Research evaluation

# EVALUATION REPORT OF THE UNIT

CRSA – Centre de recherche Saint-Antoine

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

Sorbonne Université

Inserm

**EVALUATION CAMPAIGN 2023-2024**

GROUP D

Rapport publié le 29/02/2024

High Council for evaluation of research and highter education

In the name of the expert committee[1] :

Florence Apparailly, Chairwoman of the committee

For the Hcéres[2] :

Stéphane Le Bouler, acting president

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

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

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

## MEMBERS OF THE EXPERT COMMITTEE

| | |
|---|---|
| **Chairpersons:** | Présidente :<br>Ms Florence Apparailly Institut national de la santé et de la recherche médicale - INSERM<br>Vice-président :<br>Mr Philippe Lefebvre Université de Lille |
| **Experts:** | Mr Philippe Bonniaud, Université Dijon Bourgogne<br>Ms Sylvie Claeysen, Inserm, Montpellier<br>Mr Emmanuel Clave Université Paris Diderot - Paris 7 (supporting personnel)<br>Mr José Cohen, Université Paris Est Créteil<br>Ms Magali Cucchiarini Madry Saarland University Allemagne<br>Mr Lluis Fajas Coll UNIL Suisse<br>Ms Marie Joossens, Ghent University, Belgique<br>Ms Séverine Ledoux Assistance publique - Hôpitaux de Paris (representative of CNU)<br>Mr Frédéric Lemaigre Institut de Duve, Université catholique de Louvain Belgique<br>Mr Julien Marie Institut national de la santé et de la recherche médicale - INSERM<br>Mr Kiran Patil, University of Cambridge, Royaume-Uni<br>Mr Cliff Taggart Queen's University Belfast Royaume-Uni - Citoyen britannique<br>Mr David Tulasne, Inserm Lille<br>Mr Philippe Valet Université Toulouse 3 - Paul Sabatier - UPS<br>Ms Marieke Vonlindern Sanquin Research, and Landsteiner Laboratory Amsterdam UMC Pays-Bas |

## HCÉRES REPRESENTATIVE

Ms Sophie Ezine

## REPRESENTATIVE OF SUPERVISING INSTITUTIONS AND BODIES

# CHARACTERISATION OF THE UNIT

- Name: Centre de Recherche Saint-Antoine
- Acronym: CRSA
- Label and number: UMR_S938
- Composition of the executive team:

## SCIENTIFIC PANELS OF THE UNIT

SVE6: Human Physiology and Physiopathology, Ageing
SVE7: Prevention, Diagnosis and Treatment of Human Diseases
SVE4: Immunity, Infection and Immunotherapy

## THEMES OF THE UNIT

The CRSA comprises two scientific departments of 'Oncology-Hematology' and 'Metabolism-Inflammation'. Their research topics encompass a number of disciplines, ranging from hematological cancers, stem cell transplantation, cancer cell plasticity, chemoresistance, osteoarthritis, inflammatory bowel diseases, lipodystrophies, age-related neurodegenerative disorders, fetal and postnatal growth, cystic fibrosis to liver diseases. The common focus is to investigate (stem) cell biology and therapy, (epi)genetics, microbiota and microenvironment in a variety of pathological contexts. Their goals are to (1) uncover new mechanisms, (2) identify diagnostic and prognosis biomarkers, and (3) design novel therapeutic strategies for rare and common human pathologies with strong unmet medical needs.

## HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The CRSA was first created in 2009 jointly between INSERM and UPMC as UMR_S938. It was directed by Jacqueline Capeau during one mandate (2009–2013) and then by Bruno Fève during two mandates (2014–2023). The UMR_S938 is located on the campus of the hospital Saint Antoine, in the 12th district of Paris, and occupies two neighbouring buildings: an INSERM facility (named Kourilsky) which spans 3100m² on ten floors that underwent a complete renovation in 2016, and a building owned by the Faculty of Medicine, currently covering 378m2 for CRSA that needs to be renovated to reach 2916m2 soon.
The CRSA is currently composed of two scientific departments including thirteen research teams, 4 platforms, 7 core facilities including a centralized department in charge of administrative and financial management of the center. The next contract will involve the creation of a novel unit directed by Xavier Houard, with Loïc Guillot as the deputy director. This unit will be composed of twelve research teams which will no longer be divided into scientific departments.

## RESEARCH ENVIRONMENT OF THE UNIT

The UMR_S 938 is a health research unit jointly operated by INSERM and Sorbonne University. Its activities are tightly connected with several clinical departments belonging to the Tenon, Saint-Antoine, Trousseau and Pitié-Salpêtrière hospitals (gathered as 'Groupe APHP Est'): departments of Hepato-Gastroenterology, Oncology, Haematology, Rheumatology, Endocrinology, Cardiology, Internal medicine and Infectious diseases.
The vast majority of its PhD students (82%) are affiliated to the doctoral school ED394 'Physiology, Physiopathology and Therapeutics'. Almost all researchers have teaching duties at the faculties of medicine and/or science.
Through at least one of its teams, the CRSA is involved in several local and national federative research structures: the IHU ICAN (Foundation for Innovation in Cardiometabolism and Nutrition), the RHU CARMMA, the FHU PaCeMM (University Hospital Federation Paris Center for Microbiome Medicine), the LabEx Transimmunom and the Carnot Institute.
The CRSA received several prestigious national labels: Integrated cancer research site, SiRiC Curamus (Cancer United Research Associating Medicine, University & Society), FRM team (Fondation pour la Recherche Medicale), reference center for rare diseases (rare epilepsies, rare diseases of insulin secretion and insulin sensitivity, rare liver diseases) and two CRSA scientists are members of the National Academy of Medicine.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 63 |
| Maîtres de conférences et assimilés | 46 |
| Directeurs de recherche et assimilés | 8 |
| Chargés de recherche et assimilés | 28 |
| Personnels d'appui à la recherche | 82 |
| **Sous-total personnels permanents en activité** | **227** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 30 |
| Personnels d'appui non permanents | 50 |
| Post-doctorants | 7 |
| Doctorants | 66 |
| **Sous-total personnels non permanents en activité** | **153** |
| **Total personnels** | **380** |

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

| Nom de l'employeur | EC | C | PAR |
|---|---|---|---|
| SORBONNE UNIVERSITÉ | 128 | 0 | 42 |
| AUTRES | 14 | 15 | 46 |
| INSERM | 0 | 29 | 38 |
| **Total personnels** | **142** | **44** | **126** |

# GLOBAL ASSESSMENT

The Research Center Saint Antoine (CRSA) is a biomedical research center created in 2009 on the campus of the hospital Saint Antoine, and is located in two neighbouring buildings. The center promotes close interactions of its constituting teams with several clinical departments belonging to the Tenon, Saint-Antoine, Trousseau and Pitié-Salpêtrière hospitals (gathered as 'Groupe APHP Est') to foster highly translational research programs.
The CRSA is a large research center hosting about 420 staff members and is composed of thirteen teams, five of which are headed by women) organized in two scientific departments of 'Oncology-Hematology' and 'Metabolism-Inflammation'. They develop a strong program of translational research in the field of solid and hematological cancers (5 teams) and metabolism and inflammatory disorders (eight teams). During the past mandate, the unit has developed an interdisciplinary axis on microbiota and inflammation thanks to the integration of team 13. A well-organized administrative support team and platform-dedicated technicians and engineers provide essential support for research activities that could be improved with increased interactions with research teams and homogeneous policies and importantly with a visible, concrete support from supervisory bodies.

The CRSA has an annual operating budget of 8 M€ (14% recurrent funding, 86% external). Recurrent funding was globally stable over the mandate. Remarkably, the CRSA managed to increase by 73% of its external funding resources during the current six-year mandate. The CRSA has an excellent record of success to competitive national grants (as PI: 17 out of 34 ANR grants, 4 out of 5 INCa grants, 3 out of 3 ARC grants, 11 out of 11 LNCC grants, 11 out of 12 PHRC), 4 'labelling' grants from either FRM, LNCC or SiRiC and involvement in clinical trials (>45), thereby promoting competitive research. The participation to competitive and prestigious European research programs is outstanding (2 ERCs obtained by team 13 leader). However, the CRSA should build upon these successes to define a general strategy aiming at increasing its success rate as a coordinator/PI of competitive international and European grants (currently only 8/20 as PI, including 2 ERCs).
The attractiveness and national visibility of the institute are overall excellent. The tenured workforces have increased by 20%, with a majority of university teaching researchers, three full-time INSERM CRCN, and the integration of a novel team at the beginning of the mandate. The center is well embedded into structures of excellence including the IHU ICAN, the Institut Carnot OPALE, the PIA program RADICO, the FHU PaCeMM, the SIRIC Curamus, the LabEx TransImmunom, and the RHU ATRACTION. CRSA members are highly involved in national steering bodies (1 representative at the ITMO PMN, 3 members in CNU committees, 4 in ARC/LNCC/FRM/ANR, 1 president of FRM and 2 past presidents of EBMT/OARSI/SFR, as well as chairs or members of several scientific and executive committees of learned societies).

There is a high proportion of clinicians (50%), 37 full-time tenured researchers and 51 tenured technicians/engineers (23 are dedicated to common facilities). The gender balance is in favour of men in the DR/PU/PU-PH category (60%) while in favour of women in the CR/MCU/MCU-PH and ITA/BIATS categories (62%). The institute is an attractive place for junior researchers (recruitment of 3 CRCN Inserm, 5 associate professors and many universities/hospital lecturers) and PhDs (98 defended their thesis). However, the unit should define a strategy to attract more postdocs (currently averaging 18/year), especially from abroad.
The unit has developed state-of-the-art platforms (microscopy, cytometry, mass spectrometry, histology and animal facility) to support their translational research. There is a pressing need to establish a shared bioinformatics hub that will require the support of a dedicated, yet-to-be-recruited permanent staff. Of note, the two buildings hosting CRSA are of uneven quality in terms of health and safety issues and efforts must be made to ensure compliance with standard security and safety rules. At the international level, the center is highly involved in the participation (>100 presentations) and organization (15) of national and international meetings in their specialities and won numerous awards (>40).

The scientific production of the unit is overall excellent (outstanding for one team, excellent to outstanding for four teams). The level of publication is impressive relative to the size of the center: 4004 publications including 40% with first/last/corresponding authorship, 4.6% in outstanding journals and 22% in excellent journals (ICN=2.3). Of note, 40% of the publications involved at least two teams from the CRSA, emphasizing productive internal collaborations. Highlights described important discoveries of new immunological and metabolic mechanisms involved in cancer, inflammation and metabolic diseases published in the best speciality (Blood, Gut, Hepatology, Gastroenterol, Ann Rheum Dis, JAMA, NEJM, Lancet Oncol…) or generalist (Nat Commun, Science Transl Med, eLife.) high visibility journals. The CRSA should aim at increasing its rate of publication in generalist journals, which will participate in increasing its international visibility.

The interaction with the non-academic sector has increased during the mandate and is outstanding for 6 teams and excellent for three teams. In particular, the unit is highly active for the development of innovative therapies and diagnostic tools from their translational research in cancers, rheumatology, gastroenterology, cystic fibrosis, neuroinflammation and rare diseases such as imprinting disorders. The valorization stemming from their research activities is excellent, with 33 patents and the creation of four start-up companies developing novel therapeutic agents for osteoarthritis or inflammatory disorders (4MovingBioTech, Exeliom Biosciences) and diagnostic tools for infertility or cancers (MSInsight, Alifert). They obtained several grants for industrial maturation of their clinical

research activities from the SATT, IT and BPI (435k€). The center also obtained numerous research grants from, and forged partnership with, pharmaceutical companies (Pfizer, Roche, GSK, JANSSEN, Novartis, Nestlé), as well as AP-HP (>3M€ in total). The center has employed various methods and tools, such as its website, Twitter, radio, TV, and press, to effectively communicate and promote their research activities to a lay audience.

The unit should pay attention to keep the balance between fundamental and clinical research, and to improve the level of publications in journal of general audience. The CRSA should maintain its momentum in seeking external funding to enhance the advancement of competitive and interdisciplinary research. The unit should continue their excellent technology transfer activity. Nonetheless, they have an opportunity to increase international visibility and attractiveness by capitalizing on their excellence through increased participation to European research projects and networks and by recruiting internationally-renown PIs on important unifying topics for the center (such as inflammation and metabolism). The center should strive to achieve a gender balance in leadership positions, such as heads of teams and center directors.

In conclusion, the CRSA is an excellent biomedical translational research center ideally positioned at the national level, with a strong potential towards clinical applications. However, there is room for further expansion and increased visibility of its activities at the international level.

# DETAILED EVALUATION OF THE UNIT

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

The previous HCERES evaluation recommended to the CRSA to implement several actions aiming at unifying its identity. Precisely, they advised (1) that team members of the two axes apply jointly for grants, (2) to attract a new team that should catalyze merging both research axes, (3) to reinforce collaborations between teams, and (4) to organize Journal club and seminars between PhD, and monthly meetings to bring all people together. Most of these recommendations have been taken into account. The integration of the team 13 was successful in terms of amplifying cohesion and partnership between several teams of the CRSA. Several prestigious grants have been obtained by at least two teams of the CRSA (5 teams are members of the FHU PaCeMM, three teams are members of the IHU ICAN…). Increased cohesion between both departments was promoted by funding projects between teams using the unit's common budget. The success of this scientific politic is demonstrated by the production of 44% of the publications implicating teams from both departments and by 72% increase of fund-raising in five years (mostly national grants). This facilitated increasing the common budget share and the acquisition of new equipment. The cohesion of 'Oncology-Hematology' department with the 'Metabolism-Inflammation' department is also illustrated by the award of the SiRiC labelling that includes all five teams of the former and two teams of the later.
The CRSA has also mutualized administrative and financial management. A club of young non-tenured researchers has been created to organize work in progress sessions between students and PIs, to prepare M2 students to auditions for thesis competitions, and to organize a welcome day for newcomers. A two-days annual meeting is jointly organized by young scientists and engineers of the CRSA. Regular meetings gathering all the center staff around internal seminars remain to be organized.
They were also asked to develop strategies aiming at increasing support to research by (1) creating an iPSC facility, (2) expanding animal facility, (3) making more effort on the management of technical platforms, and (4) renovating the buildings. Again, most of these recommendations have been taken into account. Indeed, the CRSA has participated to set up a novel core facility for iPSC thanks to the involvement of three CRSA teams with the IHU ICAN. The PIs of the novel team 13 raised a prestigious European funding (ERC CoG) that allowed developing new technological platforms. One engineer is in charge of the entire fleet of equipment at CRSA. The INSERM building and animal facility have been entirely renovated.
The previous committee also mentioned the low number of PhDs and HDR. Several members of the CRSA staff have defended their HDR (32) and the average number of trained PhD students has slightly risen from 10–12 to sixteen per year.
The remaining recommendation has not been implemented at CRSA during the mandate: (1) establishment of an office dealing with regulation and policies to speed up translation to clinic, (2) a person in charge of international visibility, (3) a global strategy to promote young researchers, (4) a deputy director to support the actual director, and (5) enhancement of connections with public bodies by the Onco-Hematology department.

## B – EVALUATION AREAS

Considering the references defined in the unit's evaluation guidelines, the committee ensures that a distinction is made on the outstanding elements for strengths or weaknesses. Each point is documented by observable facts including the elements from the portfolio. The committee assesses if the unit's results are consistent with its activity profile.

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

#### Assessment on the scientific objectives of the unit

The CRSA is an excellent multidisciplinary center with many successful translational programs relying on efficient and tight links between research departments and clinicians, all located in close vicinity.

## Assessment on the unit's resources

This excellent center is very successful in raising grants, at the national level, obtaining industrial resources and recruiting permanent researchers. The center is split into two different buildings with heterogeneous housing conditions. However, the strategy for obtaining international funding and hiring external PIs are lacking.

## Assessment on the functioning of the unit

General organization and management are very good and generally complies with the recommendations of governing bodies. Gender equity awareness, environmental impact of research activities, some health and safety aspects, top to bottom communication, and the frequency of common scientific meetings are insufficient.

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

#### Strengths and possibilities linked to the context

The center is engaged in strong translational research with an important diversity of expertise. The CRSA succeeded in attracting new groups, team and scientists, in optimizing the global organization of both the center and research teams. They developed new fruitful collaborations with medical departments and research teams outside the CRSA.
They produced up to 4000 publications with 4.6% in outstanding and 22% in excellent journals, among which 40% are signed as first, last or corresponding authors. Cohesion between and within both departments has been developed thanks to specific funding from the unit's common budget and is demonstrated by the 44% publications implicating teams from both departments.

#### Weaknesses and risks linked to the context

Disciplines covered by the center are still very heterogeneous. There is still neither a clear definition of a common scientific objective nor a strategy developed to unify goals, to strengthen cohesion between the twelve teams, and to promote international visibility.

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

#### Strengths and possibilities linked to the context

The implication of clinical researchers is important. Location on the campus Saint Antoine, which provides close and easy interactions with hospital departments provides an excellent research environment. The Kourilsky Inserm building has been entirely renovated and more space has been allocated at the faculty of Medicine building. The core facilities and technological platforms seem to be well equipped and new core facilities and platforms have been created. Excellent progress on optimizing the management of the core facilities and platforms has been achieved. Resources have massively increased and teams are well funded (+73% in 5 years). The tenured workforce has increased by 20%, with a majority of university teaching researchers, three full-time INSERM researchers, and the arrival of a novel team (Team Seksik&Sokol). Finally, the scientific animation is dynamic, especially the one relying on the young scientists' club.

#### Weaknesses and risks linked to the context

The new space allocated at the faculty of Medicine building is not yet entirely renovated. It neither ensures optimal relocation of teams and platforms nor proper health and safety conditions. The surface of the animal facility seems to be undersized for the current projects. There is still a lack of critical mass of immunologists and of recruitment of external PIs. Except for the two ERC grants of Harry Sokol, the amount of funding raised through European agencies remains limited.
The team of the future head of the CRSA lacks a full-time research scientist and this situation may hamper the team structuration and progress.

The CRSA does not always provide a gender-balanced support for carrier promotion.

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

### Strengths and possibilities linked to the context

The renovation of the entire Kourilsky building provides up-to-date work environment in terms of safety standards. One engineer is in charge of the entire fleet of equipment, which optimized safety management. The visibility of the CRSA has been increased thanks to a novel website and one person is in charge of the scientific animation. They have launched a Young researchers' club gathering master students, PhD and postdoctoral fellows, which is in charge of scientific outreach events (such as Fête de la Science), work-in progress sessions for PhD projects of the center, training sessions to prepare Master students to doctoral school contest, annual retreat of the CRSA and other social events.

### Weaknesses and risks linked to the context

The organigram of the 'Collective facilities and technological platforms' only mention the names for the scientific directors, while sparing the names of the operational managers, which is a strong drawback for the carrier promotion of ITA/BIATS working on those platforms. There are also no clear specifications concerning the future requirement for technicians and engineers to replace the 12% tenured support staff which will retire. There is a lack of precision concerning the recruitment strategy for the next mandate and how to reinforce understaffed teams. There are no clear actions proposed to promote carrier development, especially for young researchers, clinicians, female scientists and support staff. The parity between women and men is not respected in the bodies of the CRSA and there is no specific plan for increasing gender equality and promoting diversity. There are also no specific actions proposed concerning the environmental impact of research activities.

Similarly, there is no common policy to protect scientific assets.

Importantly, there are no indication on how the work load and different duties will be distributed between the director and deputy director.

There are no weekly internal seminars gathering all the center and most of the scientific meetings are not in English. The center should contemplate the organization of an international workshop on-site.

## EVALUATION AREA 2: ATTRACTIVENESS

### Assessment on the attractiveness of the unit

Attractiveness is excellent as demonstrated by the award of two European grants, hiring new tenured researchers and lecturers, invitations and awards. There is, however, a lack of international visibility and a relatively low number of international postdocs and students.

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

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

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

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

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

The CRSA attracted the team of Philippe Seksik & Harry Sokol, which brought new expertise in microbiota and gut inflammation. This was a strong asset to foster cohesion between teams and to successfully apply to ERC CoG. Three researchers successfully passed the INSERM competition to obtain a tenured position of 'chargé de recherche classe normale'. On average, eighteen post-doc, sixteen PhD and 33 Master 2 students have been trained each year by the CRSA teams.

European grants (ERC and EBMT) were obtained by two teams. The CRSA was granted six ANR as PI, four INCa, and other institutional awards and recognition. Furthermore, prestigious labels (IHU, RHU, FHU, LabEx, SiRiC, FRM and LNCC labelled teams…) and national and international scientific societies and charity funds (Fondation Alzheimer, Fondation de France, VLM,…) were obtained by the members.
The international visibility of CRSA members can also be appreciated by the numerous invitations at international meetings as keynote speakers, as chairs of organizing committees and as editorial board members of scientific journals.

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

It is unclear how CRSA promotes the emergence of young leaders, taking into account gender. The CRSA may provide an environment insufficiently appealing for women. The CRSA entirely relies on the doctoral schools to raise awareness on integrity and ethical research. Calls to attract young researchers and leaders from abroad are underscored. There is a heterogeneous success between teams in obtaining national and European competitive grants as well as in national and international visibility of the PIs.

## EVALUATION AREA 3: SCIENTIFIC PRODUCTION

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

The CRSA has an excellent to outstanding production, quantitatively impressive, with a high level of international and national collaborations albeit with variability between teams. The translational nature of the research predominantly leads to publications in specialized rather than in generalist journals.

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

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

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

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

The unit has an impressive productivity (4004 publications, 1601 CRSA-led studies and 1097 CRSA-affiliated corresponding authors and with about half of the papers involving a national or international collaboration). CRSA scientific production is generally correlated to staffing of the teams, but must be weighted with the clinical/translational aspect of the research project(s).
Publications as lead authorship are found in generalist journals such as The Lancet, Nature Comm., NEJM and highly esteemed speciality journals such as Gut, Diabetes, J. Hepatology, JAMA Oncol, Ann Rheum Dis, Blood … and they reach the highest international audience. The unit has put much effort in publishing at the highest level (4.6% of all publications in the top 1% citation) and in avoiding predatory journals, with about half of the papers involving a national or international collaboration. The use of social media is on the rise to ensure a larger audience for CRSA research. While research teams show heterogeneity, CRSA has clearly increased cross-disciplinary collaboration across teams, emphasizing the emergence of new innovative research areas. This is particularly noticeable with the emergence of microbiota and to a lesser extent of fibrosis as 'research interfaces', with the (potential) use of novel technologies such as the gut-mimicking SHIME system. At the

quantitative level, these increased privileged collaborations are also noticeable and could be used as a guideline to reinforce interactions.
When considering the total FTEs of the scientific staff, the mean scientific production is roughly three CRSA-led papers/FTE/year. This ratio is fully compatible with a qualitative production, ensuring that articles are highly cited (4% of total CRSA production). The Inserm DESP analysis of the CRSA scientific publications showed that both quantitative and qualitative parameters characterizing total publications (4004) are unevenly distributed between teams, but not to the two research departments. This is only partially correlated to the size of the team and reflects the collaborative network which varies between teams, as the percentage of CRSA-led studies (on the basis of first, last and corresponding authorship) is evenly distributed between teams (average: 36%, median 38%). PhD students publish, on average, 4 papers with 1 first-author paper regardless of the team and are associated with 29% of published papers. Post-doctoral fellows are also associated to publications, being first authors in 42% of relevant publications.
A website is actively maintained, as well as communication in social networks, to appropriately publicize CRSA scientific and other activities. General rules for authorship in the unit impose a specific attention to the author's position of young researchers and of research support staff, which are known sources of conflict and of psychosocial risk in many labs. Open access publication is favoured and most of the papers are deposited in HAL (the common open archive platform chosen by French research establishments, universities and Grandes Ecoles). CRSA acts in close interaction with the animal facility director and follows French regulatory rules from ethical rules to staff training for animal experimentation.

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

Although general rules have been laid down by the unit to ensure results irrefutability, rules described (or not) by each team to fulfil this goal seems to be heterogenous, varying from weekly meetings with discussion of experimental data to undescribed procedures. The editorial policy for optimum recognition of research is ensured, besides peer-reviewed papers, by other modes of communications contributing to research visibility (invited conferences, posters, books…). These means are used within the unit with, however, a noticeable discrepancy between teams (for example participation to congresses ranging from less than 5 to more 50 total). Same applies to posters which may reflect a low participation of young researchers to result discussion/diffusion and to international scientific events.
The contribution of postdoctoral fellows to publications is low (less than 50 identified papers) and related to their low numbers within the institute and teams. Authorship rules seem to be varying between teams, with some claiming considering only the true contribution of authors, while other privileging young and senior authors as first and last authors.
As mentioned above, the unit policy requires the consignment of experimental data by appropriate means. A team-by-team assessment indicates, however, that data storage relies on varying practices, ranging from NAS storage to personal external hard drives to ill-defined or undescribed procedures. There is no mention of a general unit's policy towards FAIR principles of data reuse.

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

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

The CRSA showed an outstanding activity exemplified by patent applications, start-up creations, clinical trials, in connection with industry, and public outreach.

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

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

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

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

The unit has engaged into multiple interactions with the socio-economic world. Long-lasting and well-financed interactions with big pharmas and other companies (Pfizer, Roche, Servier, Stago, Ramsay…) are noticeable

and underline the reliability of several teams of the unit in that matter. At the translational level, the unit is an ERN-coordinated reference center for rare diseases (rare epilepsies, rare diseases of insulin secretion and insulin sensitivity, rare liver diseases) favouring access to unique biological resources. Links with patient advocacy groups and lay public are maintained through fact-based websites and other communication channels (seminars to patient association, continuous formation, TV programs, high school animations…) to which young researchers and engineers participate. Finally, several unit members are connected to policy-makers, ensuring a direct link with governing bodies and the public healthcare system.
Strong relationships are established with hospitals, biotechnology and pharma companies, through numerous clinical trials, biomarkers and other diagnostic tool identification/validation. There is significant cashback for these initiatives as about 20% of the budget unit is coming from contracts with industry and PhD CIFRE contracts are obtained. Thirty-eight patents have been filled by the unit, and 4 spinoffs emerged from a few teams. Scientific expertise is also provided to companies, charities and public agencies by many senior members of the unit.
Team members have engaged in a number of mediatic and social events to promote their research and collect funds, from TV shows, radio broadcasts to printed press. A review has been carried out on how to increase CRSA visibility to the lay public.

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

Valorization endeavours induce a significant administrative burden, and the unit is not providing specific support to the teams through internal specialized support that could include a specific data management plan.
While each team contributes to CRSA outreach, again a general policy and organization seems to be lacking at the unit level, increasing the burden of such activities on scientific activities. A communication officer would be a plus in CRSA organization.

# ANALYSIS OF THE UNIT'S TRAJECTORY

The CRSA will continue and emphasize translational research programs.

Efforts should be emphasized by the new direction to consolidate the current momentum and to more accurately specify coherent global scientific objectives and targeted missions of the CRSA. This should be fully elaborated by the new direction team.

The people:
The direction will change with a new director and deputy director who proposed to split their duties based on their respective affiliations and expertise. However, this executive team should reflect the strong clinical orientation of the center and the gender balance within the center. Thus, the committee advises promoting a female clinician to help the future director.

The program:
CRSA members decided to dissolve the structuration into two departments and rather to build on their multidisciplinary teams to carry on the translational biomedical research. The leadership of five teams will change for the next contract, which unfortunately reduced the number of female team leaders to three out of twelve. Propositions aiming at increasing gender equity in the center at this level are, however, not yet matured. They also plan to attract a new team with specific expertise in cancer immunology to further increase interactions between teams. An international call should be launched.

Improvements:
The CRSA proposes to set up a novel core facility for bioinformatics (although not entirely defined) and to create two new coordinating committees (Ecological and societal transition; Ethics, scientific integrity, and conflict prevention). They have been selected by INSERM as pilot 'green CRSA'.
The participation of teams to the common budget will increase from 5 to 7.5%, to support common equipment purchase and foster synergistic projects. There is a willingness to gather platforms in a unique location to increase their visibility.
They wish to develop CRSA international visibility through a strategy that still needs to be determined. The willingness to organize on-site international meetings is strongly encouraged, as well as the use of English as a scientific communication language.
In the future, the direction of two teams will be shared between the actual PI and a new co-leader (teams 5 and 7), three teams will be headed by a novel PI (teams 2, 3 and 11) and one team will be led by two new leaders (team 6). The added value of the co-leaderships and/or synergy between two leaders was not always well justified. Except for team 2, and to a lesser extent for teams 3 and 6, the new team leaders have demonstrated a strong ability to anticipate and plan the projects to be undertaken. Their competence is grounded in their high-level scientific achievements.

# RECOMMENDATIONS TO THE UNIT

## Recommendations regarding the Evaluation

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

CRSA needs more support to 1) guarantee completion of administrative, financial and HR formalities in due time, 2) speed up the renovation of the faculty building (including a common room to foster interactions between members from the 2 separated buildings), and 3) fix health and security issues ($CO_2$ supply, confined culture rooms, unstable temperature affecting experiments' reproducibility and human wellbeing).

The executive committee should ensure direct and optimal top-to-bottom communication. The center should implement measures for 1) better integration of new incomers (especially foreigners), 2) acquisition of leadership skills, 3) implementing English for communication, 4) creating weekly internal seminars and journal clubs, and 5) support all staff for career progression (especially for support staff and by providing them with visibility in the organigram).

As already mentioned in 2018 by the evaluation committee, specific measures should be implemented to solve rapidly gender and diversity imbalances at the executive level of the organization (team leaders, decision-making bodies and direction of CRSA). Creating an EDI committee is recommended. Because of the high-translational aspects of the center research, we recommend nominating a female clinician as additional deputy director of the CRSA. Promoting gender equity involves addressing biases, providing mentorship and support for underrepresented genders, and creating a work environment where everyone's contributions are valued.

The center should re-evaluate its current strategy to build a bio-informatic hub. Allocation of part of the center common budget might be necessary to ensure stability of the recruited staff and to structure the bioinformatics community within the center.

## Recommendations regarding the Evaluation Area 2: Attractiveness

Since the visibility of the strongest teams is not reflected at the center level, the committee recommends developing the international visibility of the CRSA based on specific actions. For instance, we suggest creating an international environment within the center, to implement English for internal science communication, and to create a one-to-one mentorship for new incomers.

The center should build upon existing successful internal experience and networks, as well as resources from governing bodies to help PIs to apply to international calls (ERC, H2020…). The researchers should increase their international network with the specific goal to participate in international consortia.

The center should revise their strategy to provide an attractive starting package welcoming young external scientists.

## Recommendations regarding Evaluation Area 3: Scientific Production

The center is encouraged to continue its dynamic policy of publication, trying to target generalist journals to improve their visibility. The CRSA should pay attention to ensure all PhD and postdocs to be properly rewarded in authorship.

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

The center is encouraged to continue maintaining actions towards translating fundamental research into clinical applications, and to pursue public outreach activities. Patient organizations need to be involved in their global strategy.
Patent application and industrial valorization could be increased at the center level by using the experience and success of some teams.

# TEAM-BY-TEAM OR THEME ASSESSMENT

**Team 1:** Microsatellite Instability and Cancers

Name of the supervisor: Alex DUVAL

## THEMES OF THE TEAM

The team aims to improve diagnosis and treatment of the Microsatellite Instability (MSI) cancers with a focus on metastatic colorectal cancer (mCRC). They developed a diagnostic tool using NGS, which identifies MSI in mCRC. The team tested Immune checkpoint inhibitors (ICI) that emerged as an effective therapy against MSI mCRC. The team investigated DNA and RNA signatures to predict the response to ICI. Two signatures, highlighting the microenvironment and a small subset of microsatellite variants, were predictive for resistance to ICI. Specifically, the T17 polymorphism in HSP100, which controls HSP100 splicing, appears to affect the outcome of ICI treatment. This HSP100 variant is also involved in modification of the tumour stroma. In a broader perspective, the team identifies dramatic modifications of gene-splicing in MSI due to instability of polypyrimidine tracts around splice sites.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Previous recommendations were to complement the current analyses with immunopeptidome approaches to correlate MSI alterations with the expression of neoantigens. This was not followed up, but with the strong genetic background of the team, the suggestion of performing in-depth study of alternative splicing due to MSI, and the analysis of target genes, is understandably not a priority.
The team leader was advised to launch functional studies through collaborative approaches. The team has followed up this advice particularly they analysed the effect of MSI on mRNA splicing, which yielded information on alternative splicing of specific genes, the consequences of which were further investigated.
Regarding international networking, the team was recommended to think about how to integrate European networks (e.g. take the leadership of the organization of a small-scale cost network, participate or take the lead on an EU grant application). Although the attractiveness of the team is excellent, with many invited talks and publications with international colleagues, this has not led to European grants.
Regarding team management, it was recommended to provide a formal statement on if and how the team leader envisions to promote the researchers in his team (e.g. senior author publication, PI on grant applications, etc.). Although 2/3 of the grants were obtained by the team leader, from the five ongoing grants, three are obtained by the team leader, the other two by two distinct researchers in the team. Senior authorship on manuscripts are also held by various researchers of the team.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 6 |
| Maîtres de conférences et assimilés | 6 |
| Directeurs de recherche et assimilés | 1 |
| Chargés de recherche et assimilés | 1 |
| Personnels d'appui à la recherche | 4 |
| **Sous-total personnels permanents en activité** | **18** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 3 |
| Personnels d'appui non permanents | 2 |
| Post-doctorants | 0 |
| Doctorants | 5 |
| **Sous-total personnels non permanents en activité** | **10** |
| **Total personnels** | **28** |

# EVALUATION

## Overall assessment of the team

This team is scientifically excellent to outstanding with highly relevant work on microsatellite instability in cancer that is very well cited. The team has a high level of production with many publications in excellent journals of discipline (JAMA and NEJM).
The attractiveness is excellent with the recruitment of seven PhD students, two postdocs, one lecturer and one engineer. The team secured twelve national grants (INCa, BMS…) and competitive national labels. The team is well connected to national networks involved in research, diagnosis and treatment of cancer and could improve its international visibility by engagements in European networks and grants.
The achievement in valorisation and translational is outstanding. The team has four ongoing patents and created a start-up (MSInsight). There are excellent connections to the clinic as assessed by the involvement in several clinical trials at the national level. They truly cover bench to bedside and reverse. Finally, the team does engage in public outreach through blogs, videos and several educational book chapters.

## Strengths and possibilities linked to the context

The expertise of the team on CRC MSI together with the technologic pipelines developed by the team are major assets to extend MSI study on pan-cancer. Despite the international competition, the current and effective CRC patient treatment with ICI offers the opportunity to develop theragnostic tools together with a deeper understanding of the involvement of the tumour microenvironment. Recent development of single cell technologies is well adapted for these objectives.
The team encompasses twelve hospital practitioners and is well embedded in clinical practice. In 2022 the tenured team members are two researchers, two lecturers, twelve hospital practitioners (10 of which lecturers), and two technicians. The non-tenured staff consists of one emeritus volunteer, two researchers, one hospital practitioner and lecturer, 4 technicians, five PhD students and five M2 students. Seven PhD students successfully defended their thesis.
The team produced papers, particularly on the effectiveness of ICI in MSI cancer. They contributed to 409 publications that are very well cited (ICN=2.1), of which 154 as first (52), last (120) or corresponding (109) author, and many publications in excellent journals of discipline. Sixteen are published in visible journals (including JAMA and NEJM). Among these publications 217 (53%) arise from national collaborations and 170 (42%) from international collaborations.
The team secured more than 5 M€ during the period thanks to twelve national grants as PI (Cancéropole, Plan Cancer, ARC) or partner (INCa, LNCC, BMS, MSD...), obtained a label by the national league against cancer (330KE). They obtained SIRIC program CURAMUS, with a major involvement of the team, which is a great opportunity to develop ambitious projects, especially if collaboration with the two other teams working on cancer is developed.
Team members collectively organised a first international meeting on MSI in cancer, which will take place soon. Eight PIs were invited to talk at twenty international conferences and seventeen national conferences, which demonstrates excellent international visibility.
The team has four ongoing patents and submitted three additional patents during the evaluation period. The patents are being exploited through a start-up (MSInsight) that several team members have founded. With excellent connections to the clinic, the team is involved in several clinical trials at the national level. They truly cover bench to bedside and reverse.
The bioinformatics core that processes large amounts of genetic data is an asset.

## Weaknesses and risks linked to the context

Eight grants were obtained by the team leader, the four others were obtained by two distinct PIs. The few grants obtained by the full-time researchers of the team suggest that their visibility is limited with the risk of limiting the impact of the functional studies. In addition, most grants cover the translational research and are related to clinical trials.
Several key studies presented as main achievements are still in preparation (not accepted). The team focuses more on the genetic aspects of MSI than on immunological aspects.
A link to patient organisations is missing.
The impressive visibility of the team leader has not led to international (European) grants, which may reflect a lack of networking with international researchers, whereas networking with clinicians is excellent.
Training by research remains weak considering HDR number (7 PhD defended/12 HDR).

## Analysis of the team's trajectory

The team trajectory is divided in two main axes; first deciphering novel aspect of MSI-driven tumorigenesis including the tumour microenvironment and second improving MSI diagnosis and theragnosis in pan-cancer.

The first axe is directly related to the previous studies of the team with thus solid preliminary data. This axe involves functional analyses. The characterization of aberrant splicing in MSI by high-throughput long read RNA seq is particularly pertinent. A functional focus on a specific aberrant splicing could have been included. The specific study o CBF2 loss of function is a good illustration of focus functional study which could help to understand MSI-driven tumorigenic pathway. The study of the MSI tumour microenvironment notably by image analysis in a unique large cohort is also pertinent. Single transcriptomic analyses could be included. Importantly, in the last part of the trajectory, these studies lead to the proposition of novel therapeutic strategies, which underlines the potential benefits of the project.
It would help, however, to state a clear aim of these more fundamental studies and to set priorities such that the aim can be met. In the current proposal, the team will study how MSI induces differential splicing, the p53 stress pathways, DNA damage responses, the role of transcription factor CBF2, and the role of the microenvironment. All of these are major research topics. However, there is a risk that all topics are touched too superficially. In addition, it would be good to know who leads which study. The second axe, which aims to improve MSI diagnosis and theragnosis in pan-cancer is ambitious, but take advantage of the cohort, the expertise and technological pipelines of the team. A more precise description of the cohorts could be included. The use of AI to interpret omics data seems entirely appropriate, although the contribution of these technologies could be clarified. The approaches in the second, more translational, axes are closely related to the approaches taken in previous. However, it is not clearly described how the different parts are connected and will profit from each other.
Overall, the trajectory is ambitious and pertinent in both translational and fundamental research but could be improved by clearly formulated objectives and a better description of the coherence. The team leader has the expertise and the experience to drive such an ambitious project which is in part already financed.

# RECOMMENDATIONS TO THE TEAM

The fundamental studies cover several major research fields (splicing, mRNA translation, unfolded protein response, DNA damage repair and cellular responses to DNA damage). It seems that the team wants to cover many aspects of MSI. This is, however, overambitious. It may be better to choose in which aspects the team wants to further develop its excellence. In addition, clear aims and objectives may better indicate the feasibility of specific projects in this program. In this line, it would be important to keep the well balance between clinic and functional studies to ensure the translational strengths of the team.
Study of MSI in pan-cancer context is enthusiastic and challenging with the requirement of constitution of dedicated cohorts and necessity to develop new models for functional studies. It's not clear if single cell technologies for high throughput studies are settled in the scientific environment of the team.

**Team 2:** TGF-β signalling in cellular plasticity and cancer

Name of the supervisor: Céline PRUNIER

## THEMES OF THE TEAM

The team aims at deciphering the mechanisms leading to tumour progression and metastasis formation with a focus on TGF-b signalling. The team investigated the effects of either the E3 ubiquitin ligase or extracellular vesicles on TGF-b signalling pathways as well as the link between the plasma membrane protein recycling (particularly the protein NME) and KIF20A in cancer progression.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous evaluation pointed out that the team was a new team headed by a young PI. Having this in mind, the HCERES made several recommendations. Based on the origin of the construction of the team (the former PI took a position abroad, and Dr Prunier took the head of the team) and on its first structuration, it was recommended to focus on the topics of investigation of the team to avoid segregation and to increase the PI animation to create unicity. This point has been partially taken in consideration. The topics addressed during the evaluated period were very eclectic. Progress seems to be made in the new trajectory, but the real unicity is still missing. The animation part of the PI seems still very weak. The previous expertise recommended increasing the number of PhD students, which has been done. The same HCERES committee strengthened a lack of economic/social valorisation and very few participation to international meetings. However, this point has not been addressed yet. Finally, the previous evaluation pointed out a lack of connection with the clinics. Although the team hosts several PU-PH and MCU-PH, the self-assessment of the team considers interactions with the clinics limited to some collaborations and suggests an improvement. In sum, the recommendations have not been ignored but only partially addressed.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 2 |
| Maîtres de conférences et assimilés | 2 |
| Directeurs de recherche et assimilés | 1 |
| Chargés de recherche et assimilés | 4 |
| Personnels d'appui à la recherche | 2 |
| **Sous-total personnels permanents en activité** | **11** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 0 |
| Personnels d'appui non permanents | 1 |
| Post-doctorants | 0 |
| Doctorants | 3 |
| **Sous-total personnels non permanents en activité** | **4** |
| **Total personnels** | **15** |

# EVALUATION

## Overall assessment of the team

The scientific production of the team is good as they contributed to several publications during the contract period. Although the team is endowed with a significant number of full-time researchers, the scientific production straight from the team remains quite limited.
The visibility of the team is good; members contributed to the society through exchanges with a large public audience. They raised local and national funding and collaborated with local and international teams for other grants. The team applied to several grants but with a low rate of success. Also, the team work is not well cited and very few international invitations are noted.
There is no valorisation activity.

### Strengths and possibilities linked to the context

The team is endowed with an important number of permanent researchers (4 CR +1 DR and 4 professors and associated) as well as of one permanent PAR. The team developed different approaches to invalidate genes in cell lines, such as CRISPR Cas9, siRNA, and to monitor protein-protein interactions. In addition, xenograft models of intraductal breast cancer and wound healing mouse models were developed as well as chemical approaches for iridium chelatant, allowing the team to address the role of 1) WWP1 in actin remodelling, 2) NME1/4 in cancer progression, and 3) exosome containing FGF2, as well as to propose a way to couple drugs to iridium for future therapeutic approaches.
Six publications with a last author position for three different senior researchers of this team have been published including works in Scientific Reports, BMC Biol. Oncogen and Dalton Trans. The team raised some local funding from different associations and was associated with collaborative INCa and ANR programs allowing mainly to secure some staff salaries. Six PhD students defended during this period. Through mainly its axis on iridium, the team is involved in the SIRIC CURAMUS.

### Weaknesses and risks linked to the context

The ratio between the researcher number and the number of publications from this lab remains weak. In addition, we noticed that the lack of unicity, underlined in the previous evaluation, is still there. This lack of focus in research leads to reduced visibility of the team. The PI animation and publications as last or corresponding author, as well as the lack of topic unicity, suggest that the team is composed of several autonomous groups having their own money and topics and working separately from each other. Translational research in the team is still limited, notably in regard to the scientific policy of the center.

### Analysis of the team's trajectory

For the next period, the team proposes to keep investigating its main topics and adds an interesting and innovative new axis. It is noteworthy that the project trajectory is really too broad without any unicity. More than three types of cancers will be analyzed, and their number will not decline throughout the 4 axes of the project. A form of unicity can be found around TGF-b/TGF-b signalling but without enough logic link. A new PI will lead the team, at least transiently.

# RECOMMENDATIONS TO THE TEAM

Though the 2018 evaluation already mentioned it, important efforts still need to be done to create a better unicity within the team, both at the topic research and its structuration.
In addition, the visibility of the team still needs to be improved by increasing not only the number of publications and national and international grants but also the international meeting attendance. A strategy needs to be rapidly proposed to increase the production of the several researchers of the team. Strategy to improve the unicity needs to be improved as well as the ones to increase the visibility of the team. A strategy to improve the translational research should also be implemented for instance by recruiting clinicians.
The committee is aware that the current head of the team has not been present on site since May 2023 and that her return is not scheduled yet. An alternative head is currently taking the lead. We recommend anticipating the restructuration of this team, irrelevant of the return or not of the current head. Opening towards the clinics as suggested by the CRSA direction could be a trajectory but other options should also be envisaged.

**Team 3:** Cancer Biology and Therapeutics

Name of the supervisor: Michèle SABBAH

## THEMES OF THE TEAM

The team CaVITE is conducting several projects in the area of cancer, vascular biology and also develops new drugs or drug combinations. Due to the recent pandemic, the team has also pushed forward a new theme that is centred on the effects of COVID-19 contamination in cancer patients but also in the general population. CaVITE is composed of three groups addressing 1 – the interconnections between cancer, vascular environment, hypercoagulability and thrombosis, 2 – the cancer cell plasticity, the cross talks with the microenvironment, and 3 – the development of new drugs and drug combinations.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

It was recommended to the team to emphasize its scientific independence from the industry and to increase research quality of the projects and publications. The number of publications of clinical research projects that were conducted is high, and there is still an impression that this part of the team's activity is driven by pharmaceutical companies. Only 20% of the budget is from national competitive calls, with a limited number of European or national grants, a percentage that remained low despite previous recommendations by Hceres to increase this part. A clarification has been made concerning the leadership of the team as Dr G. Gerotziafas will become the unique team leader during the next contract. A fair repartition of the five technical staff within the three axes has been engaged as recommended. Regarding the scientific strategy, it was recommended to reduce the number of topics and subtopics. Despite the increase in the research staff of the team, the number of projects/sub-projects remained relatively high, and the novel project on COVID-19 (which is actually of high added value) added more to this dispersion. Though collaborations with other teams from the unit are numerous, recommended collaboration with Team 02 for the EMT studies could have been further accentuated.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 12 |
| Maîtres de conférences et assimilés | 5 |
| Directeurs de recherche et assimilés | 2 |
| Chargés de recherche et assimilés | 1 |
| Personnels d'appui à la recherche | 4 |
| **Sous-total personnels permanents en activité** | **24** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 4 |
| Personnels d'appui non permanents | 4 |
| Post-doctorants | 1 |
| Doctorants | 11 |
| **Sous-total personnels non permanents en activité** | **20** |
| **Total personnels** | **44** |

# EVALUATION

## Overall assessment of the team

The scientific production is excellent (>600, 37% as first, corresponding or last author in speciality journals), but not in highly cited journals, with the exception of some papers (Clin cancer Res, Annals Oncol, Autophagy). Although there are many clinical papers, most of them are not directly related to the 'in-house' fundamental projects.
The attractiveness is very good with new researchers in each axis. Numerous collaborations and high capacity to raise funding (50% coming from the industry). The number of competitive national and European grants remains null. The valorisation activity is very good, especially for the clinical and industrial aspects.

## Strengths and possibilities linked to the context

The International reputation and visibility of the team are based on the recognition of the team leaders in their respective field that is attested by many communications in national and international meetings. The Team also benefits from important European networks, especially for the clinical studies. Since 2017, the team has published a significant number of articles and reviews (over 640) with a good balance between groups, which is representative of the different projects that are developed and a rhythm of publication that is more than satisfactory. Of note some studies with senior authorship have been published in excellent generalist and speciality journals (JEM, Autophagy, Clinical Cancer Res, Leukemia, and Annals of Oncology as part of the ESMO Guidelines Committee). Some members of the team were also investigators of large clinical trials published in top-level journals (Lancet, New England Journal of Medicine, Annals of Oncology, etc.). The team has shown its capacity to obtain extensive funding (Gefluc, Cancer Sein…) with more than 2,200 kE, the major part of it coming from the industrial/private sector (47% including Boehringer) or from associations (32%).
The team has addressed pertinent questions regarding Cancer Associated Thrombosis, Resistance to targeted therapies and Primary healthcare intervention for COVID-19 associated hypercoagulability both at the fundamental and clinical levels, demonstrating its capacity to conduct large-scale translational research programs as exemplified by the development of the COMPASS-CAT score.
Dissemination of scientific results and knowledge to the public is primarily ensured by a significant number of national and international communications as well as recommendations that have been approved by health agencies.

## Weaknesses and risks linked to the context

Despite its good attractiveness, the team displays a rather low ratio between the number of students and senior scientists dedicated to their full-time supervision. Also, only two PhD students out of six who defended their thesis have a first author publication. The number of postdocs is relatively low for such a large team. Despite the quality of the project, the number of sub-projects is probably too important and does not facilitate focusing the expertise of the CaVITE team on high impact 'in-house' studies that may be published in top-level journals. While the number of publications is excellent, only a few of them with corresponding and/or leader authorship have been published in highly cited journals. Despite the potential of fund-raising (3 GEFLUC), the number of major public grants from INCa, ANR, Ligue or from the EU remains null. Finally, although one group dedicates its research to the development of new drugs and drug combinations, there is no mention of patent application.

## Analysis of the team's trajectory

For the next contract, Dr G. Gerotziafas will take the leadership of the team, which will ensure a smooth transition with Dr M. Sabbah. Though a novel organigram is proposed for the next mandate with the creation of the 'resistance, virus and cancer' group, the project will not change much in its global objectives. Most of the fundamental and clinical projects/sub-projects studying the relationships between cancer, angiogenesis and thrombosis, the tumour stromal cross-talk and the development of new drugs and drug combinations will be continued. Contrary to what has been recommended by the previous evaluation, the absence of significant reduction in the number of projects may represent a risk of dispersal and may not guarantee to increase the level of publications. Moreover, based on the investigations that were conducted during the COVID-19 pandemic, the results that were obtained on COVID-19-mediated vascular complications, and the structuration of the 'réseau Obépine', the team has decided to push forward this project in the next contract with the development of a network for primary healthcare of patients with COVID-19 at risk of disease worsening. This ambitious translational project will include AI-based technologies and databanks that will help to monitor the spreading of the pandemics and propose adapted healthcare. Despite its obvious high interest, it is difficult to evaluate the direct connection of this 'virology & public health' project with the other projects that will be

conducted by the two other groups, which does not really facilitate collaborations and may further add dispersal. Awareness regarding the need to increase the level of publications and the number of academic competitive funding (ANR, INCa, etc.) has led to pragmatic proposals that should lead to an effective amelioration of these parameters. A particular attention has been paid to students who will be recruited during the next contract with a series of measures that should facilitate the publication of their work in due course. Existing collaborations and networks will be maintained and reinforced which is definitely helpful for the visibility of the CaVITE team.

## RECOMMENDATIONS TO THE TEAM

The team is encouraged to further reduce the number of projects in order to focus on the expertise of the different groups/team members on cutting-edge translational research programs that could lead to high impact publications and facilitate collaborations within groups. The team has to implement its strategy to increase the number of competitive academic funding in order to maintain/increase its attractiveness and its visibility. The team should also increase the number of post-docs and/or of permanent scientific staff in order to ensure the supervision of the M2 and PhD students. Clinicians should develop more 'in house' clinical/translational studies originating from fundamental projects that are conducted within each group to further guarantee the scientific independence of the team.

**Team 4:** Hematopoietic and leukemic development: diseases and cell therapy

Name of the supervisor: François DELHOMMEAU

## THEMES OF THE TEAM

The team has two major themes: 1/'Nonmalignant hematopoiesis', which is mainly dedicated to erythropoiesis and production and maintenance of hematopoietic stem cells, which includes establishing hematopoiesis from induced pluripotent stem cells (iPSC) and 2/'Malignant myeloid diseases', which is focused on AML and within AML on (i) predisposition in paediatric AML (ii) on the evolution of mutations (occurrence of subsequent mutations and selection of clones), (iii) on mutation of p53 specifically, and (iv) on BM failure and subsequent AML development (for instance in Shwachman Diamond Syndrome (SDS).

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was recommended to enhance collaborations and participation in large projects, and to better define cooperation with the hospital. Two collaborations are now highlighted. Moreover the team has developed tight collaborations with expert platforms and teams at Gustave Roussy Institute (cell sorting, gene transfer, genomics and bioinformatics), Orsay (ribosome profiling), Cochin Institute (single cell analysis), Saint-Louis Hematology Institute (single cell DNAseq), as well as Team 5 at CRSA (57 collaborative publications).
They were asked to develop their outreach activity. The team has now set up a number of initiatives aimed at the general public and educational actions.
Since it was a very young team, integration and synergy between the axes were recommended to be further developed. Interaction have improved within and between the two axes of the team. Moreover, the new unit trajectory has a strong focus, which will further improve interactions.
The team was asked to improve its organization by setting up a weekly meeting and by organising journal clubs. The team as set up weekly laboratory meetings with all members to discuss the progress of each scientific project.
As the research field is very competitive, the team members working on haematological malignancies were advised to find a niche that is innovative and successful and that distinguishes them from the rest of the clonal evolution field of research. The team has made such choices, particularly in their study on SDS, clonal selection in AML, and the specific focus on red cells in studying the role of the microenvironment in AML.
They were advised to increase collaboration with other groups in the field. This is very well taken up in the 'optical twins' project, but could still be improved in other projects, such as studying the disease mechanism in SDS.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 8 |
| Maîtres de conférences et assimilés | 6 |
| Directeurs de recherche et assimilés | 0 |
| Chargés de recherche et assimilés | 3 |
| Personnels d'appui à la recherche | 6 |
| **Sous-total personnels permanents en activité** | **23** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 2 |
| Personnels d'appui non permanents | 2 |
| Post-doctorants | 0 |
| Doctorants | 7 |
| **Sous-total personnels non permanents en activité** | **11** |
| **Total personnels** | **34** |

# EVALUATION

## Overall assessment of the team

The scientific contribution is very good to excellent with 368 publications of which 88 as first, last or corresponding author in the best journals of biology and haematology.
The attractiveness is very good to excellent with five invitations to international conferences (2 PIs) and sixteen to national conferences (5 PIs). Three group leaders joined the team, however training is not optimal. Funding were obtained by INCa, the Blood Bank, FDF and local grants.
The valorisation and translational research are very good. Two patents were obtained for the production of cultured hematopoietic stem cells and red blood cells.

## Strengths and possibilities linked to the context

The team performs a highly relevant work on non-malignant haematopoiesis and acute myeloid leukemia. The team underwent major changes in the last 6 years. Just before the evaluation period (in 2016) Prof. Luc Douay left to found a company (Erypharm). During the evaluation period, two group leaders were recruited: Y. Zermati and A. Paldi. In 2022 Prof. Emeritus T. Soussi joined the team. These changes enabled the team to revise and restructure their research program. In 2022 the tenured team members are three full-time researchers, 4 lecturers, fourteen hospital practitioners (10 of which lecturers), and 1 technician. The non-tenured staff consists of one researcher, two hospital practitioners, two engineers, eight PhD students and two M2 students.
The team has actively built a coherent research program combining the strength and opportunities that were brought to the team by the new group leaders with the successful research lines that were previously existing in the team. The team has developed several innovative research lines as exemplified by its fundamental research program that combines several expertise to study the role of the microenvironment in AML, and specifically the role of red blood cells. This is a promising and novel field for which the team is well equipped.

The team was very productive with very well-cited publications (ICN=2), in excellent journals of Biology and haematology specialities (Blood, Hematologica, JID, PLOS Biology, Leukemia). Overall the team published 368 papers with among them 88 (24%) as 1st, last or corresponding author. Four percent of the papers are considered as outstanding and half of the paper are published with international co-authors. Among the 368 published papers, 275 (75%) are original articles, two are book chapters, fifteen are Editorials, 49 are letters and 26 are reviews.

The team obtained many national grants. The total financial resources (4,000 k€) are covered for 85% (3,400 k€) by grants including as PI, PRTK INCa (224kE) and Conect-AML (482kE) or partner in one ANR (74kE) projects. The team strengthened collaborations in consortia that were funded: PAIR Pediatric INCa and the Tumor Heterogeneity in the Ecosystem Aviesan program (EcoAML project).

The translational activity of the team focuses on genetic screens on large cohorts of patients to develop novel diagnostic tests. This work is facilitated by a strong connection with the clinic, as indicated by the large number of hospital practitioners. The team joined the laboratory LABCOM Optical Twins For Diagnosis, which is expected to supply high-resolution microscopy coupled to artificial intelligence in the cytomorphologic diagnosis of AML. The team reaches out to AML patient organizations by giving information on the disease and therapy on websites and in videos. Two lay publications were published.

## Weaknesses and risks linked to the context

The team holds two patents (one on the production of cultured red blood cells, and one on the production of improved transplantation of hematopoietic stem cells by increasing the number of HSC with long-term repopulation ability in the graft). Both patents were approved in 2018 but are not yet licensed. There are no patents or industry contracts based on the diagnostic assays that are being developed.

After the departure of Dr L. Douay, the team has found a new expert in erythropoiesis that initially finished ongoing research lines that were not always connected to the other research lines of the team. The threat of new research islands has been turned into the opportunity of innovative research by new collaborations, particularly for the research line involving erythropoiesis.

The topic 'Langerhans cell histiocytosis (LCH)' seems distinct from the rest of the program. It is stated that the researcher driving this line fits the team because the focus is on the hematopoietic aspect of LCH.

Although the team has secured many grants and contributed to many top discipline papers from international studies, international (European) consortium grants are still lacking.

Although the team has three full-time researchers and currently encompasses eight PhD students, only three theses were defended and there was only one post-doctoral fellow who stayed for a very short period.

Their translational activity and patents did not lead to contracts with industry or to a star – up creation.

### Analysis of the team's trajectory

The team has decided to refocus its objectives on the axis of myeloid malignancies with two main groups: 1) 'Translational research on myeloid malignancies' and 2) 'Basic research on myeloid malignancies'. The coherence of this program is depicted in a clear scheme.

The translational research aims '*to develop diagnostic tools, follow up tools, and treatment strategies for myeloid malignancies*'. The four projects consist in (i) genetic diagnostics of AML, (ii) optical diagnostics using advanced microscopy, (iii) haematopoiesis in Langerhans cell histiocytosis, and (iv) the production of HSC from iPSC to treat AML. Projects 1 and 2 are related to each other and directly address current and future diagnostics. The development of '*optical twins for diagnosis of AML*' is a collaboration with several (external) partners and involves advanced integration of technologies. Whereas projects 1–3 are described with sufficient details, project 4 is very brief in its description and remains vague. It is unclear whether the team will focus on the production of HSC or cultured red blood cells. To reach its objectives, the team may have to focus on one of these projects.

The fundamental research line on AML consists of five projects that all focus on the accumulation of mutations in HSCs, the selection of (combinations of) mutations and subsequent clonal haematopoiesis. This is a common thread through the different projects: (i) disease mechanism in Shwachmann Diamond Syndrome (SDS) (ii) p53 mutations in AML, (iii) the origins of paediatric AML (iv) the role of the microenvironment in AML, and (v) the role of metabolism in AML development. SDS is one of several BM failure condition that often develops to clonal AML. AML development is characterised by loss of p53 (the 2nd project in this line) and it is a congenital disease resulting in pediatric AML (the 3rd project). How the development of AML and the selection of mutations that enable AML development urgently need to be addressed. It also deserves mentioning that the project on the role of the microenvironment in AML combines expertise in erythropoiesis and in AML. The role of red blood cells in immune modulation, and as a 'sink' for cytokines is timely and innovative.

## RECOMMENDATIONS TO THE TEAM

The team should try to increase its attractiveness and international visibility, as well as the level of its scientific production. The team should strengthen its international network by taking part in European consortia that apply to international grants. The team has a fair number of full-time researchers to allow supervising more PhD students during the next mandate. They should also try to recruit young scientists (postdocs and CRCN).
The research line on SDS seems to lack interaction with patients' organisation, which is of particular importance when working on rare congenital diseases. The hematopoietic aspect of LCH and the specific aim of this research line could be better articulated.

**Team 5:** Graft-versus-Host Reactions after Allogeneic Hematopoietic Stem Cell Transplantation

Name of the supervisor: Mohamad MOHTY

## THEMES OF THE TEAM

The team investigates the evolution of the immune system in patients with haematological malignancies where different clinical settings and therapeutic approaches coexist. Firstly, chemotherapy or targeted therapy are administered. In case of failure or insufficient response, these patients receive an allogeneic hematopoietic stem cell transplantation (alloHSCT) from a healthy donor. In both cases, the immune system, either of the own patient for first-line treatments, or of the donor after alloHSCT, plays a crucial role in the anti-tumour response.
In transplanted patients, one axis of research consists in evaluating the impact of patients conditioning on gamma delta T cell reconstitution and the consequences for EBV-induced complications. Another axis aimed at evaluating a treatment of chronic GVHD with Rituximab. Such clinical trial represented an opportunity to study and better understand the evolution of interactions between B cells and follicular helper T cells during treatment. One of the team's leading areas of research is the impact of changes of microbiota on the anti-tumour response of transplanted patients. The team also developed a clinical trial of autologous faecal microbiota transplantation in patients treated for acute myeloid leukemia with intensive chemotherapy.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The recommendations made following the previous evaluation were globally poorly documented, probably reflecting the few weak points of the team in 2017.

A first one relied on the need for standardization of biological material collected as part of clinical trials. This recommendation can be made to any team working on such patient cohorts. Given the team leader's position on various international networks (as former president of the European Society for Blood and Marrow transplantation, EBMT or co-founder and current chair of the executive committee of the International Academy for Clinical Hematology, IACH), and the large number of studies from the EBMT in which the team is involved, this recommendation no longer seems appropriate.
It was suggested that the program between Sorbonne University and the China Scholarship Council be strengthened and better exploited. There is no mention of progress on this issue, only one previous Chinese PhD student is mentioned (defended in 2019). This project seems to be hampered by administrative issues.
The basic research team was considered to be relatively small and it was recommended to increase the number of full-time researchers (postdoc and CR). The committee notes no change on this point during the evaluated period.
The last recommendation relied on the need to prioritize the different projects. In the present document, the different projects are very homogeneous, all focusing on the cross talk between the immune system and the anti-tumour response in haematological malignancies using coherent approaches in which the team now has a validated expertise. They all stem from the clinical activities of the team leader's medical department.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 3 |
| Maîtres de conférences et assimilés | 1 |
| Directeurs de recherche et assimilés | 0 |
| Chargés de recherche et assimilés | 1 |
| Personnels d'appui à la recherche | 5 |
| **Sous-total personnels permanents en activité** | **10** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 4 |
| Personnels d'appui non permanents | 21 |
| Post-doctorants | 0 |
| Doctorants | 3 |
| **Sous-total personnels non permanents en activité** | **28** |
| **Total personnels** | **38** |

# EVALUATION

## Overall assessment of the team

This is an excellent to outstanding team, participating in highly relevant data and knowledge in the field of clinical research and clinical trials and, quantitatively to a lesser extent, in the field of basic/translational research. The team has an international profile and an excellent to outstanding levels of production. It has contributed to over 500 publications, of which 50% as first, last or corresponding author, and 5% in the outstanding ranking journals in the field (Blood) or in more generalist journals (Nature Commun, Lancet…).
This impressive list of publications underlines the team leader's central position in France and abroad, attested by a high frequency of publications in collaboration with French and foreign teams. The team has an important and growing ability to raise funds for five years, from academic organizations on very competitive calls or from charities and industry.
The research team is essentially made of hospital/university staff, with only part-time dedicated to research and a single full-time researcher. Support in terms of engineer/technicians is marginal.
This team is reinforced by a very important support structure called 'EBMT group' which probably explains the very high number of publications.
The team's attractiveness is outstanding: its director was head of the European marrow transplant network, and it has obtained a significant number of highly competitive grants. Despite the elevated financial capacities of the team, there was a limited number of PhD students and no postdoc trained.
Valorisation capacities of the team are also outstanding as attested by 4 patents, their participation as a member of the SAB of MaaTPharma, financial support from industry and clinical trials developments.

## Strengths and possibilities linked to the context

The team has been very successful in developing original and innovative research. For this, it relied on its core activity of therapeutic management of patients with malignant hemopathies and its ability to assess innovative therapeutic approaches in clinic and to develop ancillary studies on these cohorts of patients. This global approach has given rise to new knowledge that could potentially subsequently give rise to innovative and targeted therapies. As an example, the clinical trial evaluating the effect of Rituximab on chronic GvHD contributed to increasing the knowledge on the B-TFH interactions in this pathophysiological context.
Also, a PhD student evaluated in alloHSCT patients, the impact of the conditioning on gamma delta T cell reconstitution and the consequences for EBV-induced complications. This will lead to the development of a new project focused on MAIT cells in the same setting.
Another key step for the team was to identify changes in the microbiota in alloHSCT patients and to develop autologous faecal microbiota transplantations (AFMT) to normalize the microbiota in patients receiving chemotherapy for the treatment of AML. Here again, this work has led to the forthcoming development of a new European, randomized clinical trial to evaluate the impact of FMT on GVHD and overall survival.
Overall, this team represents an example of coherence between clinical activity and academic research.
The team has successfully obtained competitive funding as PI, as evidenced by very competitive PHRC-K (5 obtained) or more recently from private companies (Jansen, GSK, MaaTPharma). This team globally is giving itself the means of achieving its ambitions.
The team leader is largely invested and very active in the organization of international networks. He was the former president of the EBMT and is the co-founder and the chair of the executive committee of the International Academy for Clinical Hematology (IACH) focused to promote good clinical practice in the field of clinical hematology. This gives to the team leader an outstanding international visibility. All these elements obviously contribute to the team's impressive list of publications as well as to the very large number of collaborative works with teams from the CRSA, from France or abroad.
Team sustainability seems to be on the team leader's mind. It is noteworthy that for the next contract, Prof F. Malard will be a co-team leader of the team with Prof Mohty. Prof Malard has a good track record and international visibility. Both received worldwide invitation to give lectures in their field of clinic and research expertise.

## Weaknesses and risks linked to the context

An obvious weakness of the team is the absence of post-doctoral researchers. This point is particularly difficult to understand as the team has an important ability to raise funds for its projects and its international visibility should allow it to recruit excellent candidates. This is a key point to be consolidated for several reasons: the team is essentially composed of hospital/University researchers with a limited time devoted to research, there is only one full-time researcher. This considerably limits the possibility for this team to better exploit data from clinical trials and clinical studies towards more fundamental research and to propose new hypothesis. This limits the

possibility of identifying promising researchers to help them consolidate their profile with a view to a permanent research status. This probably also limits the number of PhD students due to a lack of management capacity. Also, technical support for this team is marginal and unrelated to the team's activity and production.

### Analysis of the team's trajectory

The team's overall trajectory is clear and coherent. It is based for the most part on the results obtained from the work carried out during the current mandate and consequently to their extension. Three axes are clearly identified:
The results obtained from the rituximab clinical trial showed that although PD-L1hi naive B cells were significantly decreased at diagnosis of chronic GVHD, they increased after anti-CD20 B cell depletion. In contrast, activated ICOShiPD-1hi circulating Tfh cells decreased after rituximab treatment. The team aims now to evaluate whether the efficacy of rituximab in chronic GVHD may, in part, be related to a direct effect on PD-L1hi B cells and Tfh cells.
Mention is also made of the development of a more clinically relevant mouse model of GVHD. It is planned to use such a model to evaluate new therapeutic approaches based, for example, on the use of arsenic trioxide (originally developed for the treatment of lupus) to prevent chronic GVHD or Venetoclax, to assess the compatibility of its direct anti-tumour effect with the maintenance of an anti-tumour T cell-based immune response. The evaluation of innovative therapeutic approaches in mouse models seems to be a new direction for the team. While scientifically coherent, this approach is very time- and cost-consuming.
*Biomonitoring:*
Mention is made of a sampling circuit for transplanted patients. This cohort has been successfully exploited in the past, leading to better characterization of the post-alloHSCT immune reconstitution and associated publications. It would be instructive to understand if this cohort is only local, and if it will be consolidated through the next alloHSCT. Does the team also plan to use national (Cryostem) or international cohorts whose potency would probably be greater?
*Microbiota*
The strength, originality and visibility of the team are obviously based on its work on the microbiota and FMT in patients treated with intensive chemotherapy. The team plans to continue and extend this theme to alloHSCT, which is strongly encouraged.
Co-leadership
This team will be led by both profs Mohty and Malard, both with clinical activity. No detail on this co-leadership is mentioned neither in the new team structuration or in the team projects.
Finally, the team has recruited a junior professor in 2023 who is a clinical haematologist, expert in myeloma, and who will study the microbiota of patients treated by immunotherapies.

## RECOMMENDATIONS TO THE TEAM

The committee strongly recommends establishing a strategy for consolidating academic research by recruiting postdoc and full-time researchers. The committee is well aware of the difficulty with regard to the low number of recruitment at Inserm, CNRS or INRAe (microbiota) but this is an essential point for the sustainability of this team.
The committee also strongly recommends to clarify the role played by each co-leader of the new team.
The committee suggests giving the priority to pursuing and developing projects directly linked to the results obtained during this mandate and reinforce a continuum from basic research to clinic research and vice versa.
The committee also warns the team to assess the risk of dispersion by developing the same approaches but applied to other indications or therapeutic approaches (CART, bispecific antibodies, etc.). Even if this extension may seem natural and timely, it could lead to the dilution of human and financial resources.

**Team 6:** Metabolic diseases and age-related joint pathologies

Name of the supervisor: Francis BERENBAUM

## THEMES OF THE TEAM

The team studies the pathological mechanisms of osteoarthritis (OA) in various models (human/murine cell culture of chondrocyte hypertrophy; pain; murine spontaneous ageing, etc.) and clinical data (tissue/serum/synovial fluid analyses: biobank, omics, etc.) to develop disease-modifying (DMOADs) therapies. Four themes are investigated by four interactive subgroups: 1) identification of local actors of osteochondral junction remodelling, 2) deciphering and targeting cholinergic signalling to treat OA, 3) phenotyping OA-related pain through cohorts, omics, and machine learning approaches, and 4) valorisation and clinical research.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous recommendations were to maintain excellent scientific production and activities at the international level. The team successfully maintained its excellent international scientific production and activities with 274 articles (203 original articles, 36 reviews, 19 letters, 16 editorials in high impact speciality journals: Arthritis Rheumatol, Ann Rheum Dis, Nat Commun, Semin Arthritis Rheum, Lancet Rheumatol), of which 117 as leaders, with 100 invited conferences (SFR, ACR, OARSI, EULAR), with participation to the board of peer-reviewed journals (Ann Rheum Dis, Nat Rev Rheumatol), with three patents and one start-up, and with international funds (FOREUM, Horizon 2020).
It was also recommended to envisage Cifre grants with the industrial partners. None was obtained but a partnership is ongoing with 4P Pharma to support a PhD and to recruit an engineer and an M2 student.
Previous evaluation recommended reinforcing the workforce and to improve the team's life and organization by recruiting full-time researchers. The team still lacks a permanent full-time researcher.
It was also recommended to collaborate with immunologists. The team developed a collaboration with an immunologist (D. Klatzmann) and co-supervised a PhD student with an Associate Professor in Immunology (E. Marriotti-Ferrandiz).
Finally, it was recommended to keep the numbers of tasks consistent with the workforce. The middle-size team has a balanced number of senior and junior researchers and research support staff that makes it united, cohesive, and flexible.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 3 |
| Maîtres de conférences et assimilés | 3 |
| Directeurs de recherche et assimilés | 0 |
| Chargés de recherche et assimilés | 0 |
| Personnels d'appui à la recherche | 4 |
| **Sous-total personnels permanents en activité** | **10** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 1 |
| Personnels d'appui non permanents | 2 |
| Post-doctorants | 0 |
| Doctorants | 4 |
| **Sous-total personnels non permanents en activité** | **7** |
| **Total personnels** | **17** |

# EVALUATION

## Overall assessment of the team

The scientific production of the team is excellent and very well cited with 274 articles (117 as first, last or corresponding author) in Top 1 and 2 speciality journals (ARD, A&R) with high clinical potential related to the pathological mechanisms of OA (OA-associated hypertrophy, cholinergic system in OA).
The international visibility is excellent as revealed by 100 invited conferences, obtention of national (ANR, FRM) and European (H2020, Foreum) competitive grants, participation to national bodies for the structuration and evaluation of the research (ITMO, CNU, ANR panels), chair or member of several learned national and European societies (ACR, EULAR, OARSI, SFR) and national consortium (OA-Bio, ROAD and NetwOArk).
The attractiveness is excellent with hiring of one engineer and one technician, appointing one Professor and one Associate Professor. The team also hosted five postdocs and eight PhD students defended their thesis.
The valorisation is outstanding as assessed by filing three patents, creating a star-t-up, initiating a phase 1 clinical trial based on the team results and industrial grants. The societal valorisation is also outstanding.

## Strengths and possibilities linked to the context

The team is currently composed of 9 permanents and 27 temporary staff, including eleven PhD students and five post-doctoral fellows. It integrates researchers with a wide range of skills from very basic science to clinical studies who cooperate well in a collegial and cohesive environment.
The team is well integrated in the CRSA and collaborates with labs of Sorbonne Université and with the other teams (24 papers in collaboration with the other teams).
Attractiveness of the team is demonstrated by the arrival of one engineer and one technician (permanent positions) and two engineers, five postdocs (although none foreigners), eleven PhD students (although none foreigners), fourteen Master students, and fifteen other students (non-permanent positions) all significantly contributing to the scientific production of the team (of note most of them published research articles as 1st or co-authors). Importantly, during the period one Professor and one Associate Professor were appointed by the team. Attractiveness is also noted by 100 invited conferences as keynotes of all PIs of the team (SFR, ACR, OARSI, EULAR…), invitations in foreign institutes (UCSD, Scripps).
The team leader is an extremely dynamic opinion leader and its research work is internationally well-recognized in its domain with a record of publications.
During the period, despite the COVID19 pandemic, the team further developed important, innovative models and tools to study the pathophysiology of OA including pain, omics, bioinformatics, and machine learning, and published 274 articles among which 203 original articles, 36 reviews, nineteen letters, and sixteen editorials including high impact journals of arthritides as PIs (Nat Rev Rheum, Annals Rheum Dis, Arthritis & Rheum) that are highly cited. Of note, the team produced a series of high impacted publications reporting new phenotypic alterations in joint cells (intra-articular adipose tissues, prehypertrophic chondrocytes) (Ann Rheum Dis. 2017), new regulators of joint and systemic inflammation (Arthritis Rheumatol. 2020), new OA biomarkers (Nat Rev Rheumatol. 2018) and the use of new DMOADs associated with the creation of a start-up and the initiation of a phase 1 clinical trial (Sci Rep. 2022). The innovative nature of this research may have clinical utility to treat human OA.
More than 117 publications are signed as first, last or corresponding author by members of the team. These publications also include collaborations with the other teams (24) and with nationally (132) and internationally (121) recognized collaborators. All researchers contribute to transversal projects of the team as noted in the publication list that reflects a good balance between the different PIs, postdocs, and students from the team.
The national and international visibility of the team is obvious as shown by participation to the Board of highly regarded peer-reviewed journals (Ann Rheum Dis., Nat Rev Rheumatol.).
Despite the COVID19 pandemic, the team highly succeed in raising funds during the period 2017–2022 (4,909.5 k€) from various public (as PI: APHP, PHRC…) and charities sources (as PI: SFR, FRM…), as well as Europe (as PI: Foreum, 120kE, partner in 2 H2020).
The team was very active in establishing interactions with industrials (401 k€: Pfizer, Novartis, Servier, 4P Pharma, Ramsay Santé) and produced three patents (1 leading to the creation of the start-up 4Moving Biotech in 2021 and to a phase 1 clinical trial in knee OA), none licensed so far.
Team members received international and national awards (OARSI Annual Clinical Research Award, FRM Guillaumat-Piel Foundation Award, Elise Jourdevant International Prize).
The team is highly involved in training, including eleven PhD and five postdocs were hosted that are involved in publications. One PhD student has been recruited as a Postdoc.
The team is involved in various national and international networks as PIs (French Society of Rheumatology SFR, Fondation Arthritis, ROAD Network, Inserm NetwOArk, FOREUM, NetwOArk EU Cost action, Eurostars H2020 OA-BIO, Arthritis Foundation, EULAR, OARSI including Presidency, ACR) and with patients' organisations (AFPric, AFS, ANDARENsemble contre les Rhumatismes, SmartApp Hiboot+) and by invitations received by team members to

visit international labs (UCSD, Scripps La Jolla, HK Polytechnic University), to participate in and organize conferences (SFR, CNU, NAR, OARSI, ROAD Network, FRM, EULAR, ACR), to attend and present in conferences (100 invited conferences as keynotes).
Several members are also active in science spreading (Fête de la Science, Journées portes ouvertes de l'Inserm) and in communicating their findings and knowledge to mass media (Inserm content on OA, thematic OA issue in FRM magazine, special issue FRIF, Referential COFER, Le Monde, Santé Magazine, France 2, France 3, RTL, RFI, Europe 1, RTS; LinkedIn, Twitter…).

### Weaknesses and risks linked to the context

Although the team has been active in recruiting some new members, there is a lack of HDRs and of women representation in the leadership that would increase the size and reinforce both the workforce and the weight of this middle-size team in the CRSA. Most publications are in specialized journals. No full-time researcher has been secured yet and no foreigner students or postdocs were hosted. The involvement of one of the co-team leaders as new director of the CRSA is an additional risk to the new team structure.

### Analysis of the team's trajectory

The team's structure, under the leadership of Pr Francis Berenbaum, has been very active in deciphering the pathological mechanisms of human OA via disease modelling with the goal of finding new targets for therapy, including via critical collaborations. This work has enabled the team to evidence new interfaces and actors of OA signalling in particular for pain, with valorisation in clinical research.
The general trajectory of the team remains unchanged by focusing on the study of the pathology of osteoarthritis (OA) in human and animal OA models and using clinical data for OA therapy. Future new projects are also being developed on osteochondral remodelling via extracellular vesicles. And on the role of pollutants with endocrine disruptors on joint homeostasis and OA.
The team's reorganization with two co-PIs (clinician and scientist) will further support translational research and allow them to investigate new therapeutic strategies that will generate new perspectives in the understanding and treatment of OA. One of the team leaders will take on the role of CRSA Director.
Funding needs to be further secured by the new team leaders as the previous team leader (F. Berenbaum) will not be in charge anymore. The scientific objectives have strong translational potential, but the project (deciphering the pathological mechanisms of OA) is highly competitive.

## RECOMMENDATIONS TO THE TEAM

The committee recommends the team to continue the excellent research activities and projects.
The synergy between both new team leaders and main topics needs special attention.
The team leadership should recruit at least one full-time researcher and encourage permanent researchers of the team to apply for national and international funding, including at the European level, in order to adapt the size and competitiveness of the team to the project.
The team should include more women clinicians and/or scientists in the leadership for the next contract.
The team should reach more general journals in the future.

**Team 7:** Cystic Fibrosis Physiopathology and Phenogenomics

Name of the supervisor: Harriet CORVOL

## THEMES OF THE TEAM:

The team conducts basic and translational research project on Cystic Fibrosis that is focused on three main research lines: 1) a translational research project with the National Phenotypic Database allowing phenogenomics research by studying the molecular determinants of CF phenotypic variability; 2) the study of inflammatory pathways and the discovery of microRNA as potential anti-inflammatory therapeutic targets in CF (a work linked to the continuation of the work on the Anoctamin antisense oligonucleotide that blocks miR-9); and 3) the study of mechanisms involved in various CF lung infections. The team took advantage of the Covid period to develop a novel research program on Covid viral infection.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT:

In the previous report, it was recommended that the team increase the percentage of publications in high impact factor journals. In the new reporting period, the team has increased the number of first, senior and corresponding author papers from 56 to 119 with 5.8% of publications in high visible journals as Nat Commun or Lancet. This is a significant rise in the number of high impact publications. Previously, bioinformatics support was considered as a requirement for future development. In response to this, the team has established a productive bioinformatics collaboration with Prof PY Boëlle (Sorbonne University) and recruited a PhD student and a postdoc to help support this area of research. This is a positive step although more local support may still be required if the collaboration with Prof Boëlle cannot be maintained. Finally, it was previously recommended that development of new technologies such as the ANO antisense oligonucleotide and microRNA therapeutics should be advanced. The team has now established a spinoff company, ANOAT, to help developing the ANO ASO with the support of 2 million Euros in funding, an excellent step forward. The development of anti-inflammatory microRNAs is at the patenting stage.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 2 |
| Maîtres de conférences et assimilés | 2 |
| Directeurs de recherche et assimilés | 1 |
| Chargés de recherche et assimilés | 3 |
| Personnels d'appui à la recherche | 7 |
| **Sous-total personnels permanents en activité** | **15** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 2 |
| Personnels d'appui non permanents | 1 |
| Post-doctorants | 3 |
| Doctorants | 3 |
| **Sous-total personnels non permanents en activité** | **9** |
| **Total personnels** | **24** |

# EVALUATION

## Overall assessment of the team

The scientific contribution is excellent. The team produces highly relevant and very well cited CF work (ICN=3.2), with some high impact core papers in best speciality (J Cyst Fibrosis, Clin Infect Dis) and generalist journals as last author (Nat Commun, Lancet).
Attractiveness is excellent to outstanding. The team has increased its international visibility and has a significant number of national and international collaborations. There is a good balance between hospital and science researchers facilitating translational research projects. They have recruited four new researchers (including one Inserm CRCN) and hosted six postdocs and ten PhD (among which 7 defended their thesis). The team obtained two ANR as PI.
The valorisation is outstanding. The team has established a spinoff company, ANOAT Therapeutics, to develop the ANO1-ASO molecule. They obtained three patents. The PI is leading a CF national cohort.

## Strengths and possibilities linked to the context

This is still a very active but small team. It is well balanced between permanent senior scientists (4) and Professor or Associate Professor – Hosp Practitioners (2 + 2) and four hospital practitioners. The significant number of hospital practitioners helps with the development of translational studies within the team. The team is also well balanced with three permanent engineers. Among fifteen permanent members, there are nine female and six male staff. Six permanent members hold the HDR (Habilitation à diriger des recherches) certificate+ (one third of the permanent members). The scientific production is at a high-level relative to the small size of the team. Overall the team published 347 papers with among them 119 (34%) as 1st, last or corresponding author, 5.8% in high audience journals (Nat Com, Hepatology, Lancet),–6% of the papers are considered as highly cited (Hepatology, J Cyst Fibros) and 40% of the papers are published with international co-authors (Lancet Respir Med, Nat Com, Eur Resp J, …).

Among the 347 published papers, 265 (76%) are original articles, fourteen are editorials, 28 are letters and 37 are reviews. The team produced eight book chapters. The team also filed three patents between 2017 and 2022. The team has enhanced its visibility due to the increase in presentations at international meetings (with 15 invitations to give talks). The participation at national conferences is also at a significant level. The number of accepted posters for national and international conferences is high (77 posters).
The total income for the team is 3 million Euros coming from international and national grant organisations as well as charities. They obtained an international contract with the Cystic Fibrosis Foundation as PI (194kE, 2016–2018) and a European ERS-RESPIRE (207kE). Regarding national grant funding, the team had two ANR grants (98kE and 203 kE) as PI, One PHC FASIC. Other funding came from the PIA (Emergence SU IDEX) or Inserm Transfer for instance. The team obtained an impressive number of grants from foundation or charity associations (51 grants for a total amount of €2.4 million) as 21 VLM, Fondation Air Liquide, Legs Poix… It appears that there are currently three PhD students within the group with ongoing contracts and 7 PhDs who successfully defended their thesis. Therefore, a total of ten PhD students during the period. Among the 7 PhDs who achieved their thesis defence, all of them published as 1st author at least one Original Article (OA) or two reviews. Two of them published two OA with one PhD student publishing 4 OA and one published five OA as 1st author (one of these ex-PhD students is now a member of the research team).
There was a total of six postdocs during the period and currently there are three postdocs in the team. One of the postdocs became a researcher and has been recruited to the team by Inserm in 2021. We also identified two foreign visiting members (one from Roma, one from Yangzhou – China-).
The team has been awarded two local scientific distinction to two staff members. Two members of the team are members of the scientific committee of the patient association 'Vaincre la Mucoviscidose'. There is some evidence of patient contact and outreach: conferences like 'research meet patients' and events organized by the 'Vaincre la Mucoviscidose' association. Finally, a start-up company (ANOAT Therapeutics founded by Adbio) has been created by the team during the evaluation period to develop the ANO1 ASO.

## Weaknesses and risks linked to the context

Although the group's grant income is reasonable, there is a lack of international funding (outside of France) with a few exceptions (CFF). It would be important for the group to consider expanding their grant funding remit to other sources (EU, more CFF etc.).
There is a lack of engagement of the group with the Pharma industry. It would be of benefit to consider stronger ties to Pharma as a way to boost grant income and to engage in more applied research.

The lack of adult respiratory physicians may slow down the development of translational research regarding research trajectory on physiopathology and pulmonary infections in 'adult' respiratory diseases like COPD.
Although the team's production is very well cited and 103 publications are in Top1 and Top10 cited journals, a significant number of them are not driven by the team.
They have not organized any scientific meetings at national or international levels.

### Analysis of the team's trajectory

The team has decided to expand its field of interest and to open research to other chronic lung diseases including pneumonia opportunist lung infections and COPD in tandem with the very quickly evolving field of CFTR modulation. The team will modify its management with a shared leadership that will improve the already existing cohesion between the hospital and the lab unit. The name of the unit will therefore evolve to '5PMed': Pulmonary diseases, Pathogens, Physiopathology, Phenogenomics and Personalized Medicine. Three main work packages will be developed: 1) the WP 'Phenogenomics and Personalized medicine' will focus on the continuation of the phenotyping activity and the follow-up of the patient cohort. The 'functional genetics' research will also continue its development; 2) the WP 'Physiopathology of pulmonary infections' will help to develop research beyond CF. This work is already ongoing with promising results; and 3) the WP 'Development of new predictive diagnostic tools and therapies' may also evolve to translational research including the development of the ANO1-ASO therapeutic. The trajectory as outlined appears quite sound and as the intention is to broaden its research focus to include other chronic lung diseases, this will help the team to move into other respiratory-relevant areas and may enhance their visibility in the respiratory field.

## RECOMMENDATIONS TO THE TEAM

The committee recommends continuing the excellent scientific work that has been developed during the period. The team should try to apply for other international or national grant funding programmes so as not being mainly dependent on patient associations and charities. The team should continue to increase its international visibility and should consider new biostatistical models to analyse modifier genes in collaboration with North American/European collaborators.
The team should consider publishing more in highly cited journals as leader of the work.
The team has to ask itself whether it is appropriate to pursue research into COVID-19, given that this is a very rapidly evolving field, with possibly much less impact on the severity of diseases in the years to come, and given the possible difficulties in obtaining funding for this area of research in the future.
One consideration may be the appointment of a co-lead (who will also co-lead the CRSA) and how this may affect the function of the team and Unit.

**Team 8:** Immune system and neuroinflammation

Name of the supervisor: Guillaume DOROTHEE

## THEMES OF THE TEAM

The team investigates the role of neuroimmune interactions and peripheral-central immune crosstalk in the pathophysiology of neurological disorders, with a particular focus on Alzheimer's disease (AD) and tauopathies, but also on other neuro-inflammatory/neurovascular diseases (cerebral amyloid angiopathy (CAA), stroke and epilepsy). Translational teamwork combines preclinical studies in animal models with cross-sectional and longitudinal clinical studies. The team is divided into 4 research groups responsible for the following work packages: WP1. T cell immunity in AD and other tauopathies; WP2. Microbiota, early neuroinflammation and neuronal function in AD; WP3. Neutrophils in AD, stroke and epilepsy; WP4. Anti-Aβ antibodies in cerebral amyloid angiopathy.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was advised to improve the interaction with companies by licensing the two patents developed. The licensing of a patent is currently under negotiation with a US company.
It was recommended to increase the number of PhD students. The number of PhD students during the contractual period is eight (five ongoing and three defended PhDs), which has increased compared to the previous period (two ongoing and three defended PhDs). The number of publications per PhD student is good since all the students who have defended their thesis have published at least one article in first position in a very good to high-level peer-reviewed journal.
It was mentioned that the size of the team was relatively small and that collaborations and exchanges with the other teams of the CRSA were insufficient. While the team faced the departure of three senior investigators for retirement, it welcomed two junior investigators. Despite this, the team performed very well under the supervision of the new PI, with a strong increase in visibility and excellent publications. Interactions with other CRSA teams are very good: among the 31 publications signed in a leading position by the team, eleven involved one to four other teams from the institute.
The previous evaluation mentioned the need to recruit a technician. Waiting for the recruitment of a second-tenured technical support staff, the team still devoted part of its funding to hiring technicians on short-term contracts.
It was recommended that the team increases the number of journal clubs. Journal clubs have been set up on a weekly basis within the team.
There was a concern that all WPs of the project were not funded. The team was able to secure a total of k€2,895 in external grants proving funding for all WP.
It was recommended to reduce the number of questions, animal models and WPs in accordance with the number of immunologists available for collaboration. During the contractual period, a focus was made on neurodegenerative diseases, even if other neurological disorders were addressed, in accordance with the clinical expertise of the team members.

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

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

# EVALUATION

## Overall assessment of the team

The scientific production is excellent, as attested by high-level publications (2 Brain, Mol. Neurodeg., Crit. Care, Ann. Neurol.) and reviews (Nat. Rev. Neurol., Nat. Rev. Immunol.) in specialized journals (ICN=1,9, 28% PDC in Top1 and Top10 cited journals).
The attractiveness is excellent, regarding the ability to obtain competitive funding (2 ANR + 1 ANRS grant, special grant FRM-Fondation Alzheimer), organisation of meetings and symposia (ISNI 2021, NeuroFrance 2019) and 50 invited talks. The team attracted three new scientists (1 CR CNRS, 1 MCU and 1 MCU-PH from Sorbonne U.). The team leader is Adjunct Professor at Southampton Univ. and well known in the field of neuroinflammation.
The valorisation is excellent, as attested by a strong translational activity, two patents, launch of a clinical trial, and a long-term fruitful partnership with Roche.

## Strengths and possibilities linked to the context

This is a relatively small team composed of one permanent senior scientist, two professors, two associate professors, one hospital practitioner and one assistant engineer. The permanent staff members are well gender-balanced (3 women and 4 men). Five permanent staff had the HDR during the next contract period.
The scientific production of the team is attested by 138 publications in peer-reviewed journals, including 39 as first or (co-) last authors. Two excellent reviews show the eminent reputation of team members in immunology (Nature Review Immunology, 2020) and their strong international positioning in the field of neuroimmune processes associated with neurodegeneration (Nature Review Neurology, 2021). A series of high-level original publications in Brain (2017, 2018, 2021), Molecular Neurodegeneration (2022) and Neurology-Neuroimmunology & Neuroinflammation (2019) demonstrate the power of the team's approach combining preclinical studies and clinical observations. The team also filed two patents and launched a clinical trial in the last contract period.
The attractiveness of the team at the international level is attested by the arrival of one foreign post-doctoral fellow (Taiwan), one visiting scientist (China) and one PhD student from Southampton University. At the national level, the team attracted three scientists (1 senior researcher, 1 assistant professor and 1 clinician) and five PhD students (3 defended their thesis).
The team is attractive as it was successful in leveraging competitive funding, of which 1,347 k€ were obtained, as the principal investigator, from national research agencies (ANR PRCE 2021; ANR JCJC 2021; ANRS) and national research foundations or associations (1327 k€). 175 k€ were granted by a European funding agency (Alzheimer's Research UK) and 68 k€ came from the team's valorisation activities and industrial interactions (CIFRE PhD funding in partnership with Roche and SATT Lutech).
The attractiveness and recognition of the team's expertise is further highlighted by its involvement in the organizing committees of national and international scientific meetings (ISNI 2021, NeuroFrance 2019, SFNV annual meetings, SRLF 2022) and its participation in the steering committees of scientific societies in the fields of neuroimmunology, neurodegeneration and the neurovascular unit (ISTAART, CFNI, CReACTIF, SFNV, France Alzheimer scientific board).
In terms of valorization, the team's translational research approach, aimed at addressing unmet medical needs, is highly effective as evidenced by both a new patent (WO2018172540A1) related to the development of innovative cellular immune biomarkers in neurodegeneration and the launch of a pilot therapeutic clinical trial (IL2-AD, NCT05468073). The team's economic valorization policy is further reinforced by a patent application in preparation and ongoing negotiations for the licensing of a previous patent. The team has a long-lasting scientific partnership with Roche and signed three industrial contracts with this company (collaboration contract; ANR PRCE, CIFRE).
Dissemination of scientific results and knowledge to the public is carried out through regular communications via interviews and articles in the public media, awareness-raising activities with foundations (FRM; Fondation Vaincre Alzheimer) and patient association (Association France Alzheimer), didactic videos (Association S3Odéon) and exchanges with young schoolchildren. Relying on industrial partnerships, the team leader also disseminates his research to pharmaceutical and biotech companies (HYBRID days 2021).
The team is also well involved in teaching with two professors and two assistant professors having teaching duties. Three PhDs were defended, and all students published at least one article in first position.

## Weaknesses and risks linked to the context

Despite good attractiveness and high visibility, the number of post-doctoral students welcomed into the team is low (one only for a few months and the other without any visible publication with the team) as well as the number of defended thesis (3) in relation to the five HDR. The team is used to hire non-permanent technical staff

funded by various academic or private contracts to reinforce his workforce. Maintaining the level of funding for the next contract is therefore a challenge to ensure the continuity of the projects. In this line, the team obtained little funding from European/international sources despite an excellent scientific reputation.
Furthermore, the retirement of three senior researchers and the integration of 4 other senior researchers with quite different expertise is a challenge for the team, as it will necessitate to 'reorganize' the different WPs in the future project. For the next contract, this small team will count only two full-time researchers, including the team leader; the other members of the team having teaching duties that could limit their involvement in research.

### Analysis of the team's trajectory

For the next contact, the team leader will be the same.
Building on previous successes and expertise in neuroimmunology and neurological diseases, the team's project is highly coherent and in continuity of the previous period. In a first axis, the team will continue to decipher the immune mechanisms induced in neurodegeneration (AD and tauopathies) to propose innovative therapeutic strategies. The exploration of the therapeutic potential of Tregs in epilepsy was recently founded by the ANR (ANR RIPLEY, 2023, partner).
Main changes will occur in the second axis, where the team will study the interaction of peripheral innate immunity, systemic inflammation, and vascular remodelling in neuroinflammatory conditions (epilepsy and sepsis-associated encephalopathy (SAE)). Leveraging the expertise of 4 new team members, the team will implement mouse models of sepsis, clinical studies on human SAEs, and real-time biosensor imaging on live cells. The team will also set up a new transversal 'immunophenotyping-immunoassay' platform, sharing its expertise in cellular immunology with the CRSA community.
The team will continue its powerful approach in combining preclinical research with clinical studies without not dispersing the strength of the team in too many clinical subjects.

## RECOMMENDATIONS TO THE TEAM

The team is encouraged to continue its excellent activity and to limit the number of clinical conditions on which its research focuses. The team leader should benefit from its excellent scientific reputation to attract more full-time permanent researchers. The committee recommends trying to build an international consortium to apply for European funding. The recruitment of post-doctoral students should be increased. Collaborations with other teams of CRSA could also be reinforced, taking advantage of the team leader's expertise in immunity. The decision to set up a new immunophenotyping platform is definitely beneficial for the CRSA community. However, due to the small size of the team and the limited number of technical staff, the way this platform will be managed should be carefully defined in order not to dilute the efforts of the team to conduct their own projects.
Funding needs to be secured for the second axis and the team will have to successively integrate the 4 new permanent scientists in a highly competitive context. Industrial collaboration should be pursued.
Finally, the team is encouraged to publish in generalist journals.

**Team 9:** Lypodystrophies, metabolic and hormonal adaptations, and aging

Name of the supervisor: Bruno FEVE

## THEMES OF THE TEAM

Through both basic and clinical approaches, the team focused its research on the pathophysiology and care of genetic and acquired lipodystrophies using translational approaches: search on the pathophysiological mechanisms, consequences on aging, genetic, diagnosis and prognostic factors, evaluation and improvements of the patient's care, and for therapeutic strategies. Four different themes are specifically investigated by four subgroups that closely interact: 1) Genetic lipodystrophies, 2) HIV-associated lipodystrophy, 3) Glucocorticoid-induced lipodystrophy, and 4) Reproductive functions and metabolic disorders.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

In the previous evaluation it was recommended, first, to improve the quality and level of the publications of the team. During the 2017–2022 period, the research unit's productivity is evidenced at both quantitative and qualitative levels by a significant rise in the total number of publications (409 including original articles, reviews, and editorials) and the publications in high-level journals (Nature Commun, BMC Med, eLife…). Moreover, a notable percentage of the articles (18.6%) are in the best audience journals. This indicates that the unit's research has gained recognition and influence within the scientific community (ICN=2.2). It was also recommended to improve the interactions between the subgroups of the team, which appears to be more effective during this evaluation period since shared publication have been performed. A clear prioritization of the projects has also been implemented. Finally, the recruitment of a new PI and postdocs has been successful.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 7 |
| Maîtres de conférences et assimilés | 5 |
| Directeurs de recherche et assimilés | 1 |
| Chargés de recherche et assimilés | 3 |
| Personnels d'appui à la recherche | 8 |
| **Sous-total personnels permanents en activité** | **24** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 2 |
| Personnels d'appui non permanents | 5 |
| Post-doctorants | 0 |
| Doctorants | 3 |
| **Sous-total personnels non permanents en activité** | **10** |
| **Total personnels** | **34** |

## EVALUATION

### Overall assessment of the team

The research performed by the group is excellent to outstanding with a remarkable scientific production in the field of lipodystrophies, elucidating the intricate mechanisms underlying lipodystrophies and their systemic implications. Their innovative approach, interdisciplinary collaboration, and dedication to excellence position them as a leading force in the field of translational research on lipodystrophies. The team has an excellent to outstanding attractiveness, as assessed by successful grant funding and remarkably active collaborations within the CRSA, contribution to European networks, and the recruitment of a young Inserm CRCN. They have an outstanding capacity in valorising their findings with two patents, a start-up creation in 2022, production of guidelines and industrial partnerships.

## Strengths and possibilities linked to the context

The team is currently composed of 21 permanents and 9 temporary staff, including 4 PhD students and one post-doctoral fellow. It integrates researchers with a wide variety of skills, ranging from basic science to clinical studies, who cooperate in a collegial organization.
They published 353 original articles and 56 reviews or editorials highly visible (ICN=2.2) including high impact journals as PI such as Nature Commun, BMC Med, eLife… More than 150 papers are signed as first, last or corresponding author by members of the team. Among these, eighteen are in high audience journals
These papers also include collaborations with internationally recognized scientists (Canada, Argentina, Spain) and 50 are co-signed with 9 out of the twelve CRSA teams. All researchers contribute to transversal projects of the team as attested by the fact that the publication list presents a good balance between the different PI and students from all the team.
The team has been attractive: I) they hosted foreign high-level scientists from Montreal, Buenos Aires, Barcelona. II) The national and international visibility of the team is attested by 31 invited conferences of all PI of the team (European Congress of Endocrinology, European Consortium of Lipodystrophies, etc. ….) And strong involvement in European or National networks (IHU ICAN, RHU, ECLip European Consortium of Lipodystrophies, European Project HIVERA-ECHAM...). III) Several team members hold leadership positions in esteemed scientific organizations, which reflects their expertise and recognition within the field. The engagement of team members in numerous medical and scientific societies is impressive and indicative of their dedication to the field. IV) The involvement of team members as editors and reviewers for prominent journals and organizations underscores their credibility and impact in shaping research. V) The team highly succeeded in finding funding during the period (around 3.25 M€) from various public (1,696 M€:>10 ANRS, PHRC, RHU…) and charity sources (1,321 M€: Equipe labelisée FRM, Sidaction, FDF, AFERO…). This substantial financial resource acquired has not only sustained their projects but also facilitated the training of postdocs, PhD students, and researchers, further contributing to the team's scientific legacy. VI) The team is highly involved in training, it includes eleven HDR (4 of them defended during the period) and ten PhD defences were supported, 4 are ongoing; 2 postdocs were hosted. VII) They recruited one Inserm CRCN young researcher.
The team was remarkably active in industrial valorization as assessed by several industrial grants (MSD, COPOC, Scipio…), three patents (1 has been licensed) and the creation of a start-up (ALIFERT). The team has a high scientific reputation which allows its participation to national scientific structures (Agency of Biomedicine, Agency of the accrediting committee for practitioners in pre-implantation, …), meeting organizations (International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, etc.), and participation to scientific expertise (evaluation FRM chair…), training and dissemination.
Several members are also active in science spreading (national and international association of families, fête de la science, Université du temps libre, Science à Cœur…).

## Weaknesses and risks linked to the context

European and industrial funding remains relatively low and requires to define specific strategies to implement and to achieve this goal.
For eleven HDR only ten theses were defended.
The team did not obtain major competitive grants as PI, such as ANR.
New PIs must be prepared to be hired to reinforce/renew the team in regard to the potential retirements in the next period.
There is no co-leader proposed for the next period as actively integrated into the team's management who could ensure the upcoming transition.

## Analysis of the team's trajectory

The general trajectory of the team remains unchanged by focusing on genetic and acquired forms of lipodystrophies. The team's structure, under the leadership of Pr Bruno Fève since January 2014, has been instrumental in fostering collaboration among experts from various fields, including genetics, cell biology, clinical pathophysiology, and patient care. This collaborative approach has enabled the team to delve into distinct themes in the field of lipodystrophies, ranging from genetic and HIV-associated lipodystrophies to glucocorticoid-induced lipodystrophies and their impact on reproductive functions. The themes are reorganized to improve the translational research and propose new therapeutic strategies. The major evolution appears to be the consequences of aging on adipose tissue and metabolic adaptations through HIV or glucocorticoid interactions. This will bring very interesting new perspectives in the understanding of age-related loss of function in such an original context.
The co-leader proposed for the next period is not actively integrated into the team's management. The upcoming transition will impact the team's research trajectory and must be anticipated.

# RECOMMENDATIONS TO THE TEAM

The reunion of the complementary expertise of basic scientists with clinicians has been a success with the achievement of successful both long-term and pilot projects. The team is encouraged to continue to extend its translational activity, but also to be careful not to lose focus on what makes its international recognition. In particular, the team is encouraged to select targets for which there is a strong expertise at the CRSA.
While the projects are described in detail, a defined plan of the interconnections between the different scientific projects and how they contribute to the overarching research goals would further improve the quality of the project.
A specific effort should be directed to develop further its international visibility, to attract postdoctoral fellows and more PhD students.
A future co-leader must be identified during the upcoming period and rapidly integrated into the team's management and direction to anticipate the future and allow a smooth upcoming transition.

**Team 10:** Neuroendocrine mechanisms of longevity and age-related diseases

Name of the supervisor: Martin HOLZENBERGER

## THEMES OF THE TEAM

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

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

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

## EVALUATION

Overall assessment of the team

Strengths and possibilities linked to the context

Weaknesses and risks linked to the context

Analysis of the team's trajectory

## RECOMMENDATIONS TO THE TEAM

**Team 11:** Metabolic and biliary fibro-inflammatory diseases of the liver

Name of the supervisor: Chantal HOUSSET

## THEMES OF THE TEAM

The team develops fundamental, translational and applied research on fibro-inflammatory, metabolic and cancerous diseases of the liver. Specifically, it implements a multidisciplinary strategy to identify molecular mechanisms and develop therapies against a set of liver diseases that represents a significant public healthcare burden, namely inherited biliary and fatty liver diseases, non-alcoholic fatty liver disease (NAFLD), liver fibrosis and hepatobiliary cancer.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous 2017 evaluation recommended publications in multidisciplinary journals. Team members now authored and co-authored papers in high impact multidisciplinary journals such as, for instance, the New England Journal of Medicine (first author: 2), Nature Genetics (co-author: 1), Cancer Cell (co-author: 1).
The committee recommended an increased involvement in thesis supervision and intra-CRSA collaborations. The number of trained young researchers (26 PhDs and 10 postdocs since 2017) is excellent. Collaborations are noted within the CRSA, as evidenced by 85 collaborative publications, out of which two with the team of Bruno Fève (eLife, BMC Medicine) and two with the team of Harry Sokol (Hepatology Communications, Gut) with shared last authorship.
A recommendation was made concerning the analysis of technical pitfalls in the projects. A decision matrix is now implemented to evaluate the level of risk of new technologies that need to be implemented. Previous evaluation also recommended considering graft-versus-host disease (GVHD) as a new collaborative research axis. GVHD was not added as a research topic, however evaluators currently considers that the team successfully addressed four themes (inherited biliary and fatty liver diseases, necroptosis in liver diseases, liver fibrosis, hepatobiliary cancer). New perspectives on adipose tissue-liver, gut-liver and brain-liver axes are proposed within these four themes, and, in the current context, this seems more relevant and focused than the proposed GVHD while maintaining intra-CRSA collaborations.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 9 |
| Maîtres de conférences et assimilés | 7 |
| Directeurs de recherche et assimilés | 0 |
| Chargés de recherche et assimilés | 5 |
| Personnels d'appui à la recherche | 7 |
| **Sous-total personnels permanents en activité** | **28** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 6 |
| Personnels d'appui non permanents | 4 |
| Post-doctorants | 0 |
| Doctorants | 11 |
| **Sous-total personnels non permanents en activité** | **21** |
| **Total personnels** | **49** |

# EVALUATION

## Overall assessment of the team

This is an excellent-to-outstanding and internationally-recognized team maintaining very high standards in fundamental, translational and applied research on liver disease.
Scientific contribution is excellent to outstanding. Several publications are in leading journals in the field of gastroenterology and hepatology (Gut, Journal of Hepatology, Hepatology, Gastroenterology).
Attractiveness is outstanding. Members actively participated in scientific meetings, international networking and collaborative research, and editorial boards of scientific journals (including Hepatology). It also has a dynamic and successful staff-recruiting policy.-The team is successful in competitive national calls and is very well funded (ANR, INCa, PHRC, FRM), including with support from European institutions (1 EIC PathFinder).
The valorisation is excellent. The team's societal impact is evidenced by partnerships with industry (2) and patent filing (five, among which one in maturation). Patient cohorts have been constituted and clinical trials to test drug efficacy against chronic biliary inflammatory diseases have been set up.

## Strengths and possibilities linked to the context

The attractiveness and impact of the team's research is ensured by numerous first/last authorship (250) and contributions to primary research papers and reviews in the outstanding generalist (NEJM, The Lancet) and speciality journals in the fields of gastroenterology and hepatology (Gut, Gastroenterology, Journal of Hepatology, Hepatology). Members of the permanent staff were invited to the most important international hepatology meetings (AASLD, EASL…) and are actively involved in the editorial board of scientific journals (Hepatology, Livers, J. Intensive Medicine…). The team has a strong collaborative policy as evidenced by the 92% of publications which are co-authored by collaborating teams of the CRSA, and 44% of papers with international collaborators. The team's coordination and participation in international networks and industrial partnerships are significant indicators of recognition and attractiveness.
The team has a dynamic staff-hosting and staff-promoting policy. It secures appropriate and diverse funding (mean 800 k€/year) and offers excellent technological environment. They obtained funds supported as PI, five ANRS, 4 PHRC, one INCa PLBIO, one ANR (390 kE), Mairie de Paris (510kE), Equipe FRM label, among others… Former PhD students (14) and post-doctoral researchers (5) developed successful scientific careers, thereby demonstrating excellent disciplinary and transversal training provided by the team. Importantly, several permanent researchers (1 CRCN Inserm, 2 CNRS CR, 2 PU-PH and 2 MCU-PH) integrated the team during the 2017–2022 period, thereby increasing the manpower of the team.

Quantitatively, the overall publication output, which includes last 179 author publications is excellent in relation to the size of the team and considering the COVID-19 pandemic years which imposed worldwide restrictions on research in 2020–2021. The citation rate is high. Beyond the number of publications and reputation of the targeted journals, the team has built and reinforced its international recognition and societal impact through publications that bring knowledge well beyond the state-of-the-art and open credible translational perspectives. The team's recent research stands out with its discoveries on ABCB4 in inherited biliary diseases and on myofibroblasts and PPAR agonists in liver fibrosis. The published data on necroptosis and hepatobiliary cancer open interesting perspectives for translational research on NAFLD and fundamental understanding of cancer progression.

The team's societal impact is evidenced by patenting diagnostic and therapeutic equipment and compounds (5 patents), and tight connection with industry (Biopredictive, Asfalia). Visibility and societal impact of the team is further ensured by involvement in teaching (including wide-ranging MOOCs and webinars) and communication to a specialized audience via textbooks, and to lay public by interviews.

## Weaknesses and risks linked to the context

Although there are clear strategies to optimally recruit PhD students with the help of the doctoral school, the strategy to actively attract the best national and international post-doctoral researchers deserves to be improved.
With regard to recruitment of permanent staff, opportunities offered to international researchers seem very limited.
The number of publications with team members as last or first author is high in the period 2017–2022, with many first/last author publications. However, the authorship and publication strategy may significantly vary between fundamental, translational and clinical researchers. A more accurate definition of the team's publication goals is required, taking into consideration that international publication and evaluation standards are evolving

towards less consideration of journal's impact factors (= a metric of the journal much influenced by commercial editorial practices) and increasingly focused on the scientific significance of the work.

The communication to lay public seems to be organised on a case-by-case basis. A more structured communication strategy, including via social media, may be considered either at the level of the team, or at the level of the Unit.

### Analysis of the team's trajectory

The team builds on its strengths to propose a program addressing the pathogenesis of liver fibrosis from the initial inflammatory stage, along the fibrotic stage, to the cancer end-stage of the disease. New research lines requiring the collaboration of CRSA teams will be developed to study the adipocyte-liver, intestine-liver and brain-liver axes. The program is consistent, builds on solid data obtained during the 2017–2022 period, and will be conducted by permanent staff that has the required expertise, under the guidance of a new team leader. The proposed work is original and is significant at the fundamental and translational levels.

Although the team's achievements in 2017–2022 clearly support that it can successfully address 4 main themes (inherited disease, necroptosis, fibrosis, cancer) assessing the feasibility to introduce additional lines of research remains difficult without description of the task distribution among the permanent researchers and of the workforce that is available for each project.

The methodology required to address the fundamental and translational projects is available and standard. There is no mention to consider the potential of three-dimensional and spatial analyses in the phenotyping of human tissue and animal models, and how large-scale datasets will be handled and analysed. Given the societal context putting high pressure on reducing the number of animals in research, it is surprising that no mention is made to consider alternative model systems and prepare for a future where animal use may become less accessible.

Past results demonstrate that the clinicians have the capacity to set up patient cohorts and conduct successful clinical trials. However, there is little information on how this will be performed in future studies.

## RECOMMENDATIONS TO THE TEAM

A new team leader will be appointed. His involvement in the fundamental, translational and applied research aspects of the team should be clarified and how this might affect the new group leader's research has not yet been evaluated with care.

Setting up a clear strategy for recruitment of national and international post-doctoral researchers is expected to boost the team's attractiveness. Recruitment of international permanent staff should be encouraged, as well as more extensive funding from European institutions.

The team had an excellent scientific production so far, but its productivity may be at risk as a result from insufficient staff for implementing evolving methodology. Three-dimensional imaging, spatial analyses, handling and analysis of large-scale datasets, non-animal models and implementation of artificial intelligence need to be considered by means of recruiting competent staff or establishing collaborations with teams sharing the required expertise and which offer solid guarantees for continued collaboration.

Finally, a strategy for optimized communication to non-expert audience deserves to be set up with help of communication experts. This can be designed at the level of the team, but ideally at the level of the Unit.

**Team 12:** IGF system and fœtal and postnatal growth

Name of the supervisor: Irène NETCHINE

## THEMES OF THE TEAM

The team's main research concerns the pathophysiological mechanisms involved in fœtal and postnatal growth regulation and imprinted disorders.
They have created the first European cohort of patients with rare diseases associated with growth retardation and identified syndromes associated with a defect in the type 1 IGF receptor gene that they characterized and for which they set up a functional test to assess the pathogenicity of the genetic variants. Through international collaborations, the team has also developed an NGS screening of genes involved in fetal growth restriction and overgrowth to detect new genetic variants of specific imprinted genes, most of them part of the IGF system. They also showed that DLK1 variants were not predictive of fœtal growth restriction. Using an animal model of fœtal growth restriction, they identified microRNAs associated with metabolic associations.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has achieved the recommendation to maintain its level of publication, an international visibility, and an ability to obtain national grants as ANR and several pharmaceutical industrial grants. The team has also filed a patent for the culture of pluripotent cells from dental pulp.
It was recommended that the junior members of the team should take part in conferences. Two of the junior faculty members participated in international web conferences and gave several talks at the ESPE congress.
The team was encouraged to increase the participation of junior members in educational events and social activities, beyond the sole leaders' engagement. The team is heavily involved in patient family associations for rare diseases. Junior members are involved in social activities by welcoming students into the CRSA and by participating in the 'fête de la science'.
The team was recommended to improve its connections with the industrial network. They have been able to get important contracts with pharmaceutical industries (Pfizer and Merck Serono).
The team was encouraged to increase the number of PhD student training. Two HDR were obtained and 4 theses were defended during the period (for a total of 5HDR).
It was recommended to the team to extend their interaction with other teams of the CRSA. On a total of 130 publications, eighteen of them were co-signed in collaboration with other CRSA teams, mostly on the team leader's scientific topic, and common budget (IHU ICAN grant) was obtained with 4 teams of CRSA (teams 6, 9, 11 and 13).

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 2 |
| Maîtres de conférences et assimilés | 3 |
| Directeurs de recherche et assimilés | 0 |
| Chargés de recherche et assimilés | 2 |
| Personnels d'appui à la recherche | 3 |
| **Sous-total personnels permanents en activité** | **10** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 2 |
| Personnels d'appui non permanents | 1 |
| Post-doctorants | 0 |
| Doctorants | 1 |
| **Sous-total personnels non permanents en activité** | **4** |
| **Total personnels** | **14** |

# EVALUATION

## Overall assessment of the team

The scientific production of the team is very good regarding the team size, with a leading position on 44 articles in speciality reviews, including two guidelines published in Nat Rev Endocrinol and one study published in Science Adv.
The team has a very good visibility. The team was successful in recruiting an associate professor and hosting two European visiting professors for six months to a one-year period. The head of the team occupies a paediatric chair of the rare endocrine disorders network, organized two international conferences, and obtained two ANR as leader, two industrial contracts, and cochairs a COST.
The valorisation of the team's research is excellent. The team has a strong translational activity and obtained relevant results with high clinical potential. The team also has strong interaction with national and international patients support groups on rare diseases.

## Strengths and possibilities linked to the context

The team is composed of teaching researchers (5 and an emeritus Pr) with two full-time researchers from Inserm and two research supporting personnel and a total of five HDR. The team's equipment was not mentioned but the team operates in a rich environment within the CRSA, at Sorbonne University and at ICAN, and can rely on collective equipment and technological platforms. The studies of the team on imprinting diseases and growth retardation were in line with their deep expertise, with several preliminary encouraging results both in human cohorts and recent experimental cell model differentiation with methylation status that differed in cells from patients with SRS and BWS that led to the submission of a patent. The team also developed expertise in NGS for detecting mutations of IGF pathway with an application for diagnosis testing of growth retardation diseases.

The team is engaged in a strong translational research and implication of clinical researchers is important. Team members are active members of European research and care networks for rare growth disorders and endocrinology. Two team members coordinated rare disease consensuses published in Nature Rev Endocrinol in 2017 and 2018, leading the team leader to coordinate two international conferences on imprinting disorders in 2021 and 2023. The team leader also received the European Society of Paediatric Endocrinology (ESPE) research award in 2019 and is the paediatric chair of the endocrine network for rare disorders (ENDO-ERN) for the thematic group of rare growth and obesity disorders, attesting to her reputation and visibility in this specific and important field.

Team members have produced 130 articles published in international journals with good or very good audience (Nat Rev Endo; Science Advances Human Genetic). Team members have a leading position (first and/or last authors) in 44 articles (34% of the list), among which 15% of the articles were written with international collaborators and eighteen publications with other CRSA teams.

Doctoral students contributed to twenty articles, with the exception of one student who did not publish after completing her thesis. The team makes its publications available to the scientific community (all publications are included in HAL for open science). The team respects ethical rules and scientific fairness.

A young associate professor and an assistant professor have been recruited. Each member has a good to excellent record of publication and are fully involved in student formation. The team members have given 30 international conferences and at least 4 of them are invited internationally to present their work in plenary conferences or symposium and performed webinars for a European Reference Network on rare endocrine diseases.
The team has also attracted international researchers, as demonstrated by the arrival of a professor from the UK for six months and an Italian professor for twelve months.
During the period 4 thesis and two HDR were defended.
The team collaborated with various CRSA teams on the technical development of the generation of epi-mutated stem cells in order to differentiate them into various cells of interest involved in imprinting diseases, in particular adipocytes (Team 11) or skeletal muscle or hepatocytes (Team 9).
The team has a good ability to obtain funding at national level (1.4 M€) including three ANR (2 as PI and 1 in collaboration, for a total of 432 k€). The team also obtained two significant funding from major pharmaceutical companies such as Pfizer and Merck Serono (for a total of 361 k€) and two from foundations as ESPE and FRM (PhD grant) (for a total of 300 k€).

## Weaknesses and risks linked to the context

The number of full-time research members is quite low and will even be reduced for the next period, that is quite worrisome and lead to suppress one of the historic topics. The lack of research support personnel could also be a disadvantage, specifically in a team whose research is mostly done by professors, associate professors and clinicians with few young researchers. Three persons recently left the team, who were in charge of an interesting topic on metabolic programming that was potentially linking the team to several CRSA teams. One permanent researcher and one technician will also retire.

Given the team's reputation and scientific merit, the attractiveness of the team remains low. The team has welcomed masters students and five doctoral students were enrolled during the evaluation period, only one of whom is still in progress. Overall this may seem insufficient considering the size of the team. No postdoctoral researcher has been taken on, and there are no plans to do so. Communications and poster presentations by the youngest members of the team at international meetings appear to be fairly low and one PhD student (2021) has no publication or communication yet to her record.

No other activity of a general nature (Broadcast, TV…) was listed by the team members.

Interactions with the other CRSA's teams appeared limited to technical aspects without sharing scientific aims.

The sharing of experimental results and the consignment of experimental data are preferred using a common electronic laboratory and a weekly laboratory meeting. However, data storage is undescribed and there is no mention of a general team's policy towards FAIR principles of data reuse.

The majority of the grants were obtained by the team leader with only a few and minor grants obtained by the other's full-time researchers of the team. There is no strategy plan to increase fund-raising.

The fundamental aspects of the research project are weak.

## Analysis of the team's trajectory

For the future, the team plans to focus on research in human and cellular models of imprinting disorders and on IGF system anomalies and will follow three axes of research: (1) to understand the pathophysiology of fœtal growth defects on cellular models of imprinting disorders, (2) to characterize the role of IGF system in fetal growth defects by a better biological profile of the components of the IGF system in cohorts of patients, (3) to assess the environmental impact on imprinting disorders and fœtal growth defects focusing on the impact of the assisted reproductive technologies on the methylation profiles at ICR.
The team's new title will be: 'Pathophysiology of fetal growth: IGF system and parental imprinting'. Consequently, only the subgroup involved in imprinting and IGF abnormalities will be part of the new team. The departure of three persons will fragilize the team, partially compensated with the arrival of a senior INSERM researcher whose research program is not yet precisely defined but with experience to create animal models of imprinting diseases. Reducing the size of the team and concentrating research on the specific scientific topic of the team leader could be a strength, but also a risk.

However, the project is totally consistent with their excellent expertise on the IGF axis and their leading role on the first French cohort of patients carrying a defect in the gene of type 1 IGF receptor. They aim to progress in the comprehension of fœtal growth defect, mainly focus on imprinting disorders thanks to their development of dental pulp stem cells and pluripotent stem cells in hypertrophic chondrocytes with stable imprint methylation. They also plan to generate epi-mutated stem cells (pluripotent or dental) using CRISPR editing to allow a targeted demethylation at selected imprinted control regions and to differentiate them in various cells of interest involved in imprinting diseases, including adipocytes, skeletal muscle or hepatocytes in collaboration with CRSA teams, in order to assess the transcriptomic differences between controls and patients with imprinting disorders. They could then submit the obtained cells to experimental conditions and drugs in order to identify therapeutic targets for imprinting diseases.

They also will improve the description of the phenotype of patients with imprinting diseases, in a European cohort, notably cardiovascular risk, and better characterize 'multilocus imprinting disturbance' (MLID) in these patients, in relation with their phenotype.
They also will study the effects of embryo environment in imprinting diseases, including the effect of assisted reproductive technologies both in human cohorts, in frozen embryos, and sperm banks but that project needs to be better defined in terms of scientific questions and dedicated team's members.

Although the budget was limited from 2021 to 2022, the team leader has obtained an ANR funding as PI (306 k€) in collaboration with R Feil and D Noordermeer (2022–2025). This will ensure the feasibility of the future project on

epi-mutated stem cells that keep their methylation status on ICR and will be useful to decipher molecular mechanisms of imprinted disorders.

Overall, teams projects on imprinting diseases are in line with their very deep expertise and previous research themes, with several encouraging preliminary results both in human cohorts and experimental cell models, and with financial supports.

## RECOMMENDATIONS TO THE TEAM

The team is encouraged to maintain the quality of its research and its European visibility through clinical research. The team should reinforce the fundamental aspects of its research program to increase the level of its publications and its attractiveness. It should also capitalize on its international clinical visibility to develop strategies for obtaining European and international competitive grants.

We recommend adopting a strong strategy of recruitment, increasing the number of PhD students and postdoctoral researchers and amplifying the internal and external collaborations to guarantee the dynamic of the team, and to bring fresh minds to promote cultural/scientific stirrup.

As funding momentum appears to be decreasing, we recommend encouraging the young scientists in fundraising through the ARN's JCJC competition or funding from scientific foundations.

The new theme on the effects of the embryo environment in imprinting diseases maybe oversized as the team will have reduced human resources.

Despite international collaborations during the previous period, little or no European or international collaborations are mentioned for the future and could be strengthened.

**Team 13:** Microbiota, Gut and inflammation

Name of the supervisor: Philippe SEKSIK & Harry SOKOL

## THEMES OF THE TEAM

The team 'Microbiota, Gut, and Inflammation' investigate microbiota-host interactions in the context of inflammatory gut diseases, particularly IBD. The team has expertise in gastroenterology, microbiology, metabolomics, and immunology. Using these, the team tackles complex microbiome-host interactions and how these are altered in inflammatory diseases. Owing to the constellation of the team and its location in a hospital, basic research on the role of bacterial metabolites is linked with clinical studies.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The points raised were all addressed satisfactorily.
The team was new in the unit and therefore was mainly evaluated based on the previous production of the two team leaders. Overall, the team was encouraged to continue its 'very impressive' research quality and productivity.
The team has expanded their clinical work (involvement in different (inter-–national clinical trials on IBD) making the recommendation on animal models and *in vitro* models less critical. Further, by acquiring the SHIME platform for *ex vivo* experiments with human material, the team is ensuring better (compared to animal models) representations of the human microbiota dynamics in terms of the microbial diversity.
Attention was drawn to the gender ratio in the group, especially at the team and scientist level. Based on the information available, this has now been satisfactorily addressed through excellent new recruitment at PI level.
Questions with respect to bioinformatics and biostatistics analyses were addressed by having two bioinformaticians and there is a plan to employ a permanent bioinformatics researcher.
Concerns were raised regarding the lack of plan for the mass spectrometry platform development. There is now a team in place for the platform development with links both to the Seksik-Sokol team and others at the CRSA.
The small number of researchers with permanent positions was raised as a point of concern and this appears to be addressed through the hiring of additional young PIs.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 7 |
| Maîtres de conférences et assimilés | 4 |
| Directeurs de recherche et assimilés | 0 |
| Chargés de recherche et assimilés | 4 |
| Personnels d'appui à la recherche | 6 |
| **Sous-total personnels permanents en activité** | **21** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 3 |
| Personnels d'appui non permanents | 7 |
| Post-doctorants | 3 |
| Doctorants | 7 |
| **Sous-total personnels non permanents en activité** | **20** |
| **Total personnels** | **41** |

# EVALUATION

## Overall assessment of the team

The team has an outstanding scientific output, driving high-level publications and public outreach, connecting basic research to clinic and industry. Members demonstrated an outstanding attractiveness for talented early career researchers (1 CRCN Inserm and 2 MCU), and competitive funding (2 ERC, H2020, 2 US). This success underscores their international recognition in the host-microbiome field and explains the impressive track record of invited talks. The valorisation is outstanding with eleven patents, two start-ups, meeting organisation and appointments to editorial and steering bodies.

## Strengths and possibilities linked to the context

Within the CRSA, the team has been successfully integrated as assessed by collaborations with all teams. They are also very well integrated within the local and national ecosystem (in 2 RHU, FHU PaCeMM…), and have successfully built an internationally recognised microbiota-research group.
The combination of basic and clinical research is both attractive for training young researchers and important for creating impact through translational work. The international visibility of the team leaders has continued to be strong (illustrated by a total of 70 invitations of both team leaders to international conferences and by the international collaborations in publications (136/326)), attesting to their effort in staying at the cutting-edge of the field. In the past period they have published 326 papers, of which 129 as first, last or corresponding authors, and many in high visibility journals (Gut, Cell Metabolism, Science Translational Medicine, Cell Host Microbe and Gastroenterology among others) including 30 highly cited papers. With respect to valorisation, the team has successfully contributed to eleven patents and two start-ups.
The team raised more than 10 M€ over five years, including very competitive national and European grants (2 ERC, 10 ANR.). Moreover, sustained funding from industry has been obtained attesting to the relevance of the research.
The team is very attractive as evidenced by its expansion over the five-year period with five postdocs, thirteen PhD (7 still ongoing), 6 contractual engineers, two new MCU and one young CRCN Inserm newly recruited. The scientific meetings within the team are well thought out, suggesting a strong learning environment for young scientists.
The acquisition of the SHIME platform will allow them to perform high-level *ex vivo* experiments towards personalized medicine approaches, especially for FMT, and illustrates their knowledge on the latest technological advances and opportunities in microbiome research.

## Weaknesses and risks linked to the context

The distribution of the eight PhD students between senior scientists is currently not balanced. Not all research themes appear to be hosting a PhD student.
So far, the team's attraction of international postdocs appears limited and the number of postdocs (8 in total over the evaluation period of which 3 are ongoing) is not distributed over all subjects.
The retirement of five researchers (2 CR, 1 PU EPHE, 1 PUPH, 1 PH) of the team in the next five years will potentially have an important impact on the team structure and projects.

## Analysis of the team's trajectory

As a starting team during the previous evaluation, they have consolidated an outstanding output in terms of research funding, infrastructure, training, translation to clinic, and industry interactions during the past years. Based on this, an upwards trajectory is anticipated. More specifically, the research innovation potential of this team is very high and should become more and more apparent in the coming years.
The impact and visibility of the different PIs within the team, besides the team leaders, is also expected to flourish. The PIs secured a number of national and international grants (including 2 ERC grants), allowing the continuation of their ambitious plans. The size of the team seems appropriate to the level of scientific ambition while the funding also allows further growth and scientific flexibility. So far, twenty PhDs have been trained in this team, of which thirteen have defended so far.
Philippe Seksik is now also head of the clinical department further strengthening their link with the clinic. Although five researchers will retire, a young CRCN has just been recruited at Inserm in 2023 and an engineer is recruited for the SHIME system. Scientifically, they will continue to build on their strong expertise on small molecules impacting on intestinal homeostasis, especially the tryptophan pathway, by studying their role on IBD and inflammation and deciphering basic processes. They will also open a new track on the dialog between neutrophils and microbiota.

# RECOMMENDATIONS TO THE TEAM

The team is recommended in general to keep up with their high scientific standard with respect to publications, scientific and public outreach, valorisation and grant writing.
The team has a unique constellation closely linking basic and clinical research. To exploit this strength, we highly recommend embarking on ambitious projects that go through the full circle of clinical-basic-clinical research. To facilitate such projects, the team's effort for better organizing research support is encouraged, as it would allow them to focus more on innovative elements of research.
To enable further growth and cohesion within the team, the new roles replacing five (2 CR, 1 PU EPHE, 1 PUPH, 1 PH) retiring team members are recommended to be integrated from the onset in outlining the team's organizational and functional structure.
In addition to the team leaders, the scientific output and visibility of the different PIs should be a point of attention.
The ratio of PhD students versus senior scientists could also be improved, creating more training opportunities in this scientific field of clinical importance.

# CONDUCT OF THE INTERVIEWS

## Dates

**Start:** 04 octobre 2023 à 8 h 30

**End :** 06 octobre 2023 à 18 h

**Interview conducted: on-site**

## INTERVIEW SCHEDULE

**Day 1. Wednesday, October 4**

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

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

9:15 a.m. – 10 a.m. Unit overview by the head of the CRSA: Bruno FEVE and Xavier HOUARD

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

Team Leader Presentations

10:15 a.m. – 11 a.m. Team 02: 'TGF-ß signalling in cell plasticity and cancer'
Current team leader: C. Prunier (Next team leaders: C. Prunier & J. Sobczak)

11 a.m. – 11:45 a.m. Team 03: 'Biology and therapeutics of cancer'
Current team leader: M. Sabbah (Next team leader: G. Gerotziafas)

11:45 a.m. – 12:30 p.m. Team 01: 'Microsatellite instability and cancer'
Current and next team leader: A. Duval

12:30 p.m. – 1 p.m. Closed doors meeting of the committee

1 p.m. – 2 p.m. Closed doors lunch (lunch boxes)

Team Leader Presentations

2 p.m. – 2:45 p.m. Team 04: 'Hematopoietic and Leukemic Development'
Current and next team leader: F. Delhommeau

2:45 p.m. – 3:30 p.m. Team 05: 'Graft versus host disease after allogeneic hematopoietic stem cell transplantation'
Current team leader: M. Mohty (Next team leaders: M. Mohty & F. Malard)

3:30 p.m. – 4:15 p.m. Team 11: 'Biliary and metabolic, fibro-inflammatory diseases of the liver'
Current team leader: C. Housset/J. Gautheron (Next team leader: J. Gautheron)

4:15 p.m. – 5 p.m. Team 07: 'Cystic fibrosis: Physiopathology and phenogenomics'
Current team leader: H. Corvol (Next team leaders: L. Guillot & H. Corvol)

5 p.m. – 5:45 p.m. Team 06: 'Joint pathologies associated with age and metabolic diseases'
Current team leader: F. Berenbaum (Next team leaders: X. Houard & J. Sellam)

5:45 p.m. – 6:30 p.m. Closed doors meeting of the committee

**Day 2. Thursday, October**

8:30 a.m. – 8:45 a.m. Arrival of the experts/Coffee/Installation

Team Leader Presentations

8:45 a.m. – 9:30 a.m. Team 08: 'Immune system and neuroinflammation'
Current and next team leader: G. Dorothee

9:30 a.m. – 10:15 a.m. Team 12: 'Pathophysiology of fetal growth: IGF system and parental imprinting'
Current and next team leader: I. Netchine

10:15 a.m. – 11 a.m. Team 09: 'Lipodystrophies, metabolic and hormonal adaptations, and aging'
Current and next team leader: B. Feve

11 a.m. – 11:45 a.m. Team 13: 'Microbiota, intestine, and inflammation'
Current team leaders: P. Seksik & H. Sokol (Next team leaders: H. Sokol & P. Seksik)

11:45 a.m. – 12:30 p.m. Closed doors meeting of the committee

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

Meetings with the personnel representatives (closed doors)

2 p.m.-2:30 p.m. Meeting with ITA (Engineer, technicians, administrative staff)

2:30 p.m.-3 p.m. Meeting with young researchers (PhD students and Post-docs)

3 p.m.-3:45 p.m. Meeting with researchers not team leaders

3:45 p.m.-4:30 p.m. Closed doors meeting of the committee

4:30 p.m. – 5:30 p.m.

5:30 p.m. —Meeting with institution representatives

Sorbonne Université/Faculté de Santé de Sorbonne Université
Anne-Geneviève MARCELIN
(vice-doyenne recherche de la Faculté de Santé)
Wilfried LE GOFF
(vice-doyen recherche délégué de la Faculté de Santé)
Vincent MOULY
(chargé de mission pour le CRSA au Comité de la Recherche de la Faculté de santé)
Violaine DESIRE
(directrice de la recherche et de la valorisation de la Faculté de Santé)
Marie-Aude VITRANI
(responsable coordinatrice HCERES à Sorbonne Université)
Elisabeth ANGEL-PEREZ
(vice-présidente recherche de Sorbonne Université)

Inserm/Délégation Régionale Paris-IDF Centre-Est
Raymond BAZIN
(Institut thématique Physiologie, Métabolisme, Nutrition)
Alain EYCHENE
(Institut thématique Cancer)
Camille CHAUDONNERET
(déléguée régionale Paris-IDF Centre-Est)

APHP/Hôpital Saint-Antoine
Bertrand GUIDET
(président de la Commission Médicale d'Établissement Locale (CMEL))

18 h 30 Closed doors meeting of the committee

7:30 p.m. Closed doors dinner: Sawan, 72 boulevard Diderot, 75012 Paris, France

**Day 3. Friday, October 6**

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

9 a.m. – 10 a.m. Closed doors meeting of the committee
10 a.m. – 11 a.m. Meeting with the present and future head of the CRSA and deputies
11 a.m. – 12 p.m. Closed doors meeting of the committee

12 p.m. – 1 p.m. Closed doors lunch

1:30 p.m. – 5 p.m. Closed doors meeting of the committee

6 p.m. Departure

## PARTICULAR POINT TO BE MENTIONED

The team leader of T2 was absent and replaced by a colleague.
The expert Mr Cliff Taggart, was tested Covid+ and could not assist at the visit.

# GENERAL OBSERVATIONS OF THE SUPERVISORS

SORBONNE UNIVERSITÉ

Marie-Aude Vitrani
Vice-Présidente Vie institutionnelle et démarche participative
Sorbonne Université

à

Monsieur Eric 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

Paris, le 8 janvier 2024

Objet : Rapport d'évaluation CRSA - Centre de recherche Saint-Antoine

Cher Collègue,

Sorbonne Université vous remercie ainsi que tous les membres du comité HCERES pour le travail d'expertise réalisé sur l'unité de recherche « CRSA ».

Sorbonne Université n'a 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

**Marie-Aude Vitrani**
Vice-Présidente Vie institutionnelle
et démarche participative

The Hcéres' evaluation reports are available online:
www.hceres.fr

**Evaluation of Universities and Schools**
**Evaluation of research units**
**Evaluation of the academic formations**
**Evaluation of the national research organisms**
**Evaluation and International accreditation**

Évaluation • Recherche • Enseignement supérieur
Hcéres

2 rue Albert Einstein
75013 Paris, France
T.33 (0)1 55 55 60 10

hceres.fr @Hceres_ Hcéres