themes to study.

Considering the reputation of the group, international funding could be obtained to further enhance attractivity of the team.

RECOMMENDATIONS TO THE TEAM

The team should continue to perform important and fundamental work on gene expression and DNA repair, in link with the genetic diseases resulting from the dysfunction of the TFIIH complex.

Team 28: Regulation of gene expression in cancer

Name of the supervisor: Mr. Irwin Davidson

THEMES OF THE TEAM

The research in the team is divided in three different axes: the role of transcription factor Taf4 during embryonic development and in specific organs using genetic models; the role of TEAD transcription factors in myogenic differentiation using various genetic models; tumor progression in melanoma combining genetic and metabolic approaches. The recent recruitment of a PU-PH opened a fourth thematic on tumor progression mechanisms to other cancer types.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

There were no recommendations in the previous report.

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	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)	2
Subtotal permanent personnel in active employment	**6**
Non-permanent teacher-researchers, researchers and associates	1
Non-permanent research supporting personnel (PAR)	0
Post-docs	4
PhD Students	7
Subtotal non-permanent personnel	12
Total	**18**

EVALUATION

Overall assessment of the team

The team has an excellent to outstanding production. Both their basic and cancer researches are of major interest and at the cutting edge. The team has an outstanding visibility. The different axes were pursued in parallel with a high level of scientific production. Intra-IGBMC and external collaborations yielded top-range publications. The team has a high capacity to obtain grants from various national sources. Although one patent and two declarations of invention were filed, the main findings are mechanistic and belong to fundamental research, but with potential medical benefits on cancer.

Strengths and possibilities linked to the context

The team has an outstanding visibility and recognition in the field and is attractive for students and postdocs, although not as many as they would like to. They have a strong capacity to lead research projects with three full-time tenured researchers (among which the head of the team) and one medical professor, recruited during the last contract. Four post-docs were hired during the last six years, which is excellent for a team of this size. Five students defended their thesis during the contract and seven are ongoing. PhD students were authors of 2-8 publications, among which one-three as first author, which is excellent. The Team has a very good capacity to obtain grants (530 k€ /year in average) from national agencies (ANR, INCa, Inserm) and from charity associations, such as La Ligue contre le Cancer and ARC.

The team has an excellent to outstanding scientific production with a long-lasting expertise in deciphering the transcriptional machinery and developed relevant genetic models to analyse the role of transcription factors (Taf4 or TEAD family) during embryonic development and in specific adult tissues, like pancreatic beta cells and in the myogenic lineage. This work was published in high range journals, such as Nat Comm, Cell Death Dis, PloS Genet… The work on transcription factors was extended to characterise cell heterogeneity in melanoma by the expression of specific factors and to understand their role in each lineage. These studies were completed by the identification of a novel metabolic pathway in tumor cell proliferation. This body of research also lead to high range publications, such as Clin Cancer Res, Embo Rep and Nat Comm. The recruitment during the last contract of a PU-PH brought a new thematic that comprises the study of molecular and cellular mechanisms of tumor progression or large-scale investigations in various cancer types. This last thematic was also very productive with articles in high-range journals: J Immunother Cancer, Genome Biol and Cancers. The research axes of the team are somehow connected to each other (mainly by the study of transcriptional and tumor progression mechanisms), and all of them are highly productive in terms of scientific advances and publications. In addition, their collaboration with IGBMC or international teams is very active and produced top-range publications, including Cancer Cell, Gastroenterology, Mol Cell, Gut. Team 28 is very well inserted into the local organisation of IGBMC.

The non-academic activities are excellent to outstanding with patents developments and biotech collaborations for developing inhibitors of long non-coding RNAs activities.

Weaknesses and risks linked to the context

Although all axes developed in parallel by the team are highly productive, there is a risk to lose capacity to be at the cutting edge on each topic, and also a risk of dispersion.

There is only one tenured PAR, which is low for a team of this size, and two with private contracts. The PARs are poorly associated in the team publications.

The team did not apply to or obtain European grants, which should be possible because of the international reputation of the team.

Although one international patent and two declarations of invention were filed, none of these inventions resulted in licensing and in general, there is no interaction with industries. There is no vulgarization/interaction with the general public while melanoma is a main public health issue, for which the society was made aware.

RECOMMENDATIONS TO THE TEAM

The main recommendation of the committee is to continue or even increase their excellent scientific production and to pursue their collaborations with high-level national and international labs.

Although the 4 axes have been productive in the last period, the team should consider to focus on fewer axes.

The team should apply to European grants to increase their sources of funding.

The remaining tenured researcher without an HDR should apply to obtain it to increase the capacity of the team to hire PhD students.

Team 29: Pathophysiology of vitamin A signalling pathways

Name of the supervisor: Mr. Norbert Ghyselinck and Mr. Manuel Mark

THEMES OF THE TEAM

The research of the team employs a combination of genetic, morphological and molecular approaches to understand the role and molecular mechanism of action of the naturally active metabolite of vitamin A-retinoic acid, with a particular emphasis on cell fate, differentiation and morphogenesis.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:

1) *to recruit new postdoctoral fellows and to consider diversification of research to broad concepts in testis development, rather than exclusively on specific molecules in particular cellular pathways.*

The team continues to have difficulties in recruiting new post doctoral researchers. There is however evidence that the team has diversified their research activities into broader aspects of testis development.

2) *to develop internal collaborations with other teams with different expertise in the department of Functional Genomics and Cancer, to help further develop novel research directions.*

This has been addressed to some extent with the team developing partnerships with Programe Hospitalier de Research Clinique (PHRC) and is taking part in a clinical trial FERTICovid. The team has also collaborated within IGBMC to study male gamete formation.

3) *In the previous report it was recommended that the impact of additional permanent staff members to which the team leaders have delegated some management duties be evaluated at the next review*.

The additional staff members do not appear to have significantly contributed to decreasing the management burden on the team leaders who was heavily involved (approx. 50% of their time) in covid related issues within the IGBMC. This appears to have had a detrimental effect on the overall scientific productivity of the 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	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)	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	2
Subtotal non-permanent personnel	2
Total	**9**

EVALUATION

Overall assessment of the team

Overall, the scientific quality of the work is very good and is of an international standard in this field of research. The team is very well established scientifically in the pathophysiology of vitamin A signalling pathways. They are particularly focused on retinoic acid (Atra), an active metabolite of vitamin A and in Atra- dependent processes that are involved in cell differentiation in vivo focusing on mouse germ cells, given that Atra and its nuclear receptors play a key role in gametogenesis in mice. They have also begun to focus on Atra involvement in the differentiation of stem cells.

Strengths and possibilities linked to the context

The team has unique resources and models in which a variety of different Atra signalling pathways that have been interrupted exist, which together with expertise in the characterisation of tissue and molecular abnormalities has allowed them to make a very good overall impact in this field of research.

The team has made meaningful contributions to its field of research, in particular they have reported that Atra-responsive cells are scarce in the ovary which is contrary to the current dogma in this area, that meiosis is triggered by endogenous Atra in the developing ovary. The team has also shown that Atra signalling is dispensible for meiosis initiation in female germ cells.

The scientific capability of the team in the area of vitamin A signalling pathways is reflected in their involvement in two ongoing Programme Hospitalier de Researche Clinique (PHRC) projects focusing on fertility issues. They are coordinating an ANR funded project (Ardigerm, Retinoic acid in germ cell differentiation and meiosis) and are a partner in another ANR funded project on Gametes and AR degradation.

A team member Nadege Vernet received the CNRS bronze medal in 2021. The visibility of the team is excellent overall.

With respect to scientific productivity each team member has published at least 1 paper as principal author, while each doctoral student has similarly published a paper as either first or co-first author. Some of the papers have been published in highly visible journals (for ex Science Advances (2020).

Some of the team's published work have made contributions to the field, which is reflected in the number of citations that they have received. The paper in the Journal Development (2019) has been cited 107 times. With respect to interdisciplinary and collaborative interactions, this is reflected in the publications involving local national and international collaborations. These include IGBMC and the University of Strasbourg and Cote d'Azur at the local and national level together with international teams from Heidelberg and the University of Geneva, amongst others. Overall, this is a very good team which continues to perform original relevant research, while exhibiting very good productivity.

With respect to non-academic interactions the collaborative interactions with groups in the study of the possible effects of Covid on male sterility are positive. A team member contributed to the production of an OECD review on retinoid signalling with the objective of updating existing test guidelines to identify chemical effects on the pathway. A team member also contributed to the evaluation committee of CNRS section 22 on the current research landscape in France and the potential future landscape in cell biology, development and evolution.

The team has been quite active in outreach activities associated with relevant stakeholders in the subject area. This is very good.

Weaknesses and risks linked to the context

The team has not acted on some of the previous recommendations. For example, they have made little progress in recruiting new post doctoral researchers.

The number of publications is quite modest in terms of numbers and this lack of productivity was acknowledged in the self assessment by the team.The reasons given centre on difficulties surrounding framing a new research theory, which counters an existing dogma in the field, together with increased teaching roles by team members coupled with problems encountered by covid; have some credibility.The team also stated reasons for modest

productivity involved the fact that they were outcompeted on particular publications by rival research groups. This is less credible.

Only a limited number of the papers published by the team over the period have been heavily cited.

The additional staff members do not appear to have significantly contributed to decreasing the management burden on the PI.

RECOMMENDATIONS TO THE TEAM

The expert committee recommends that the team significantly increase their overall scientific productivity and where possible target publications to higher levels so to increase the citations and visibility of the research work.

The expert committee recommends that care be taken that the expertise of the PU-PH who will be leaving in 2023 is not lost to the team, as this could have a long-term detrimental effect on the team's long-term sustainability.

The expert committee recommends team makes a concerted effort to recruit new post doctoral researchers to strengthen the team and help with its long-term sustainability. This could be achieved through Horizon 2020, MCSA Doctoral Networks, and or Postdoctoral Fellowships schemes, which are ideally suited for this type of recruitment.

The role of the newly appointed staff in alleviating the managerial duties of the team leaders within the IGBMC needs to be reassessed, as their desired effect in helping the team leaders with these duties does not appear to have been successful. The expert committee recommend that the team leaders cease their role with responsibility for Health and Safety within IGBMC.

Team 30: Transcriptional regulation of neural and immune development

Name of the supervisor: Ms. Angela Giangrande

THEMES OF THE TEAM

The team started during the evaluation period a new project to understand the biology of the fly immune cells within and outside the nervous system (heterogeneity, role/involvement in development and physiology and evolutionary conservation of a transcriptional cascade). To succeed, they developed several techniques (bulk and single cell transcriptomics and Cut&Run). Interestingly, they run comparative analyses in flies and mice to tackle potential functional and molecular conservation in those mechanics. The team achieved their previous objectives by extending their work on the molecular pathway shared by glia and hemocytes (in mice and *Drosophila*) and also used genome-wide approaches thus providing new information on glial and hemocyte biology.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Previous recommendtions were:
1) *To recruit a staff scientist.*
One scientist was recruited in 2017 as CRCN at CNRS. Since then, he published four primary articles including first and co-corresponding author (Embo J, Frontiers in Cell & Dev Biology, eLife and J Neuroscience).
2) *To improve publications of the PhD students.*
During the period, each PhD student published at least one article as first author, except one that did not terminate the PhD program.
3) *That the funding source are more "regular/ secured".*
From 2018, the team secured > 1 M€.

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)	3
Subtotal permanent personnel in active employment	**5**
Non-permanent teacher-researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	0
Post-docs	1
PhD Students	3
Subtotal non-permanent personnel	4
Total	**9**

EVALUATION

Overall assessment of the team

The team is excellent to outstanding and continues to perform original research, while also exhibiting an excellent productivity. The team is very well established scientifically, which is reflected in its participation in a number of research projects, congress and recent publications, using new approaches, which is to be commended, particularly given the "small size" of this team. These contributions are in many cases very novel.

Strengths and possibilities linked to the context

The visibility of the team is outstanding with key complementary collaborations: new technologies, including RNA seq bulk and single cell to identify the transcriptional landscape of the immune cells and epigenomics to characterise the chromatin state of those cells (CUT&RUN approaches). Those approaches needed a heavy load of bioinformatic analysis. The team became familiar with those approaches, which is a strength for the future and ongoing projects. The team also extended its collaboration, including by creating an International Associated Laboratory with India (LIA CNRS-Unistra) as well as several collaborations that involved the co-supervision of two PhD students and two postdoctoral fellows. During the period, four PhD students defended their PhDs, the team co-organised 11 international meetings/symposia and workshops. The team was awarded with several grants (> 1 M€ in the period). As suggested by previous Hcéres committee the team recruited several young investigators (PhD), postdoctoral fellows and importantly a former postdoc in the team was recruited as a CRCN CNRS in 2017. His experience in bioinformatics helped significantly the new approaches used in the lab for the actual and future projects (bulk & single cell RNAseq, CUT&RUN).

The scientific production of the team is excellent to outstanding with key publications in the field exemplified by manuscripts in Embo journal and Cell report. The last five years have been very important and challenging for the team as they started new and challenging projects. The team extended its expertise from fly to mouse.,. All these efforts will soon give rise to publications (4 manuscripts were in the final preparation stage when evaluation was deposited).

The non-academic activities remain non-relevant, the team being mostly focused on fundamental science.

Weaknesses and risks linked to the context

The team is growing in terms of permanent positions (5 including the team leader, 3 PARs and 1 CRCN). The team should, if possible, regarding the complicated national context, consider hiring new research collaborators.

The team has a complicated experience with a PhD student who manipulated data and did not have a behavior compatible with other lab members. The whole team was affected. This student finally left the team and his PhD studies.

As with many teams, the pandemic significantly slowed down the team activity (flies and mice strains have been discontinued).

RECOMMENDATIONS TO THE TEAM

The committee encourages the complementary use of *Drosophila* and mammalian models. This should help (partly) to solve the financial support needed for basic research that is actually limited.

The projects developed by the team now include mice investigation that should help to apply for specific translational research grants.

The committee also encourages the pursuit of outstanding national and international collaborations, including local collaboration.

Team 31: Chromatin and epigenetic regulation

Name of the supervisor: Mr. Ali Hamiche

THEMES OF THE TEAM

The team is investigating how histone variants are deposited by histone chaperones and how this impacts chromatin structure and gene regulation. More specifically, they focus on connections between histone variants (H2A.Z, H3.3, CENP-A and the linker histone H1) and DNA methylation based on the notion that variants can counteract DNA methylation. They combine biochemical and structural approaches in their work though also applying functional genetics to investigate the biology of histone variants.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:

1) *to continue with the chosen research lines. Strengthen the impact of the group further, taking leading roles in analysis as well as structure solution. Looking forward, the team should consider which area offers the best opportunity to establish its research identity. That does not mean they cannot operate on three lines, but choose one, to establish the visibility that will help in getting funds.*

The team has followed a clear line of research with success during the period of evaluation. The case of leadership is no longer relevant as the team more evidently leads collaborations.

2) *The experts committee recommends to visit conferences in the area of epigenetics to become (even) more visible in this field.*

The team has become more internationally visible participating in conferences.

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	2
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)	2
Subtotal permanent personnel in active employment	**7**
Non-permanent teacher-researchers, researchers and associates	3
Non-permanent research supporting personnel (PAR)	0
Post-docs	1
PhD Students	4
Subtotal non-permanent personnel	8
Total	**15**

EVALUATION

Overall assessment of the team

This is an outstanding team that is very well established and contributes to science at the highest level. It is well-funded, and visible with top publications. The team succeeds in utilizing various existing experimental/approach possibilities and they are excellent at collaborating when necessary. Finally, the team also excels in non-academic aspects being well involved in outreach activities and is at the origin of a start-up.

Strengths and possibilities linked to the context

The visibility and attractiveness of the team are excellent to outstanding. The team is currently constituted by three permanent researchers, one postdoc, one Ph.D. student, and three technical staff. The team recruited 8 PhD students and nine post-docs during the evaluation period. One postdoc got a permanent position during this period of time. All PhD students in the team published/will publish papers as first-author. The team is internationally recognised in the epigenetic field and the team leader is regularly invited in meetings. It got six ANR grants during the evaluation period.

The scientific production of the team is outstaning and very-high profile with several seminal studies in different aspects of the epigenetic field. In particular, the team published as a lead in: Science (2021), J Mol Biol (2021), NAR (2020), Sci Rep (2019), Nature Comm (2019), Gene (2019), Mol Cell (2018), Mol Cell (2017), Genome Research (2017), Mol cell (2016), PLos Genet (2016)….and published also several excellent articles in collaboration. Altogether, the production is outstanding.

The non-academic activities excellent. From 2016-2019, the team also set up a collaboration with a pharmaceutical company, got numerous competitive funding and created a start-up. The team members have been involved in sharing their knowledge with the general public and taking part in debates in society.

Weaknesses and risks linked to the context

The team would benefit from recruiting one-two permanent staffs to ensure continuity while also allowing the team to maintain the focus on pioneering research questions. Furthermore, the team has the qualities to apply for top level European grants, which will strengthen visibility, funding and likely help in attracting permanent staffs.

RECOMMENDATIONS TO THE TEAM

The committee recommends continuing to publish high-quality work and further establish as a world-class team. To reach this potential, the committee recommends applying for ERC advanced grant.

Team 32: Pathogenesis of inflammatory diseases

Name of the supervisor: Ms. Mei Li

THEMES OF THE TEAM

The team mainly studies the inflammatory response and networks in skin diseases, namely atopic dermatitis and psoriasis.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous report were:
1) *The next five years must be funded.*
The team was funded with 1165 k€ during the 2016-2021 period, which represents 194 k€/an in average.
2) *The recruitment of a new permanent person or of post-docs would help to secure the various projects of the team.*
No researcher with permanent position was recruited; two postdoctoral fellows were hired, including one for a very short time.
3) *To improve interactions with industry and with the cultural environment.*
The team interacted with five different companies in the period.
4) *New members should be recruited soon to reinforce the team and to carry out such an extensive work plan.*
Eight PhD students (5 defended their thesis and 3 are ongoing) and two postdoctoral fellows were hired.
5) *Clearer priorities should be made among the proposed projects. The team would become stronger and more recognised if focus is only some of the proposed projects.*
The team focused on two main projects, and collaborated on 2 projects for which they were not leaders.

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	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)	1
Subtotal permanent personnel in active employment	**1**
Non-permanent teacher-researchers, researchers and associates	1
Non-permanent research supporting personnel (PAR)	0
Post-docs	2
PhD Students	4
Subtotal non-permanent personnel	7
Total	**8**

EVALUATION

Overall assessment of the team

The scientific production of the team is excellent, with regard to the low number of tenured researchers (1), and with only one PAR. The work is published in top range journals. The thematic is well-focused and the results are original. They deciphered important inflammatory networks in two skin diseases, by creating and using valuable models. The team was well granted (from ANR and charity associations mainly). Interaction with industry is very good. The main weakness of the team is low number of permanent positions.

Strengths and possibilities linked to the context

The team visibility is excellent. The team established local, national and international collaborations leading to publications. The team created sophisticated and valuable models to study skin diseases and the action of inflammatory cytokines. These models can be a source of collaborations. They have been very successful with ANR grants (5, mostly as coordinator), and also with charity associations (2 including "equipe FRM)). All PhD students published as first (or co-first) author. Some of them obtained prizes at meetings or at the doctoral school, which is a good marker of recognition.

The scientific production is excellent for a team with one permanent rechearcher and one PAR: two articles on the action of TSLP in skin inflammation in a top-range journal in the field of allergy (J. Allergy Clin. IMmunol.; 1 describing the action of 2 pharmacological agents in psoriasis, published in a high range journal (JCI Insight); one published in a middle-range journal on the action of diphteria toxin in the depletion of GM progenitors. The team leader also published three excellent articles in collaboration with other IGBMC teams or with another French lab.

The non-academic activities of the team are excellent since the team is funded by industrial partners, including contracts with Galapagos, Merck, and in connection with AstraZeneca. They participated to La fête de la Science, and published vulgarization articles.

Weaknesses and risks linked to the context

Altogether, eight PhD students (5 with defended thesis and 3 ongoing) were hired during the last period, which is high and probably overwhelming for one HDR. PhD length is four years for all, which is above the three years recommended.

RECOMMENDATIONS TO THE TEAM

In terms of production, the main recommendation of the committee is to keep publishing high quality work.

The research project on DT and hematopoiesis should be abandoned.

The main weakness of the team is the lack of additional permanent scientist to face all the team leader responsibilities and management. Co-optation of a tenured researcher could be considered to share responsibilities and grant applications.

Team 33: Pathophysiological role of nuclear receptor signalling

Name of the supervisor: Mr. Daniel Metzger

THEMES OF THE TEAM

The team investigates hormone signalling mediated by members of the nuclear receptor superfamily. They study in particular the role played by steroids (androgens, estrogens, corticoids) and secosteroid (vitamin D) hormones on the development and cellular homoeostasis in mammals. Three lines of research are conducted: initiation and progression of hormone dependent cancers, steroid receptor and epigenetic co-regulator function in tissue homoeostasis, and the pathophysiological role of vitamin D signalling.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report indicated that the research plan was lacking focus on clear research goals, potentially generating problems developing synergy between the different projects. In addition to a number of collaborative projects, three main lines of research are developed by the three staff scientists, two of them recruited in 2016 and 2017. Results obtained by P. Chambon, former team leader still in activity are not described in this report; only the publications are listed.

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	2
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	1
Subtotal permanent personnel in active employment	**4**
Non-permanent teacher-researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	0
Post-docs	3
PhD Students	4
Subtotal non-permanent personnel	9
Total	**13**

EVALUATION

Overall assessment of the team

The team has an excellent to outstanding production with twelve articles as last or co-last author in international journals (PNAS (4), Oncogene, J Exp Med, Mol Cell Oncol, Nature Com, Siences Adva., Nucleic Acids Research) and more than 30 articles in collaboration. The team is internationally recognised and develops outstanding non-academic activities.

Strengths and possibilities linked to the context

The visibility of the team that host P. Chambon is outstanding with numerous international collaborations mainly for the use of the genetic engineered system they developed (CreLox) but also from the side of clinicians with collaborations with medical doctors. The team has a large number of local, national and international collaborations, including clinicians that led to more than 30 publications. The team leader co-leads a consortium funded by the "Cancéropole Est" for the analysis of precancerous lesions of various cancers. This is a well-established team composed of four permanent members, attracting PhD students (7), postdoctoral fellows (7) and Master internships (16). The team has been successful every year to obtain national fundings (AFM, FRM, INCa, Ligue contre le Cancer, ANR, ARC, Rare Disease Foundation).

The scientific production of the team is excellent to outstanding with twelve publications as main authors (including PNAS (4), Oncogene, J Exp Med, Mol Cell Oncol, Nature Com, Siences Adva., Nucleic Acids Research) and 35 collaborative publications. Using conditional somatic mutagenesis techniques developed in this laboratory, the team analyzes the effects of steroid hormones and vitamin D under physiological and pathophysiological conditions in the whole organism. They use phenotypic and genomic analyses to identify and characterise the cell populations involved in pathogenesis. Two systems recapitulate mammary and protaste cancers that can be used to unravel the mechanisms of disease initiation and progression, and to search for new markers and drug targets. Team members are in a position where they can characterise the molecular determinants conferring tissue specificity to glucocorticoid and androgen receptors by analysing their action in various tissues. The team characterized novel vitamin D analogues with dissociated procalcemic, anti-inflammatory or antiproliferative activities useful for the treatment of rare diseases, auto-immune disorders or cancers. Team members also identified a vitamin D receptor antagonist that could be used in therapy against hypercalcemia.

The non-academic activities are outstanding with patents and rare disease treatments strategies.

Weaknesses and risks linked to the context

A large portion of the work is collaborative.

RECOMMENDATIONS TO THE TEAM

The team should continue to focus on a limited research goals to develop synergy between the different projects and maintain international visibility.

There is a need to increase the international visibility of the current team leader to ensure continued success in recruitment and funding when P. Chambon will stop his activity.

Team 34: Eukaryotic mRNA decay

Name of the supervisor: Mr. Bertrand Séraphin

THEMES OF THE TEAM

The team's research concentrates on the main mRNA decay pathway in eukaryotes (5'-3' mRNA decay, deadenylation, decapping and 5'-3' exonucleolytic digestion), processes that contribute to the regulated production of proteins. RNA decay that performs elimination of aberrant or damaged RNA molecules (RNA Quality Control) is also studied. The team works mainly with yeast. Mammalian models are also used for disease related research.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Previous recommendations stated that "*The disease related work should be intensified. Further interactions within IGBMC could usefully be fostered*".
The team has clearly considered the recommendations from the previous evaluation report, including a collaboration with a team at Hôpital La Timone, Marseille on the study of the human SKIV2L and TTC37 genes in a rare genetic disease (THE syndrome). Also, in collaboration with the team at IBMC, they have focused on the potential role of these genes in viral infections. Regarding interactions within IGBMC, the team has collaborated with one group in the area of male gamete formation, and a collaboration with another is also settled with secured grant.

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	2
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	2
Non-permanent research supporting personnel (PAR)	0
Post-docs	1
PhD Students	2
Subtotal non-permanent personnel	5
Total	**10**

EVALUATION

Overall assessment of the team

The scientific quality of the work is excellent to outstanding and is of an international standard for decades. The team works on the main mRNA decay pathways with a particular focus on the 5'-3'. Recently, they focus on genes involved in the human SKI complex in the context of genetic diseases and viral infections and on a role for deadenylases in male gamete formation. The team also tackles the role of m6A post-transcriptional modification on meiotic recombination. The team has a strong expertise in the TAP method (invented by the team leader in 1999) for the purification of protein complexes.

Strengths and possibilities linked to the context

The visibility of the team is outstanding with numerous collaborations over the years, locally and internationally. With respect to interdisciplinary and collaborative interactions, this is reflected in publications involving local, national and international collaborations. These include IBMC, IGBMC, the University of Strasbourg, Institut Jacques Monod, Paris, University of Mannheim, the MRC in Cambridge, EMBL Heidelberg, ETH Zurich, and the Boston Children's hospital among others. In addition, the team leader has been and is involved in the management of the research (former Unit director, CERBM GIE delegate director and LabEX INRT director).

The team's excellent to outstanding scientific track record is reflected in members of the team being involved in several productive collaborations and in their participation in international meetings as keynote speakers. This is also reflected on the impact that their publications have in the field with over 500 citations per year over the review period. Some of the team work has been published in highly visible journals in the research field (Nature Communications, PNAS Nucleic Acid Research). The team is very well established scientifically which is reflected in its participation in a number of ongoing research projects. They perform original research which has a significant impact in the field.

The team has been involved in very good to excellent outreach activities targeting appropriate stakeholders including the general public. The team leader as director of IGBMC was involved in a number of activities in the socio-economic area.

Weaknesses and risks linked to the context

The lack of "direct funding" for the team leader during his mandate as IGBMC director had a negative impact on the productivity of the team.

Biocomputing needs to be strengthened even if they were partly solved by lab members recent training as well as appropriate postdoc recruitment.

RECOMMENDATIONS TO THE TEAM

The committee encourages the complementary use of yeast and mammalian models. This should help (partly) to solve the financial support needed for basic research that is actually limited.

The committee also encourages the pursuit of national and international collaborations, including local collaboration.

Importantly, the team leader still has important load of responsibility (IMCBio graduate school, Embo members). This load is reduced when compared to the previous mandate (*e.g.* as IGBMC director). This, in addition to the outstanding visibility and research of this team, should help to secure direct funding.

The team should try to hire a permanent position biocomputing person or to use a dedicated platform to strengthen this aspect of their research.

Team 35: Spatial organisation of the genome

Name of the supervisor: Mr. Thomas Sexton

THEMES OF THE TEAM

The team studies the inter-relationships between the programmes of gene expression and the response to developmental signals, at the level of chromatin topologies (TADs). The team developed an expertise in following single cells differentiation in real-time and in identifying cis and trans-acting factors required to build and stabilize chromosomal domains.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

At the previous Hceres evaluation the team was just created so no specific scientific recommendations were issued except that the *"New team members with required expertise should be recruited soon to reinforce the team and to carry out such extensive work. The team should first focus on specific WPs to make sure its investment is acknowledged through high profile publications in this very competitive field. Because of the very strong competition in the field, the team should focus on specific niches. "*
It appears that the team focused on methodologies and reinforced several national and internatioanl collaborations. However, it has not been sufficient to secure permanent positions and a second ERC grant (ERC consolidator). The team is currently in a transition state with several high profile mansucripts published in 2022, in revision or in preparation.

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	0
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	**2**
Non-permanent teacher-researchers, researchers and associates	1
Non-permanent research supporting personnel (PAR)	0
Post-docs	0
PhD Students	0
Subtotal non-permanent personnel	1
Total	**3**

EVALUATION

Overall assessment of the team

The team has an excellent scientific production and visibility, but has mainly produced important methodology publications and set up strong collaborations during the period. The team is in transition with several manuscripts already published and grant applications successful in 2022. There is no relevant non-academic production so far as the team focused on scientific production for now.

Strengths and possibilities linked to the context

The team leader has an excellent visibility with a Paoletti price awarded in 2016 and a very ambitious project following an ERC starting grant. The team has an excellent network of collborations in France (Grenoble, Lyon, Marseille, Montpellier, Paris and Toulouse) or internationally (UK, USA, Italy, Germany and Spain). In addition, the team has close contacts within the IGBMC (team 18) and the IGBMC GenomEast platform and co develop algorythm to adress TAD/ChIP-related studies (GP-tool). The team has 2 very good funding with 1 ANR and 1 USIAS (University of Strasbourg Institute for Advanced Study) grants.

The team has an excellent scientific production with three computational and experimental methodology papers for TAD analysis (1 genome biology, 1 Nat comm, one Frontier in genetics) in addition to four collaborative works (1 in NAR, 1 Nat com, 1 Cell reports, 1 PLOS one). This is complemented by three publications from the team leader post doc (1 Nat comm, 1 Science advances, 1 Embo reports).

The team participated in some outreach projects, including "layman science" seminars to adults of the general public, and visits to elementary schools to participate in experiments.

Weaknesses and risks linked to the context

The team lacks key top-impact publications to consolidate its excellent projects. Currently under state of transition, several manuscripts are in preparation or in revision or just accepted (e.g Genes&Dev, 2022). They should allow accessing to a top international grant and secure the next step forward.

The team lacks permanent postions at the level of CRCN to secure the know-how and development of the research project.

RECOMMENDATIONS TO THE TEAM

Given the situation of funding for the team, efforts will have to be concentrated on the coming papers. In the coming period, it is highly recommended to focus on the high-impact last author projects that are in the pipeline.

Team 36: Molecular and cellular biology of breast cancer

Name of the supervisor: Ms. Catherine-Laure Tomasetto

THEMES OF THE TEAM

The team studies the role of MMP11 and STARD3 proteins in breat cancers, with a focus on lipid metabolism and organelle dynamics. They seek to understand how protein and cellular function deregulation in tumors impacts the growth and progression of cancer in order to use this knowledge to improve patient care.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations from the previous reports were:
1) *Team members have to maintain the international academic reputation of the group despite the recent departure and should go on with their efforts of gaining visibility in their very competitive field in order to broaden their appeal to national and international funders.*
A number of indicators suggest that the team is making efforts for gaining more visibility both nationally and internationally. Dr C. Tomasetto is editor for the journal Cancers. PhD students of the team have obtained a number of prices: Prix de la meilleure présentation Club endocytose exocytose & Prix de Thèse Société de Biologie de Strasbourg – Prix de L'Ecole Doctorale des Sciences de la Vie et de la Santé (DI Mattia Thomas), Prix de thèse & Prix de Thèse de la Société de Biologie de Strasbourg (Gerli (Wilhelm Lea). The team participated in the organisation of scientific meetings: International meeting on current advances and challenges of breast diseases especially breast cancer - 20TH World Congress of Senologic International Society on Breast Heathcar & Parallel workshop to the 20TH World Congress of the SIS on Fundamental research in breast cancer - Novel insights on RNA, membrane biology and immunotherapy (2018). Finally, the team has animated a Science and Society debates: Conference-debate on the occasion of the Foulées Roses of Kochersberg-Ackerland, Truchtersheim.
2) *Through their links with the hospital of Strasbourg, the team might think of developing non-academic partnerships.*
The team is now engaged in two trranslational studies, for studying the impact of anaesthesia on cancer cells and for the identification of specific biomarkers for breast cancer patient monitoring. Notably, the team was responsible of a patient's cohort in the context of the prediction of breast cancer neoadjuvant systemic treatment response with STARD3 immunohistochemistry assay.
3) *The reasons for the poor publication record of some graduate students should be examined and dealt with.*
The team has made substantial efforts in this matter. Five out of five students that have defended their PhD published an original article as a first or co-first author, accounting for the high quality of the students' supervision. This is also demonstrated by competitive thesis prizes (regional and national) obtained by two students.
4) *The team should refocus their research on specific fields.*
The main research projects focused on the function of two genes products MMP11 and STARD3 implicated in breast cancers, supporting the relevance of MMP11 and STARD3 as potential therapeutic targets. These studies have revealed novel links between cancer, lipid metabolism and organelle dynamics.
5) *The team should diversify the models of breast cancer. Indeed, as three physicians joined the group recently including a surgeon, the team is in capacity of testing their hypotheses directly in human breast cancer samples.*
The team is now engaged in two trranslational studies, for studying the impact of anaesthesia on cancer cells and for the identification of specific biomarkers for breast cancer patient monitoring.

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	2
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	2
Non-permanent research supporting personnel (PAR)	0
Post-docs	0
PhD Students	6
Subtotal non-permanent personnel	8
Total	**12**

EVALUATION

Overall assessment of the team

The team made several original contributions in the fields of intracellular communication and lipid transport at the interface of fundamental and clinical research. International visibility and outreach activities could still be improved in order to promote the excellent work.

Strengths and possibilities linked to the context

The team has been attractive, hosting over 30 people during the rerporting period. The team has in particular be very attractive for physicians, encouraging them to come in the team as graduate students to have a coherent training by completing a degree in basic science. The team has had a large number of national panel activities (CoNRS 21 and 22, CNU44, Inserm CSS, Ligue National contr le cancer, Scientific concil of Starsbourg University Medical Science). Team members were invited to international meetings (7 including a Gordon Research Conference) and wrote 6 reviews in international journals. Sufficient funding was obtained (1.3 M€; Fondation ARC, Ligue Contre le Cancer 'équipe labelisé, INCA, ARA, ANR, Région Alsace, Inserm). The team established collaborations with excellent teams with complementary expertise (lipid biochemist and biophysicist in Nice, molecular biologist in London, structural biologists and protein biochemist at the IGBMC).

The team has published 24 original research articles, four editorial materials, and six reviews in international journals. The team had major contributions (last authorship) in fourteen original research articles, including publications in highly visible journals (Embo Journal, 2017, 2020; Embo Reports 2018). Work allowed (i) the characterisation of the StAR related lipid transfer domain 3 (STARD3) protein which represents a vulnerability for HER2-positive breast cancers; (ii) the study of cellular structures called membrane contact sites that physically connect organelles; (iii) the determination of the function of matrix metalloprotease 11 (MMP11), a microenvironment protein acting in the dialogue between tumor cells and mammary adipocytes; (iv) the study of the link between environment and breast cancer. The work also included methods for the development of new protocols to study tumor metabolism *in vivo*. Collectively, these studies, multi-disciplinary in nature, bridging

clinical and fundamental researches, have revealed novel links between cancer, lipid metabolism and organelle dynamics.

The team devopped a partnership with the Quantmetry company to implement AI based medical tools.

Weaknesses and risks linked to the context

The team composition is large and diverse. More publication relative to the size of the team and continuous efforts for translational studies is expected.

The international collaboration network is limited.

The training of physicians joining the team is suboptimal because they cannot be on leave of their medical practice and are only part-time in the lab.

Limited outreach activities given the team size were reported.

RECOMMENDATIONS TO THE TEAM

The committee recommends extending the team collaboration network internationally, in order to increase the visibility of the team and the chance of success to competitive European fundings.

The committee encourages the team to pursue their efforts to maintain translational studies.

Transational medicine and neurogenetics (TMN)

Team 37: RNA Diseases

Name of the supervisor: Mr. Nicolas Charlet-Berguerand

THEMES OF THE TEAM

The team is focused on human genetic diseases that are caused by microsatellite expansions; such as tri-tetra-penta and hexa-nucleotides, over a threshold size which are located in the non-coding parts of the genome. They are specifically focusing on the following human genetic diseases: Amyotrophic Lateral Sclerosis with Frontotemporal Dementia (ALS-FTD), Fragile-X-Associateed Tremor/Ataxia Syndrome (FXTAS) and Neuronal Intranuclear Inclusion Disease (NIID) together with Mycotonic Dystrophies (DM).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has addressed some of the recommendations from the previous report particularly with respect to expanding its connections with international networks to gain visibility. In addition, they have increased their interactions with social, economic and the cultural environment, through participation in relevant patient and charity organisations. They have been less successful in recruiting new post-docs and students to strengthen their team and optimise training, although six PhDs and one HDR have graduated during the reporting period.

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	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	**3**
Non-permanent teacher-researchers, researchers and associates	1
Non-permanent research supporting personnel (PAR)	0
Post-docs	0
PhD Students	2
Subtotal non-permanent personnel	3
Total	**6**

EVALUATION

Overall assessment of the team

The team is excellent to outstanding and continues to perform original research. The team is very well established scientifically in the area of Mycotonic Dystrophies (DM) which is reflected in its participation in a number of research project with funding being obtained from National, European and Charity sources. The team has made meaningful and significant contributions in its field of research, which is to be commended, particularly given its small size. These contributions are in many cases very novel.

Strengths and possibilities linked to the context

The visibility of the team is excellent and this is reflected in the quality of their research publications and in their ability to attract funding from multiple sources to implement the work. Their interdisciplinary and collaborative interactions are reflected in publications involving local, national and international collaborations. These include IBMC and the Institute de Mycologie (Paris) at the local and national level, together with international teams and universities.

Given the size of the group, the scientific productivity of the team is excellent to outstanding with 18 publications. It involves all the team members. Some papers have been published in highly visible journals, such as Nature Communications and Neuron. A number of these papers have made an important contribution to the field, reflected in their number of citations. The recent Neuron papers (2020, 2021) have already been cited 49 and 24 times respectively, while the previously published Neuron paper (2017) has been cited 133 times. The team continues to work in the area of DM with a focus on FXTAS, NIID and ALS-FTD. They are employing molecular based approaches together with cell culture, GFP fluorescence, immunohistochemistry, immunofluorescence and a transgenic models. They have reported some novel finding including the molecular mechanisms underpinning cardiac conduction delay and heart arrhythmia in DM patients, which they attributed to splicing alterations in the cardiac sodium channel SCN5A. In this way they have been able to explain fatal cardiac dysfunctions that are observed in DM patients. The group have further clarified the mechanisms underlying the severity of the symptoms of patients with DM type 1 and DM type, which occurs as a result of competition of RNA binding proteins. With respect to FXTAS and NIID they have reported on a novel mechanism of human genetic diseases, involving the translation of (GGC) repeats into novel toxic polyglycine-containing proteins and for ALS-FTD. They have identified a protein whose expression is linked to the toxic accumulation of DRP proteins.

The team has been very active in outreach activities associated with relevant stakeholders. These activities include laboratory visits and providing research updates to relevant stakeholders. The translational medicine aspects of their activities are excellent. The group have developed a patent “Dynamin 2 inhibitor for the treatment of myotonic dystrophy, involving pharmacological compounds and/or antisense oligonucleotides. A spin-out company Dynacure was involved in testing these approaches. The group are currently testing therapeutic options they have developed for FXTAS and ALS in model systems, which maybe valorised through partnership with commercial companies. Overall, the contribution of the team to no-academic activities is excellent.

Weaknesses and risks linked to the context

None of the scientific staff of the team appear to be involved in teaching at the University of Strasbourg.

The strategy which will be employed in order to recruit additional scientists into this thinning group is not clear.

RECOMMENDATIONS TO THE TEAM

The expert committee recommends that the team continue to attempt to attract more PhD and postdoctoral researchers to strengthen their team and help with its long-term sustainability. This could be achieved through Horizon 2020, such as with MCSA Doctoral Networks, and or Postdoctoral Fellowships schemes.

The expert committee recommends the continued targeting of publications in high-profile journals to continue the visibility of the research work.

Team 38: Regulation of cortical development and disease

Name of the supervisor: Ms. Juliette Godin

THEMES OF THE TEAM

The team studies the cellular mechanisms underlying mammalian cortical development, focusing on genes related to neurodevelopmental pathologies. The first axis focuses on the study of cytoskeleton-associated proteins, including microtubule-binding proteins and microtubule motors, and the second axis concerns the regulation of protein translation.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was created in 2015. It was only evaluated on the strategy and five-year plan. Recommendations was:

This very promising team and should be strongly supported by the institute. Mentoring and advice on grant applications would help this team to grow to a size that is commensurate with their scientific achievements to date. The team should make sure it has the collaborators needed to carry out the technical aspects of the proposal, particularly, in the area of proteomics. It should also start to think about specific cell biological hypotheses that link microtubules/centrosomes to neuronal migration that they might be able to test with newly identified proteins and which might help to lay the future cell biological mechanisms of their work.

The team does not seem to have continued developing the proteomic approaches proposed in the previous project, which aimed to identify components of the centrosome and proteins associated with microtubules specifically involved in cortical development. The work of the team has been refocused on the study of proteins identified through mutations linked to human pathologies, work that has been carried out in the framework of collaborations. Despite its small size, the team has demonstrated an excellent ability to develop its projects and to obtain funding, culminating in 2022 by the award of an ERC consolidator grant.

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	0
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	**2**
Non-permanent teacher-researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	0
Post-docs	1
PhD Students	3
Subtotal non-permanent personnel	6
Total	**8**

EVALUATION

Overall assessment of the team

This young team founded in 2015 has produced excellent research, with 3 main publications in highly visible journals. The team's reputation is already very good and will undoubtedly continue to grow in the years to come. The addition of a second permanent researcher would be important in the long run to bring more stability to this small team.

Strengths and possibilities linked to the context

This young team has a very good visibility. The team leader achieved very good international visibility as evidenced by her editorial activities (International Journal of Developmental Neuroscience, Frontiers in Neuroscience), and she also garnered recognition at the regional level (Prix Wallach académie des Sciences d'alsace 2019, Prix Espoir université de Strasbourg 2020). The team has attracted five PhD students since its creation, two of whom have already defended (one with a very good first author paper, the second with a first author manuscript in preparation, as well as two other second or third author publications, respectively). The team has developed very good interactions within the IGBMC (3 ANR PRC grants as partners obtained over the period with other IGBMC teams), and outside (1 ANR PRCI grant as coordinator with the team of D. Nedialkova, MPI-Biochemistry). The principal investigator has demonstrated an excellent ability to secure funding, with several small grants in addition to those mentioned above.

The scientific output of the team is overall excellent, with the two main papers from the team published in prestigious journals (Nature comm 2020; NAR 2021), as well as several high-quality collaborative studies (Nature genet 2016; PNAS 2017; Hum. Mol. Genet. 2018; Nature comm 2019). In addition, three manuscripts signed by team members as first and last authors are in preparation. For axis 1, on which the team was founded in 2015 (thanks to ATIP-AVENIR and ANR JCJC funding), the team showed that human mutations affecting the kinesin Kif21B at the origin of neurodevelopmental abnormalities are linked to a loss of Kif21B autoinhibition, a mechanism possibly conserved for other kinesins (Nature comm, 2020). On the other hand, they have demonstrated a non-canonical role for Kif21B in the origin of some aspects of the phenotype (manuscript in preparation). For axis 2, the team obtained in collaboration with Christophe Romier's team (team 7) the structure of the ADAT complex which catalyzes the deamination of an adenosine to inosine in a subset of tRNAs to allow wobble pairing. They showed how mutations affecting one of the components of the complex, ADAT3, which are associated with neurodevelopmental abnormalities in humans, disrupt the structure of the complex and its activity (NAR, 2021). A second manuscript in preparation describes the impact of these mutations on neural development.

Weaknesses and risks linked to the context

Three studies from young researchers have not yet been finalised. This includes a first author paper by a student who defended in September 2020, a first author paper by a postdoc who has been in the team since 2015, and work from a postdoc who spent 3 ½ on the team and not listed on any publications. Finalizing these publications is not only important for the visibility of the team but also for the future of its young researchers

The team is still small in size and includes only one technical staff (AI Unistra), which is insufficient considering the diversity of the research projects.

RECOMMENDATIONS TO THE TEAM

Continue this excellent work and quickly finalize the manuscripts in preparation, which all look very promising, to further strengthen the international reputation of the team.

The team is small at the moment, but the recent award of an ERC consolidator grant in 2022 will help to solve hiring and funding issues in the next term.

Team 39: Study of copy number variants in autism spectrum disorders and their comorbidities

Name of the supervisor: Ms. Christelle Golzio

THEMES OF THE TEAM

The team aims at understanding how genetic variations can impact the development and homoeostasis of the nervous system, studying the impact of gene dosage defects on fundamental processes of neurodevelopment. Noticeably, the team developed whole organism and cellular models to discover genes and alleles that contribute to diseases, to delineate and validate genetic interactions and to identify novel genes involved in comorbidities associated with autism.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendation from the previous report was to provide mentoring to the team leader so to promote high impact papers and obtain significant grant income. While it is not clear whether mentoring was put in place, the team succeeded with bot aspects.

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	0
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)	4
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	3
Subtotal non-permanent personnel	3
Total	**8**

EVALUATION

Overall assessment of the team

The team is a junior group recruited in 2016 as laboratoire d'excellence (ANR call). The publication record of the team is excellent both in term of quality and quantity, including core projects and collaborations, especially considering the short period of team activity. The team used and developed innovative approaches to address key questions in syndromic autism research by combining in vivo modelling in zebrafish, mice, and genomic tools. The team leader develops a robust national and international visibility with numerous collaborations. Interactions with the social and economic environment are outstanding.

Strengths and possibilities linked to the context

The team is setting a national and international visibility, developing a wide collaborative network. The majority (12/13) of the scientific production of the team involves multiple collaborators, mostly clinicians, in France (Centers in Nantes, Montpellier, Strasbourg and Dijon), in Europe (Germany) and worldwide (3 partners in the USA, 1 in Australia). Since 2019, the team leader co-coordinates the Integrative analyses of Gene Expression and the Epigenome (IGEE). The team leader is currently co-coordinator of the Axis 3 "translational medicine" of the renewed INRT LabEX. The team leader has organised an international meeting (2019). The team raised a good level of fundings at the national level (ANR Labex team and ANR JC) and attracted 4 PhD students.

The team has an excellent scientific production, with 13 papers (including a 2021 BioRxiv preprint). Highlights of publications includes American Journal of Human Genetics (3), European Journal of Human Genetics (1), Human Molecular genetics (1), Molecular Psychiatry (1) and collaborative work published in Nature Neuroscience (1) and Nature Communications (1), Of note, in eight articles, PhD or postdoctoral students are appearing as first author/co-author.

The team is active in diffusing current genetics research on autism disorder and participating in societal events. The team leader has been invited by the Jardin des Sciences in Strasbourg (2018) and to a patients' conference in Madrid (Spain, 2017). The team leader is a member of the Strasbourg Translational Research on the Autism Spectrum & Neurodevelopmental Disorders (STRAS&ND Center) organising family gala (2021).

Weaknesses and risks linked to the context

The team has only one permanent position (the team leader), which is Insufficient to pursue studies on potential therapeutic targets. The team has troubles to retain good students who prefer to enter the industrial world.

Despite high capacity to raise national fundings, the team is lacking an international European funding to secure more advanced research.

Translational research might also be secured by private collaborative fundings.

RECOMMENDATIONS TO THE TEAM

The team should attempt to reinforce its ability to obtain international grants. In this context and thanks to its expertise and publication record, the committee encourages the team leader to apply to an ERC funding.

The team has an excellent publications record. However, the situation of the team seems precarious because there is only one permanent staff member. International funding will be absolutely necessary to attract brilliant researchers in order to offer them the perspective of a future permanent position.

Team 40: Pathophysiology of Down's syndrome and rare dose-effect diseases causing intellectual disabilities (ID) or autism spectrum disorders (ASD) and other comorbidities

Name of the supervisor: Mr. Yann Hérault

THEMES OF THE TEAM

The team projects aim at elucidating the mechanisms of Neurodevelopmental Disorders (NDDs) and their comorbidities and to develop new efficient therapies. The main pathologies examined are Down syndrome, Alzheimer's disease, craniofacial and orodontal developmental disorders, and others neurodegenerative and genetic diseases, including the 16p11.2 and 17q21.31syndromes.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

There were two main recommendations.
1) *To take careful decisions for their future work in order to publish at the highest level.*
The overall level of publication is heterogenous with relatively numerous papers in journal of medium influence in the field
2) *To shift to the generation of new rat models better distinguish themselves from the competition.*
The report does not indicate any development of rat models (particularly in AD) of the pathology aimed at distinguishing the group from others in this very competitive field.

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	1
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)	5
Subtotal permanent personnel in active employment	**10**
Non-permanent teacher-researchers, researchers and associates	3
Non-permanent research supporting personnel (PAR)	0
Post-docs	3
PhD Students	6
Subtotal non-permanent personnel	12
Total	**22**

EVALUATION

Overall assessment of the team

The team is excellent. The team leader also leads the "mouse clinical institute" which is a reference in the field. The publications record is excellent quantitatively and very good qualitatively. Importantly many docs and post-docs are signing papers. The team was able to obtain numerous financial supports from national and international grants. The team has produced two patents and has strong interactions with industrial companies. Several members of the team coordinate european organisations/clusters. The team has strong non-academic interactions linked to the care of patients and contribute to many lay public exhibitions.

Strengths and possibilities linked to the context

The team is clearly an excellent group in the field of neurodevelopmental disorders and comorbidities. It is aimed at developing potential novel therapeutic probes. The main pathologies examined are Down syndrome, craniofacial and orodontal developmental disorders and others neurodegenerative and genetic diseases, including the 16p11.2 and 17q21.31syndromes. Because of its interest for Down syndrome, the team recently entered the field of Alzheimer's disease through the study of one of the risk factors identified for this pathology, namely BIN1 and also by studying Tau pathology and one of its phosphorylating kinases DYRK1A. The team has supervised numerous PhD and post-docs students who contributed to 32 original articles. The team has successfully responded to numerous contracts at national level (6 ANR, 1 FUI BPU France, 5 ICS-Celphadia-CNRS)…) and at the European level (4 on going-H2020, 1 IMI, 1, LEIT-BIO, 1 FP7 Health Innov…).

The study of all the above-described diseases has led to numerous publications. The team has produced 142 articles, of which 118 are original papers. A subset of them is published in high level journals of genetics such as PLoS Genetics. It should be noted that 33 papers are linked to methodological descriptions, new tools and diagnosis that could be seen as clues of team's creativity at the forefront of methodological advances. Part of the articles are published in top specialised journals in the field (Hum Mol Genet, Plos Genetics, Cell rep, NAR, Redox Biol…). However, many of them are also published in lower impact journals (J Med Chem, Front Pharmacol, Front Mol Neuroscience…).

The non-academic activities are outstanding. Two patents have been produced by the team for the "Treatment of Down Syndrome" and on the RHOA pathway in NDD. The team has developed interactions with the industry to develop a clinical probe for Down syndrome. The team leader is member of the board of the Gircor that links biological and medical research in France, and of the AFNOR/S96R "Biotechnologies" panel to define new international guidelines. One member of the team is expert for Sanofi-Aventis and another member of the team has developed a database and software in collaboration with the hospital of Strasbourg. The team members are involved in sharing knowledge and professional experience with high school students, through interventionsin the "Dialogue Between Researchers and High School Students for the Construction of Knowledge" days. They participated to the Telethon and Brain awareness day and other manisfestations (cafés de l'orientation, Ose la Recherche).

Weaknesses and risks linked to the context

Weaknesses are very few. Perhaps the team should reinforce the Alzheimer field and, in this context, strengthen its links with both fundamental scientists and clinicians. This remark could also stand for the Down syndrome field. Interplay with clinicians who can bring characterized cohorts could also be of help.

Concerning publications policy, the team has produced numerous (118) original papers. Some of them have been published in high level journals of genetics such as PLoS Genetics, American Journal of Human Genetics and Journal of Medical Genetics. However, many of them are also published in less visible journals that overall lead to a rather qualitatively heterogenous production (JMed Chem, Front Pharmacol, Front Mol Neuroscience…).

RECOMMENDATIONS TO THE TEAM

The team should pursue its excellent work to stay at the forefront in their fields and continue to develop industrial interactions.

Clinical interactions in DS and AD fields should be strengthened.

The team should aim at homogenizing the level of their publications.

Team 41: Pathophysiology of neuromuscular diseases

Name of the supervisor: Ms. Jocelyn Laporte

THEMES OF THE TEAM

The team is working on rare and severe neuromuscular diseases in particular myopapthy. Its work ranges from identification of novel mutations by NGS, validation of these hits using preclinical models, mechanistic analyses of the identified genes as well as identification of potential therapeutic targets. The work covers very wide aspects with impacts at the clinical level (genetic council and potential treatments) as well as in basic research.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The assessment of the team was highly positive. The team was recognised as outstanding in many aspects. It was recommended not to put much effort on NGS sequencing due to a potential lack of competitivity and to adapt the project with a particular focus on cellular aspect. This has not been completely followed but the team has been successful. The team has identified 10 new mutated genes in neuromuscular degeneration with some works focusing on cellular and molecular aspects.

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	2
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)	4
Subtotal permanent personnel in active employment	**7**
Non-permanent teacher-researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	2
Post-docs	1
PhD Students	6
Subtotal non-permanent personnel	11
Total	**18**

EVALUATION

Overall assessment of the team

This is an outstanding team, quite large and well-structured. It has a broad expertise ranging from clinics, genetics, and experimental models, translational and basic research. Overall, in terms of production, sharing and collaborations, the team meets a very high standard in quantity and in quality with some publications in journals with very broad audiences. Publications are well shared among members of the team. The team is also well funded. Regarding non-academic activities, the team also meets top standards with several patents licensed, creation of a start-up and interaction with lay audience.

Strengths and possibilities linked to the context

The team visibility is remarquable both at the national and international levels. The team has attacted eighteen PhD/postdoctoral fellows and eight staff scientists. The team obtained international funding from the Myotubular Trust (UK), the MD association (USA) as well as from international private donators. Excellent level of funding was also obtained by national agencies (FRM, ANR…) as well as charities (AFM). The team leader organised an international meeting (World Muscle Society 2017 (Saint Malo) gathering 700 persons, and the team leader and members wrote a total of 9 reviews. The team is part of a European PhD training network (ITN). The team also has a strong collaborative network that led to a total of 29 collaborative articles.

The team had an outsanding scientific production with 42 original articles (and 6 reviews) published as main contributors (last authorship) either in excellent specialised journals (Acta Neuropathol, Hum Mol Genet; Am J Hum Genet…) or in generalist journals (Nat Cell Biol, Sci Transl Med, JCI, Nat Comm, PNAS…). Using massive sequencing, the team has identified 10 mutated genes in different neuromuscular syndromes either as main authors (Am J Hum Genet, 2x Acta neuropathologica…) or as collaborators (Am J Hum Genet…). For some of these genes, the underlying mechanisms have been studied leading to important basic discoveries. They studied in detail the role of the myotubularin protein MTM 1 and showed that it acts as phosphoinositide phosphatases and is a key regulator of phosphoinositide conversion (Nature 2016, collaboration), participates in a complex that allows clearance of unfolded cytoskeletal protein aggregates (Nat Cell Biol 2018) and controlled focal adhesion (Sci Transl Med 2019). They have also generated and characterized 5 novel murine models (JCI insight 2020, Dis Model Mech 2020, Human Mol Genet 2019). They identified therapeutic targets as well as tamoxifen as a potential drug that improves myotubular myopathy (Nat Commun 2018, collaboration). They showed that down regulation of dynamin-DNM2 prevents and importantly reverts myotubular myopathy and also of several forms of centronuclear myopathies leading to the creation of the start-up Dynacure in 2016). Researchers and professors all published at least one publication as last author and all fifteen PhD students have at least one publication, thirteen having a first author publication. For the remaining two, the manuscript is in preparation.

Regarding interaction with society, the team obtained fundings from industries (Valerion (USA) and Dynacure) and tech transfert (SATT Alsace). They have issued seven patents, six being licensed. A start-up, Dynacure, has been created in 2016 based on the impact of dynamin-DNM2 on myotubular myopathy and several forms of centronuclear myopathies. Three members of the team care cofounders of Dynacure. The start-up is now gathering 20 people and hired former members of the team. In terms of translation to the clinics, the team is involved in drafting standards and recommendations and 3 clinical trials are based on the teams finding. New diagnostic approaches validated by the team has been transferred to diagnosis laboratories. The team is also involved in science dissemination with discussions with patients and conferences, had press release (Web and journals: Dernières Nouvelles d'Alsace, AFM/Téléthon, Myotubular Trust UK).

Weaknesses and risks linked to the context

The team may be more involved in international meeting organisation.

RECOMMENDATIONS TO THE TEAM

The team has done an oustanding work during this term both in term of scientific production and interaction with the society. It should follow on the same line with studies including both genetics, development of models and mechanistic analyses to publish in generalist journals with very broad audience and should keep its strong interactions with the clinics and industry.

Team 42: Genetics and pathophysiology of neurodevelopmental Disorders

Name of the supervisor: Ms. Amélie Piton and Mr. Hervé Moine

THEMES OF THE TEAM

The team is interested in delineating the genetic causes of neurodevelopmental disorders (NDDs) including intellectual disability (ID), autism-spectrum disorders (ASD), developmental and epileptic encephalopathy (DEE) and malformations of cortical development (MCD). The genetic causes of NDD are examined through genotype/phenotype correlations and the natural history of the patients. The pathophysiological mechanisms involved in certain frequent genetic mutations are studied (Fragile X syndrome, DYRK1A syndrome, etc).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was created in 2018. It was not evaluated in the previous report.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	2
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	**6**
Non-permanent teacher-researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	1
Post-docs	1
PhD Students	4
Subtotal non-permanent personnel	8
Total	**14**

EVALUATION

Overall assessment of the team

The team research is outstanding, making significant advances in the field of NDD and more precisely on the genetic causes and clinical consequences. The publication record of the team is outstanding both quantitatively (96 journal articles) and qualitatively (Nature Genetics, JAMA Neurol., Mov. Dis…). The team is highly attractive due to its international outreach and has been reinforced by the hosting of two PU-PH and four post-docs during the last four years. The team has several national and international collaborations and tight links with the clinics and particularly with the Strasbourg University Hospital. The team has connections with patients and charity organisations and participate to two to four events/year including family's days, money collects, update on research and treatments.

Strengths and possibilities linked to the context

The actual team is a new one that resulted from the merge of the groups of Jamel Chelly and Jean-Louis Mandel that occurred in 2018. Since 2020, the young team is headed by Amélie Piton (MCU-PH) and Hervé Moine (DR2-CNRS). This governance change did not alter the visibility and research quality of the team. The team is attractive and welcomed two PU-PH and 4 post-docs during the period. The team has national (IBPS, CRBM, etc) and international collaborations (Sick Children, DGIST, etc) and participates in different research and hospital networks. The team has obtained numerous competitive fundings from ANR, IUF and SATT amongst others.

The team made important advances in the field of NDD. They identified several novel genes, delineated the functional and clinical consequences of these candidate genes in various NDD, and developed bioinformatic tools to confirm the relevance of uncertain genes potentially involved in NDD. This has led to a really impressive amount (96 papers in which 44 by researchers of team as main authors) of data often published in high level journals such as Nature Genetics, PNAS, JAMA Neurol., Mov. Dis. etc... This publication record is well distributed within the members of the team, including PhD, postdoctoral fellowss and engineers.

The team has strong links with the socio-economic world and has obtained several patents. One concerns the possibility to design a conditional knock-in model in which a desired mutation can be introduced at any position in the gene and at any time and another one of X Fragile syndrome. Along with this side, the team has developed mice models but also developed human neural stem cells to transiently knock-down expression of genes involved in several NDD. The team also developed partnership with industrial partner (Lysogene) to develop gene therapy application for Fragile X syndrome. The team has strong links with the clinics and more particularly with the Strasbourg University Hospital. In this context, the team contributes to establish guidelines for variant interpretation and is involved in the formation of professionals in various networks. The team does not neglect the family organisations and charities, participates in two-four yearly events and coordinates the organisation of family meetings.

Weaknesses and risks linked to the context

No clear weakness identified

RECOMMENDATIONS TO THE TEAM

To correlate genetic observation with clinical pictures require a huge amont of patients to recruit in well characterized cohorts. Subsequent to this, the analysis of data could be difficut. The team should strengthen links with bioinformaticians and perharps help developing bioinformatic tools to validate and strengthen their genetic and functional data.

In the field of NDD, the huge amount of informations make difficult to follow all putative interesting tracks, partly due to limited staff and variety of functional read-outs. Perharps, the team should focus on a subset of target genes and deepen the functional/clinical approaches on these targets.

CONDUCT OF THE INTERVIEWS

Dates

Start: Monday October 10th 2022, at 08h30

End: Wednesday October 12th 2022, at 16h00

Interview conducted: on-site

INTERVIEW SCHEDULE

DAY 1, October 10th

8:45:- 9:00	Preliminary meeting of the expert committee (closed hearing) *Attending: expert committee, Scientific Officer (SO, Y. Graba, I. Attrée, MJ Stasia))*
9:00- 9:15	Presentation of the Hcéres evaluation to the unit (SO) *Attending: expert committee, SO, representatives of institutions and all unit members*
9:15 - 11:00	Presentation of the research unit by the unit director (including 30-45 min questions) *Attending: expert committee, SO, representatives of institutions and all unit members*
11:00 - 11:15	**Break**
11:15 - 12:15	Parallel meetings (3 sub-committees) - Meeting with technical and administrative personnel (in French) *Attending: Technicians, Engineers, Administrative staff, sub-committee 1 of expert committee, SO* - Meeting with thesis students and post-docs *Attending: PhD students and postdocs, sub-committee 2 of expert committee, SO* - Meeting with researchers and professors *Attending: Researchers except group leaders, sub-committee 3 of expert committee, SO*
12:15 - 14:00	**Lunch**
14:00 - 16:00	Committee debrief (closed hearing)
16:00-18:00	Parallel scientific team presentations (3 sub-committees/4 teams) 30 min/team (15 min presentation + 10 min questions + debriefing of the committee) *Attending: Team members, expert committee, SO, director of Unit, department heads, representatives of Institutions*
20:00	**Diner**

DAY 2, October 11th

9:00-10:30	Parallel scientific team presentations (3 sub-committees/3 teams) 30 min/team (15 min presentation + 10 min questions + debriefing of the committee) *Attending: Team members, expert committee, SO, director of Unit, department heads, representatives of Institutions*
10:30 - 10:45	**Break**
10:45 - 12:15	Parallel scientific team presentations (3 sub-committees/3 teams) 30 min/team (15 min presentation + 10 min questions + debriefing of the committee) *Attending: Team members, expert committee, SO, director of Unit, department heads, representatives of Institutions*
12:15 - 14:00	**Lunch**
14:00 - 16:00	Parallel scientific team presentations (3 sub-committees/4 teams)

	30 min/team (15 min presentation + 10 min questions + debriefing of the committee) *Attending: Team members, expert committee, SO, director of Unit, department heads, representatives of Institutions*
16:00 - 18:00	Sub-committees debrief (closed hearing)
20:00	**Diner**

DAY 3, October 12th

8:30 - 9:00	Parallel scientific team presentations (sub-committees 1 and 2) *Attending: Team members, expert committee, SO, director of Unit, department heads, representatives of Institutions*
9:00 - 10:00	Committee debrief (closed hearing) *Attending: expert committee, SO*
10:00 - 11:00	Meeting with the representatives of CNRS, Inserm and Unistra *Attending: expert committee, representatives of Institutions, SO*
11:00- 11:15	Break
11:15 - 12:15	Meeting of the Committee with the head of the unit. *Attending: Unit Director, expert committee, SO*
12:15 – 14:00	**Lunch (plateau repas)**
14:00 – 17:00	Final Committee deliberations (closed hearing) *Attending: expert committee, SO*

PARTICULAR POINT TO BE MENTIONNED

None

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 29 mars 2023

Objet: Rapport d'évaluation DER-PUR230023156 - IGBMC- Institut de génétique et de biologie moléculaire et cellulaire

Réf.: RB/FF/ 2023-193

Rémi Barillon
Vice-Président Recherche, formation doctorale et science ouverte

Cher Collègue,

Affaire suivie par:
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Responsable du département Administration de la recherche
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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 « Institut de génétique et de biologie moléculaire et cellulaire » (IGBMC - UMR 7104 / UMR_S 1258).

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

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