Research evaluation

EVALUATION REPORT OF THE UNIT

CRI - Centre de Recherches sur l'Inflammation

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Paris Cité

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

Centre national de la recherche scientifique - CNRS

EVALUATION CAMPAIGN 2023-2024

GROUP D

Report published on May, 14 2024

High Council for evaluation of research and hihter education

In the name of the expert committee :

Emmanuel Barbier, chairman of the committee

For the Hcéres :

Stéphane Le Bouler, acting president

In accordance with articles R. 114-15 and R. 114-10 of the Research Code, the evaluation reports drawn up by the 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

Chairperson:

Mr Emmanuel Barbier, Inserm, La Tronche

(Following the interviews, Ms Nathalie Vergnolle Inserm, Toulouse, who was initially nominated chairwoman, has recused herself)

Experts:

Mr Yves Delneste, Inserm, Angers (representative of CSS Inserm)

Ms Isis Fernandez, Helmholtz Center Munich, Germany

Mr Joachim Lupberger, Inserm, Strasbourg

Mr Matthias Mack, University Hospital Regensburg, Germany

Ms Jennifer Molle, Inserm, Lyon (supporting personnel)

Ms Eve-Isabelle Pecheur, CNRS, Lyon (representative of CoNRS)(Vice President)

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Mr Jean Christope Sabourin, CHU Rouen (representative of CNU)

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Mr Philippe Ruszniewski, Faculté de Santé - Université Paris Cité

Ms Sabrina Shanoun, Inserm

Mr Michel Vidal, Faculté de Santé - Université Paris Cité

CHARACTERISATION OF THE UNIT

- Name: Centre de Recherches sur l'Inflammation
- Acronym: CRI
- Label and number: U 1149/ ERL 8252
- Composition of the executive team: Mr Renato Monteiro (director), Ms Sophie Lotersztajn (deputy director), Mr Ulrich Blank (Dept NIH) and Mr André Bado (Dept HE)

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE4 Immunité, infection et immunothérapie

THEMES OF THE UNIT

A central thematic of the CRI is the question of how inflammation impacts on metabolism, organ dysfunction, fibrosis and cancer. Research within the Nephro-Immuno-Hematology department seeks to understand how the immune system controls inflammatory signals in renal and other inflammatory diseases with focus on immune regulation by Immunoglobulins and Fc receptors, inflammatory signaling processes, gene polymorphism and SNPs, the study of innate immune cells such as mast cells, basophils, NK cells, neutrophils and monocytes/macrophages applied to various pathophysiological inflammatory contexts. Adaptive immunity regarding the antigen presentation process between dendritic and T cells in various pathophysiological contexts has also been investigated. Research within the Hepato- Gastro-Enterology department focuses on the pathophysiology of the digestive system including the gastro-intestinal tract, liver and pancreas using molecular, cellular and imaging approaches and both animal models and patient cohorts. The future scientific structuration of the CRI will include three axes on the pathophysiology of inflammatory and fibrotic diseases, oncogenic inflammation and tumor development as well as immunology signaling and cell dynamics.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The CRI is located for the most part at the Bichat Medical Faculty with some outposts at the Beaujon and Bichat hospitals. The CRI was created in 2014 via a merger of three existing entities (UMRS 699, CRB3/Inserm U773, Inserm U843 and two additional independent teams) and renewed in 2019 with eleven teams as the first center for medical inflammation in France with endorsement from Inserm, CNRS and Université Paris-Diderot (PRES Sorbonne Paris Cité). In its current form CRI is split into two departments: i) Nephrology, Immunology and Hematology (NIH) composed of five research teams and ii) the Hepato-Gastroenterology (HGE) department, composed of six research teams and two ATIP-Avenir teams and covering digestive, kidney and immunological diseases.

In the future, the CRI will be restructured into three transversal axes. The inflammation axis will consist of eight teams, the oncogenesis axis of four teams and the immunology axis of four teams including two junior teams. The unit will extend its fields of interest towards lung diseases supported by the fusion with research unit Inserm 1152 and multimodal imaging through fusion with the team of R Sinkus at U 1148. At the horizon of 2028, all teams including clinical and basic research will be relocated on a new campus (campus Nord) with support from AP-HP and UPC.

RESEARCH ENVIRONMENT OF THE UNIT

The CRI is based on a strong association of basic and clinical research, allowing a successful bench to bedside translational approach, with access to relevant experimental models, innovative technical platforms (including imaging) as well as human cohorts. The close interactions are facilitated by the close proximity of the Bichat Medical Faculty, which is part of the Bichat Hospital, with some outposts at the Beaujon Hospital at 10 min from the Bichat site.

The translational research performed in the CRI is fostered by the participation in clinical research networks such as DHU FIRE and UNITY, FHU Mosaic, Appolo, FHU PaCEMM (Paris Center for Microbiome Medicine), RHU QUID NASH and Operandi, with some of them being led by members of the CRI. In addition, the INFLAMEX laboratory of excellence led by the current CRI director, gathers several teams of the CRI through a research network on inflammation and inflammatory diseases. This labex also includes an interdisciplinary master program (IMI) with focus on inflammation research.

International associated laboratories (Liver Biliary Sciences, New Delhi), consortia (EASL, H2020), Marie Curie fellowships and international grants as well as set up of two start up companies are proof of CRI's international visibility and its interactions with society.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	46
Maitres de conférences et assimilés	21
Directeurs de recherche et assimilés	11
Chargés de recherche et assimilés	15
Personnels d'appui à la recherche	106
Sous-total personnels permanents en activité	**199**
Enseignants-chercheurs et chercheurs non permanents et assimilés	5
Personnels d'appui non permanents	4
Post-doctorants	11
Doctorants	44
Sous-total personnels non permanents en activité	**64**
Total personnels	**263**

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

Nom de l'employeur	EC	C	PAR
Université Paris Cité	51	0	18
Inserm	0	19	36
CNRS	0	6	0
Autres	16	1	52
Total personnels	**67**	**26**	**106**

GLOBAL ASSESSMENT

The global performance of CRI unit is from excellent to outstanding. The CRI is a large research unit composed of 11 research teams plus two ATIP-Avenir young investigator teams. CRI's research is focused on elucidating the mechanisms of chronic inflammatory disorders. The organisation of the CRI in departments has fostered collaborations between teams, and the very large involvement of clinician scientists in most teams provides the CRI with a very strong dynamic in translational research; many of the team leaders in CRI are clinicians who provide important medical inputs on the scientific questions that are being addressed. The clinical departments of Bichat and Beaujon hospitals provide essential access to patient cohorts and access to tissues. Research between basic science, translational science and clinical science is very well balanced at CRI. Very strong basic scientists and basic science research programs are also present at CRI.

CRI has continued in the last mandate to achieve outstanding scientific production, publishing highly original papers in highly visible journals. The international recognition of some of the CRI researchers is a strength of the unit, which should be extended to more researchers. The unit has addressed previous recommendations, publishing in more generalist journals, recruiting young scientists, fostering collaborations between the teams, and setting up state-of-the-art technologies. Implementation of computational biology and bioinformatics are a strength of the unit.

Several of the CRI teams have strong socio-economic connections, and are involved in technology transfer with over 30 patents obtained in the evaluation period.

CRI has been a center of excellence in teaching and training on inflammation, thanks to the Inflammex program, training the next generation of inflammation scientists. This program has proven to be quite attractive to trainees and has helped the teams in their research programs. The end of this program will be a challenge to face for CRI. In particular, CRI will have to work on its attractivity towards PhD and foreign post-doctoral fellows.

CRI is facing partial restructuring with different teams. To what extend this reshuffling is going to impact the scientific productivity, and the career path of agents, as well as the inter-team collaborative programs, is difficult to anticipate. An important strength of the unit is the dynamism and the vision of the director and of the executive direction.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Recommendation 1: The CRI needs to continue delivering high impact factor journal publications and narrow the gap by increasing the number of publications in journals with IF>4.

This has been implemented. Publications over the last evaluation period include high-profile generalist journals, such as Nature Medicine (1), Nature Immunology (2), Science Translational Medicine, Immunity (3), New England Journal of Medicine (2), Nature Communication (13) as well as high profile specialized journals such as Hepatology (43), Blood (2), Gastroenterology (11) or Gut (12), with unit's members often as leaders.

Recommendation 2: Scientific collaborations between teams within the CRI should be encouraged. The links between the CRI, the labex, DHU and RHU in the strategy, steering and financing of projects need to be clearly documented. The CRI should develop a strategy to maximize its potential income from particular teams' activities. The technical staff ratio should be strengthened according to the high quality research of the CRI. The CRI technical staff should be increased in the areas of bioinformatics, AMNIS instrument support and surgery in the animal facility. IT support should be to be reinforced. The CRI should provide common space for its personnel and should consider holding a rolling series of public lectures. The CRI needs to improve its presence on social media.

Several recommendations have been implemented. For centralized expenses or strategic investments, CRI retains 10% from incoming research contracts. Regarding common space, the CRI is actively involved in planning the new location which will regroup different laboratory spaces and hospitals hosting CRI clinicians. Several researchers/engineers with skills in bioinformatics have been or are in the process of being recruited. CRI has also developed links with PR[AI]RIE, the Parisian center dedicated to research in artificial intelligence, and with several teams from INRIAE. Interaction between CRI teams is now ensured via organization of weekly CRI seminars. The presence of CRI on social media has also improved (see EVALUATION AREA 4).

Recommendation 3: A 5-year strategy should be developed to determine and acquire key technological tools. The CRI should engage with the APHP to discuss concrete support for research and should continue to focus on generating synergistic external collaborations.

This recommendation has not been implemented at the unit but rather at the team level. High throughput Mass Spectrometry, CAR T cell therapy, organoids and other tissue culture models as well as other technical expertises are being developed by teams. In the future, these technologies will likely play key roles at the CRI and are being developed into platforms. MRI imaging and associated bioinformatic analyses, currently part of the UMS FRIM will be reorganized into the federated core facility Claude Bernard. Excellent external collaborations are being fostered by basically all CRI teams.

B - EVALUATION AREAS

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

Assessment on the scientific objectives of the unit

The units scientific objectives are outstanding.

Assessment on the unit's resources

The unit's resources are excellent.

Assessment on the functioning of the unit

The functioning of the unit is excellent.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The CRI is the only French research unit exclusively dedicated to the study of inflammation. The main scientific goal of CRI is to elucidate pathophysiological mechanisms of chronic inflammatory diseases, aiming at better diagnosis, identification of biomarkers, and therapeutic targets. CRI's research focuses on inflammation as a common feature leading to aberrant immune response, fibrosis and cancer.

The research projects of the CRI are based on models as well as research studies with patient cohorts. The presence of teams developing innovative imaging approaches for diagnostic, progression and therapy of chronic inflammatory diseases, fibrosis and cancer has allowed cross interactions between teams and departments. Units of the CRI are closely connected with hospital university networks, including FIRE (Fibrosis, Inflammation, REmodeling in cardiovascular, respiratory and renal diseases), RHU-QUID-NASH (Quantitative Imaging in Diabetes) OPERANDI, FHU Mosaic, Apollo. Together with the INFLAMEX laboratory of excellence, CRI participates to interdisciplinary master and PhD programs on Inflammatory Diseases (Master IMI) training the new generation of scientists in the field of inflammation research. Scientific expertise and clinical recognition of CRI members has led to the development of several national and international funded networks (Mikinaute, EF-CLIF, French-India LIA) investigating how chronic inflammatory diseases impact on the societal and economic burdens.

Weaknesses and risks linked to the context

No weaknesses detected.

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 center is composed of twelve teams and includes 46 professors, eleven Directors of Research, 21 Associate professors, 15 Researchers and 106 technicians and engineers. Including trainees, a total of 263 persons are present in the CRI. CRI receives recurrent funding (1.1 M euros/year) from its supervising institutions, part of which (>30%) is dedicated to common expenses or development of new teams. These resources are complemented by external competitive funding to CRI's investigators via national and international agencies (4-5M euros/year), of which 10% is held back for centralized expenses or strategic investments.

What sets apart CRI from analogous institutions is the close connection with clinical centers (Bichat, Beaujon, Robert Debré, Louis Mourier hospitals) that provide privileged access to primary human samples. Furthermore, CRI research has led to the development of several highly specialized experimental approaches that have been developed into core platforms such as the imaging facilities. The complementary expertise between teams allows efficient sharing of knowledge and human resources within the center, which translates into shared authorships on publications and good communication within the center.

Construction and relocalization into a new building (Campus Paris Nord) should alleviate the current need for modern and efficient lab spaces, as well as for areas to further promote social and scientific interactions between teams.

Weaknesses and risks linked to the context

Implementation of key technologies and/or platforms in the domains of single-cell genomics, spatial (in situ gene and/or protein expression) analysis and computational biology/AI-based data processing appears as highly needed strategic investment for the next funding cycle, as already pointed out in the latest assessment.

Access of teams to platform use is sometimes limited by the shortage of technical staff.

As the relocalisation onto the new campus is still at least five years ahead, the unit may be at risk of insufficient support during the transition phase in terms of logistics and infrastructure.

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

Equal gender representation has been achieved in leadership positions. Over the last funding period, the CRI made substantial efforts to address open issues pertaining to gender balance, diversity and inclusion (DEI), work-life balance and research integrity. These include actions to promote team (co-)leadership by female investigators, adoption of family-friendly policies for institutional activities and the establishment of committees for gender and equality, and for mediation, ethics and scientific integrity. Health and safety measurements are set up and enforced by dedicated offices. The CRI promotes education and training initiatives via the participation to interdisciplinary master and PhD programs in the field of inflammation research, as well as to various national and international initiatives exploring the societal and economic impacts of chronic inflammatory diseases.

Weaknesses and risks linked to the context

The outlay of the future management structure is unclear at the time of writing. The unit should clarify the representation of the different classes of personnel in the steering committee as soon as possible.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

Technical equipment and platforms as well as grant leverage are excellent, attractiveness for foreign PhD students is good to very good, the scientific reputation is excellent to outstanding.

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 CRI members are nationally and internationally recognized as attested by more than 750 invitations to conferences and meetings such as the Asian, American and European societies of Nephrology, Immunology, Pathology, Hepatology and Gastroenterology. CRI members also have organized and/or contributed to the organization of more than 70 national and international meetings or symposiums (Faseb summer research conference, European and national monothematic conferences in Hepatology, Gastroenterology, Pathology, Immunology, Nutrition, Transplantation and Imaging, etc.). Several members were distinguished by awards (Emerging leader award and International Recognition award from European Association for the Study of Liver diseases, Rising Star from United European Gastroenterology, recognition from Bettencourt Fondation, grand Prix de la Fondation du Rein). Visibility is also attested by editorial responsibilities (editors, associate editors, members of editorial boards) for national and international journals (Journal of leukocyte Biology, Frontiers in Immunology, Journal of Hepatology, J Hep Reports). A number of CRI members are, or have been involved in research steering bodies, including responsibilities in national and European scientific societies (president and/or president of scientific council for EASL, AFEF, UEG, AFERO, SFN, SFI, SFNCM, SFP), evaluation committees as chair or members for Inserm (CSS3, CSS5 and CSS7), CNRS (CSS27), University (CNU 4401, 4302, conseil scientifique UFR Médecine), ITMO (PMN) and ANR (CE17, CE15).

Specific policies are in place for recruiting and training students and early career scientists through CRI's participation in national doctoral schools. An open call for new investigators (equivalent to junior Group Leaders positions) was launched in 2023 and is currently being finalized. The unit dedicates substantial resources and has developed formal procedures for internal promotions of researchers, technicians and engineers. The CRI has welcomed and/or recruited eight scientists with permanent positions, among whom two obtained an ATIP/Avenir grant. It has launched a call for welcoming junior groups, offering an intramural research grant support (selection by SAB). Two applications have been selected. Master and PhD students benefit from regular mentoring and project supervision and participate at national/international conferences. Communication of students with senior researchers at CRI is promoted by a yearly CRI Young Investigator meeting. Interaction between CRI teams is ensured via organization of weekly CRI seminars. Despite the difficulty in replacing permanent staff that are leaving/retiring, the center has been successful to obtain permanent positions ten during the contract, (3 Inserm and 7 UPC) that are essential for platforms. Three new permanent positions for engineers were additionally obtained in the last 2023 Inserm and UPC campaigns.

The CRI has also been highly successful in obtaining external resources from national (Agence Nationale pour la Recherche, Ligue contre le Cancer, ARC, Pair Inca, Fondation pour la Recherche Médicale, Inflamex labex etc…) and international funds (H2020, EF-Clif, international ANR-funded grants etc.) for a total amount of 4 to 5 M€/year. The lab manager has undergone training to apply for highly competitive European funding (H2020, ERC, etc.). CRI members have successfully applied to PIA programs such as DHU UNITY, FHU Mosaic RHU QUID NASH and Operandi, led by members of the CRI (DHU Unity and RHU QUID-NASH, FHU Mosaic, RHU Operandi, and contribute to DHU FIRE, FHU Appolo and FHU PaCEMM. PIA grant leverage amounts to over 4 M€ in total. Of note, a SIRIC grant led by CRI has just been obtained, with participation of half of the CRI teams as well as a 10 M€ RHU grant, LIVER-TRACK.

The CRI hosts five platforms. Among them, two imaging platforms, including iMAP, a unique mass spectrometry imaging (Rapiflex in 2023), which allows precise mapping of molecular species in tissue sections from animal models or patients. IMA'CRI provides access to a unique equipment and expertise for cell and tissue imaging, photonic imaging and clearing and expansion microscopy of organs, and in particular a recently acquired Clarity system that will be associated with a lightsheet phase view microscope. Three platforms are dedicated to biochemistry, cytometry and animal facilities. The CRI is also part of the UMS "FRIM" dedicated to the preclinical in vivo imaging analysis based on MRI and PET imaging together with computer tomography and ultrasound elastography.

Three additional core facilities were recently created (extracellular vesicle production, isolation and characterization, 16S metagenomic facility, electrophysiology device (Ussing chambers)).

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

Overall the number of PhD students and post docs present at the CRI is low, a problem that is in big part due to the living costs in Paris. There is a significant heterogeneity in PhD student recruitment amongst the CRI teams. The inclusion of technicians (lab or platform associated) as co-authors into publications is not implemented throughout the center.

While the overall grant leverage is impressive, there is heterogeneity amongst teams, with some being much more successful than others. The number of international and European grants is somewhat limited given the size of the CRI. Of the five obtained European grants, only one is led by a CRI team. No PhD student training networks have been set up to attract foreign students.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

Overall, the scientific production is outstanding.

The scientific production of the unit is extremely profused in terms of number and quality of research articles that have been led and published by members of the unit. The inter-team contributions are highly commendable.

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's is distinguished by a profuse scientific production (more than 2 500 research articles within the past 5-years), but also by the diversity of the scientific production that includes original articles, reviews, software development, clinical trials (47), encyclopedia. The quality of the publication is excellent, several of them being published in high-profile generalist journals, such as Nature Medicine (1), Nature Immunology (2), Science Translational Medicine, Immunity (3), New England Journal of Medicine (2), Nature Communication (13). On approximately 1/3 of them the members of the unit appear as leaders. An impressive number of articles is also published in high-profile specialized journals such as Hepatology (43), Blood (2), Gastroenterology (11) or Gut (12), where the unit's members appear often as leaders.

The contribution to knowledge is also evidenced by the number of citations of CRI scientists.

A major strength are the inter-team contributions to scientific production, with an evident collaborative research environment. Inter-team collaborations have allowed the unit to demonstrate the protective role of autophagy in endothelial and monocytes/macrophages against inflammation- driven fibrosis, in particular in patients with obesity associated non-alcoholic fatty liver diseases (J Hep 2020 and S Sci Transl Med 2020). Other collaborative key findings demonstrate that in the context of obesity, gastric GLP-1 expressing cells undergo plasticity changes after bariatric surgery, and contribute to restore circulating GLP-1 levels (Nat Commun 2021) and revealed a previously unknown role of endosomal TCR signaling in T cell activation, leading to a defect in peripheral T cell survival, T cell activation and anti-tumor cytotoxic T cell responses (Nat Commun 2020). The portfolio presented illustrates furthermore the translational nature of the research that is performed at the CRI and the bench to bed side strategy of the Center.

Between the teams, the number of published research articles range from 33 to 475 per team for the period. These variations are related to the size of the team and their composition, but also to the type of articles produced by each team. When high-profile research articles were produced within a team, the number of articles was lower compared to the production of teams that published many clinical reports. Overall, all teams significantly contributed to the publication output of the unit.

Electronic lab-books are used by all teams. Raw data are shared and stored on a common server. Strategies to train young researchers with good laboratory practices have been developed at the unit level. All rules and regulations for animal experimentation and for the use of human samples are well known and complied at the unit level. Most teams seem to put forward collegial decisions, including collective discussions on the projects and scientific strategies. The soundness of theories and methods that are implemented at CRI are also demonstrated by the high standard quality of the journals in which CRI members publish and the fact that many of these journals have implemented reports of detailed methods, reproducibility checklists, standards for statistical analysis. Finally, articles are deposited in the HAL open science site to be available for scientists, and whenever possible articles of the CRI teams are published in open science journals.

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

Specific policies or resources have not been adopted by the unit to mentor young investigators in their publication and scientific production strategies. This might be particularly relevant for future teams to be led by young investigators.

It is not clear how raw data from the acquisition machines are stored and traceable.

It is not clear if the unit has set means to support its staff in the choice of appropriate dissemination media, in order to avoid so-called predatory journals or conferences.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The CRI has developed excellent interactions with industry and has significantly increased its public engagements since the last evaluation.
The unit has made a significant effort to join scientific associations and increase visibility.

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

Clinicians of the CRI have strong interactions with different patient associations, covering all disease aspects studied within the CRI (obesity/nutrition: "les poids plumes", "la vie à un fil"; liver disease (Vascular disease association AMVF, SOS hépatites, seminars between clinicans and patients in the context of inflammatory bowel disease (Mikinaute)…). Several CRI members have contributed to clinical practical guidelines (for example hepatic encephalopathy, coagulation, occupational liver diseases, HCC diagnosis and management) and basic guidelines (for example autophagy).

The unit has been (directly or indirectly) involved in 49 clinical trials on viral hepatitis B, hepatitis D, HBs antigen seroclearance, use of CD71 and CD89 antibodies in Leukemia in phase 1b, and treatment of HCC and other liver cancers.

Diverse non-academic interactions have been developed through academic-industrial research projects involving several French SME dedicated to biomarkers and Imaging (Abbelight, BioPredictive, Intrasense, Metafora and Biocellvia, Association François Aupetit) and large industrial and drug companies (for example Philips, Sanofi and Servier). A total of 22 industrial contracts (ENVISION, EXPLORE, Johnson&Johnson, Terra Firma, Enterome, PGE-MUM, JellyNov, Tissium, Eukarÿs, Takeda, R&D MODERNA, R&D SELECTA BIO, ASTRA ZENECA, SANOFI, Nanostress, etc) for a total of over 1.6 M€ and six fees for service contracts for 347 k€ have been obtained.

Over 30 patents have been obtained by CRI teams. These are related either to new disease targets, biomarkers or methods for imaging. The unit has created two startups (Inatherys, monoclonal antibody development), carembouche (nutrition/food substitute) and has developed strong links with two additional startups (Eukarys, JellyNov).

Outreach activities included amongst others annual participation to "Apprentis chercheurs", DECLIC (https://www.cerclefser.org/fr/declics/), "L'arbre des connaissances. There is good dissemination of results through social media, press releases and interviews (Twitter, press releases, radio interviews and newspapers). A senior CRI scientist participates at "les expertes" to address journalist questions regarding fake news, and increase the visibility of woman in media.

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

No weaknesses were detected.

ANALYSIS OF THE UNIT'S TRAJECTORY

For the next contract, some reorientations are proposed but the focus on inflammation remains strong in the future reorganisation. For the next term, the unit proposes an organization based on three main scientific research axes. In the axis "Pathophysiology of inflammatory and fibrotic diseases" the aim will be to identify common features of inflammatory mechanisms, in immune cells, endothelial cells and fibroblasts across organs, (i.e, lung, kidney, digestive...) and in autoimmune disorders. The axis "Oncogenic inflammation and tumor development" aims at unraveling the sequence of events promoting cancer development in the context of inflammation, and decipher tumor heterogeneity by studying the microenvironment. In the third axis "Immunology, signaling and cell dynamics" the molecular events of the inflammatory response, focusing on oxidative stress, intracellular trafficking and signaling in immune and infectious-related diseases will be unraveled. This last aim will be closely linked to the new eCellTherapy core facility that will be set up to generate signaling oriented therapeutic tools notably new CAR-T cell technology.

Studies of lung diseases will be reinforced by arrival of teams/ researchers from U1152 and U996; Multimodal imaging, reinforced by the arrival of R Sinkus (U 1148) will strengthen expertise within the CRI applicable to carcinogenesis, in lung and digestive tissues with a specific interest on the impact of inflammation and intratumor heterogeneity. Creation of two junior teams in the context of a very recent international call, will reinforce studies on monoclonal immunoglobulins in chronic kidney diseases. Recruitment of a computational scientist with expertise in single cell protein expression atlases will help to address the lack of expertise in bioinformatics within the unit and strengthen collaborations. In particular, the unit plans to develop a task force on data mining and bioinformatics.

The scientific projections of the unit are totally in line with the new research challenges of the field. The vision of implementing expertise in bioinformatics, multimodal imaging is commendable. The unit has clearly analyzed its strengths and weaknesses, and the proposed structuration will continue to foster the dynamics of the unit, and place it at the forefront of inflammation research in France.

The management structure of the future unit will be based on an executive committee (monthly meetings, 7 members: director, deputy director, general administrative manager, 2 elected representatives for axis (1) and 1 representative for the two other research axes). A steering committee (team leaders, volunteer PI researchers (not team leaders), and representatives of engineer/technicians) will be created to assist the executive committee to develop and discuss scientific strategy, budget, operational actions (equipment acquisition, recruitment, internal calls for projects), draft internal regulations etc. The duration of election of steering committee members needs further clarification (2 years?). Unit decisions will be formally approved by a center council (meeting every 3 months) gathering the executive committee, all the team leaders and elected representatives of each professional's staff. The precise composition of the council remains to be defined at this stage.

In the future organization of the unit, the management and direction of the unit is clearly a very important strength. The director and deputy director, helped by the executive committee have a very clear vision of the most efficient organization they could propose.

RECOMMENDATIONS TO THE UNIT

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

Set-up of structured and protected modalities of communications between the management and early career investigators is strongly encouraged.

The future management structure should be clarified as quickly as possible, participation of technical personnel be ensured where applicable, and be communicated efficiently to all personnel.

We recommend that postdoc representatives are included in the steering committee to ensure active participation of the workforce to the Unit development.

All official meetings, institutional and training activities should be conducted in English to ensure equal opportunities to international scientists.

Young talented PhD students and post-docs, as well as young scientists should be strongly encouraged to apply to competitive European or international calls (ERC, HFSP, EMBO...) and be efficiently trained / assisted with the application / selection procedure.

Efforts should be dedicated to the implementation of bioinformatics and AI core facilities within the CRI, with dedicated staff. A minima and on the short term, a think tank should be set up in order to coordinate the participation of volunteers to this platform, and organise (students) training as a first step. On the long term, this platform will require highly specialized and dedicated staff. The implementation of such core facility should be accompanied by reflection and efforts around data management (intellectual property, data storage, transfer to/exchange with private companies, computer facilities...)

Recommendations regarding the Evaluation Area 2: Attractiveness

Recruitment of PhD students and post doctoral researchers should be improved. Application to PhD training networks should be considered, as well as opening new prospects to hire foreign students.
The number of international and European grants should be increased.

Recommendations regarding Evaluation Area 3: Scientific Production

Specific policies or resources should be set up by the unit to mentor young investigators in their publication and scientific production strategies. This might be particularly relevant for future teams to be led by young investigators.

Data management and tracing needs to be structured.

Guidelines for the choice of appropriate dissemination media, in order to avoid so-called predatory journals or conferences should be available to Unit members.

The number of engineers and technicians should be increased and they should also be associated to publications. This should be formalized by a written document adopted by all teams.

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

The committee encourages the CRI to continue its important outreach activities and links with clinical and industrial entities. PhD students and post-docs should be more closely associated to activities associated to industrial entities, in order to improve their recruitment possibilities at the end of their contract. In particular, CIFRE PhD programs should be encouraged.

TEAM-BY-TEAM ASSESSMENT

Team 1: Physiopathology and treatment of viral hepatitis

Name of the supervisors: Mr Tarik Asselah & Mr Abdellah Mansouri

THEMES OF THE TEAM

1) Immunological mechanisms associated with HbsAg seroclearance in chronic hepatitis B: B-cell functions in infected and healthy patients.

2) Mitochondria / Hepatitis B virus (HBV) interactions

3) HBV cure programme

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Key recommendations made to promote a sustained basic research program have not been followed:

1) Re-balance the disequilibrium between clinicians and scientists: this issue has not been solved. On the contrary, this imbalance seems more pronounced for the next mandate.

2) Improve the attractiveness for students and postdocs: this issue is to be solved. The team struggles to recruit students and postdocs.

3) Reinforce basic science: (i) A major study dealing with the link between mitochondrial function and chronic HBV infection in patients has been recently published (Hepatology 2023), however, no follow-up program on mitochondria-HBV interactions has been described. (ii) No basic science has been implemented in the project focusing on B-cell function in chronic HBV patients. This project is addressing purely clinical questions (clinical trial). No publications in this project since the last mandate.

4) Reinforce collaborations with other CRI teams: this issue has not been solved. No new collaborations have been mentioned, apart from those already involved in the team's projects (El Benna, Paradis).

5) Develop new prospects with emerging countries, such as India, African countries. This recommendation has not been followed.

6) Possibility of cross-funding of basic science projects with funding from clinical trials. This recommendation has not been elaborated.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	5
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	21
Sous-total personnels permanents en activité	**27**
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	**31**

EVALUATION

Overall assessment of the team

The team's PI is an expert in the field of chronic hepatitis B (CHB) and viral hepatitis infection (notably hepatitis delta virus HDV), with international recognition, excellent visibility, and excellent publication record (mostly clinical trials). The team leads or participates in several clinical trials on novel treatments against CHB or HDV infection, for which the current therapeutic options are limited. The team develops cutting-edge therapies against viral hepatitis, thanks to the high number of clinicians who are members of the team. The overall assessment for this team is excellent.

Strengths and possibilities linked to the context

The team has international recognition and excellent visibility in the field of antiviral therapies, through the design of, or, participation into clinical trials (against hepatitis B and more recently hepatitis delta). A recently developed topic in the team led to the identification of several mitochondrial dysfunctions (mitochondrial DNA alterations, altered role in oxidative stress generation) translatable into viral pathogenesis (HBV, HCV), and related to liver fibrosis or cirrhosis mediated by such viruses and also by metabolic disorders (non-alcoholic steato-hepatitis NASH). Several members of the team have been awarded with prestigious prizes: Laureate of Emergence en Recherche (2020), Prize JPHOD (2017), prize of "association Française de chirurgie", prize EAHPBA (Manchester, UK). Team members have been invited to give talks and lectures at several occasions, of which "Hepatology on the Nile" postgraduate course in Egypt (2022), "Expanding HBV treatment criteria, new biomarkers and future treatment" in USA (2021).

The team head has (co) organized several national and international meetings on viral hepatitis (Paris Hepatitis Conferences, EASL). The PI is member of the board of experts in liver diseases of the EASL (for which he contributes to guidelines writing). The team has an excellent publication record, with 196 publications in total over the past five years, of which 80 are led by members of the team as either first or last authors. Most of these publications refer to ongoing or completed clinical trials, and are published in the top five journals in the field: NEJM, Lancet, Lancet Infectious Diseases. In these clinical trials, the team either leads or participates in clinical trials, dealing with novel treatments against CHB or HDV infection, for which the current therapeutic armamentarium is very poor and unspecific. Several publications are invited reviews, which confirms the international recognition and visibility of the team. Basic science dealing with mitochondrial dysfunctions in liver fibrosis and cirrhosis has been published in the more specialized journal Hepatology.

The team is involved in public outreach through close contacts with patient associations.

Weaknesses and risks linked to the context

The team has essentially been funded on national grants (ANR, ANRS), for a total of 313 k€. Importantly, this includes a funding for a PhD candidate, already present in the team. The balance between public and private financial support is approx. 1/3 - 2/3 (220 k€ from Inserm, 600 k€ from industrial partners GSK and Janssen & Janssen). However, it remains unclear whether this funding is fully secured for the next mandate. Additionally, such amounts appear "short" compared to the size of the team and the requirements for a sustained basic research program.

In the next mandate, the team will be composed of fifteen clinicians and only one scientist, creating a dangerous imbalance between clinical and basic science projects. A major weakness is that the team would become a mere clinical team, involved in major clinical trials but increasingly risks being disconnected from basic (fundamental) science.

The attractiveness of the team with two docs and no post-doc for the next mandate is insufficient, although a post-doc position is open at present. This could increase the imbalance between clinical and basic science already mentioned above. Only three members of the team hold the HDR, which is an impediment to attract docs and post-docs students. No information has been provided on the training of students during their stay in the team, neither on their future after their PhD or post doc.

Currently, the team has no supporting personnel (i.e. ITA), which could have further deleterious repercussions on basic science research.

As it stands, details provided on a future basic science program deal with the extension of already published data on patients with liver fibrosis and cirrhosis (Hepatology 2023) to patients with liver hepatocarcinoma, in link with mitochondrial dysfunctions. This is a weakness that had already emerged in the previous report.

Most of the project presented for the next mandate is either already published (mitochondria and CHB), or purely clinical studies (B-cell function in chronic HBV-infected patients).

The risk at short or mid-term perspectives is that the team becomes an only clinical team.

Analysis of the team's trajectory

The team seems to become more and more clinical, through its publications and human resources (more clinicians than scientists or PhD students, no ITA). Although the level and quality of publications are and remain high, the team mainly publishes clinical studies and reports of clinical trials, and very little basic science studies (for the last 7 years: Hepatology 2023). The team's scientific activities are highly pertinent they respond to urgent unmet medical need for novel antiviral therapies. However, and as a matter of fact, the team appears as mainly clinical instead of oriented toward basic science.

RECOMMENDATIONS TO THE TEAM

The team should solve the imbalance between clinicians and scientists, as well as between permanent positions and contractual personnels (ITA, docs, post-docs). More basic science should be injected to the projects. Attractiveness toward docs and post-docs should be improved, by posting jobs offers, etc.

The balance between clinical and wet lab studies should be re-established to strengthen basic science in the team.

In terms of funding, since some aspects remain unclear from the provided documents, the team should find new prospects, while maintaining strong contacts with industrial partners, and secure more substantial grant amounts with regard to the large size of the team.

Team 2: Basophils, mast cells and immunopathology

Name of the supervisors: Mr Nicolas Charles & Mr Ulrich Blank

THEMES OF THE TEAM

The main research theme of the team is the role of basophils and mast cells in inflammatory kidney diseases and autoimmune disorders with special focus on signalling events leading to release of inflammatory mediators like prostaglandin D and chymase. The group combines in vitro studies, animal models and translational studies in patients with autoimmunity.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

1. Recommendation: Increase the level of collaboration with other teams in the CRI:

The BMI teams strongly interacts with other teams of the CRI both in terms of the research focus on inflammatory diseases and in terms of providing technical support and organizing core facilities like animal facilities, interaction with clinical departments and biobanking, flow cytometry and surgery platform. Multiple high level publications were performed in collaboration with other teams of the CRI and further national and international collaboration.

2. Recommendation regarding team organization: maintain cohesive and good spirit

Numerous publications often with several team members indicate a good team spirit. The team structure seems to be challenged by retirements and movings. The team needs to find adequate personnel and consolidate again. A new MD/PhD candidate with a tenure position at the Bichat hospital and impressive track record with a postdoctoral fellowship at the University of Edinburgh and an own junior group funding will join the team. He has a strong focus on research in nephrology and will clearly strengthen the team.

3. Recommendation: More translation of mechanistic studies to human physiology and disease

The team clearly has spent many efforts to fullfill this recommendation by building a strong collaborative interface with the clinical departments. In addition, several publications including one in Nat Communications was performed with a large cohort of SLE patients. This shows that translation has become an important focus of the BMI-group and also enabled them to file patents for clinical use of PGD2-receptor antagonists.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maitres de conférences et assimilés	1
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**12**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	2
Doctorants	4
Sous-total personnels non permanents en activité	**8**
Total personnels	**20**

EVALUATION

Overall assessment of the team

The BMI team has proven to successfully combine cell culture studies on mast cells and basophils, with functional studies in animal models and translational studies, including therapeutic and diagnostic clinical trials in patients. Numerous high-level publications, extensive fund raising, patents and the contribution to a start-up are good indicators of high quality and output. The future scientific projects are logical extensions of the current work and expertise. A new very promising and dedicated team member has recently be recruited to the team. Overall assessment of the team is excellent to outstanding.

Strengths and possibilities linked to the context

Over the years, the BMI team has gathered great experience in the field of immunopathology with a special focus on renal inflammatory/autoimmune disease, basophils / mast cells and their signaling. This is demonstrated not only by several high-profile publications but also by the development of important new tools in the basophil-area. A new basophil-specific mouse model was generated (CT-M8 mice) that allows the identification of basophils via tdTomato and basophil-specific Cre-mediated gene deletion. By breeding with the ROSA26flox-stop-DTA mice, this model also allows the generation of basophil-deficient mice for functional analysis in disease models. This mouse model was used in two very recent publications (Front. Immunol. 2022 and Immunity under Revision) and is supposed to be an important tool for further work. The basophil and mast cell research field has been hampered by the lack of appropriate tools in the past.

In terms of basic research, the team also has vast experience in basophil and mast cell signaling and analysis of downstream events including release of new mediators. This know-how is nicely combined with subsequent in vivo studies in mice and translational studies in patients.

The team has published 261 papers in peer reviewed journals among them several first / last author publications in top journals like Nature Communications, J Allergy Clin Immunol., Kidney Int. and Science Signalling. The overall publication output is excellent to outstanding. In addition, the team has listed 29 conference invitations (ESPU, Congrès Francais de Rhumatologie, SFNDT), with talks by several different members of the group and a PI has been involved in organisation of a Faseb Conference. The PIs serve on editorial boards (Frontiers in Lupus/Immunology) and are members of national committees (ITMO, CNRS CSS27) and the European Mast cell and Basophil Research Network (EMBRN).

Since the last evaluation, the BMI group has established strong clinical collaborations. Several members of the group have a clinical background or work as clinicians, thus being able to provide biomaterial, clinical data from well-characterized cohorts of patients, as well as expertise regarding potential study design and clinical needs. It seems that the team has successfully gone or paved the way from basic research to clinical application via patenting (Patent related to compositions and methods for treating or preventing lupus (W020120710042) and patent WO2016128565A1 related to the use of PTGDR-1 and PTGDR-2 antagonists for the prevention or treatment of systemic lupus erythematosus) and future involvement of one team member in the creation of a spin-off biotech.

Another important asset of the group is their engagement in promoting and attracting young talents. They describe in their report several activities of knowledge and competence transfer starting at under-graduate level, up to post doc level. Together with a high visibility also in the research community (e.g. EMBRN) this should enable the BMI group to successfully go through pending restructuring processes. During this mandate, the team trained nine post-doctoral fellows, eight PhD students, twelve master students and twelve technician students. Five Theses were completed. Several team members fulfil important teaching tasks, e.g. coordination of two of the six teaching units of the labex Inflamex master program and managing a third one; Members of the team also train several technical students each year and teach in immunology master programs and presents biomedical research to elementary school pupils.

In the past years, the BMI group was very successful in acquiring third-party funding from several sources including five ANR grants and the PIA-funded labex INFLAMEX and private industry funding. In total over 2 M€ were raised. The team was labelled by the FRM in 2019 for their work on lupus-related photosensitivity.

Weaknesses and risks linked to the context

The BMI group has to go through a restructuring process due to retirements and moves. Although a new very promising team member has been recruited, the group still needs to attract postdocs and PhD students taking into account the gender balance to perform the ambitious new projects. This should be possible based on the high amount of third party funding.

No HDRs were completed.

As personnel-decisions have a great impact on the long-term success of a group hiring of adequate new researchers and consolidating the group is of high importance. The number of permanent positions should not fall below a certain level to keep know-how and competences in the group. This enables new people joining for a limited time span to become integrated into the group quickly and to be productive right from the start. These aspects are important for recruiting talented young people that are more and more sceptical regarding an uncertain scientific career.

Another challenge is the limited availability of research tools, especially for mast cell research. In addition, validated antibodies for identification of mast cell subsets and basophils in human tissue are lacking at the moment. Also in mice, identification of mast cells and functional studies are still a challenge despite recent development of a new mast cell deficient mouse strain.

Rising costs and the current economic crisis make adequate fund-raising more difficult, not only for scientific projects but also for start-ups. The BMI group seems to be able to compete in more difficult environment.

Analysis of the team's trajectory

The BMI team successfully combined basic research (signaling events in mast cells / basophils and identification of new mediators) with functional studies in mice and translational studies in patients, including the performance of clinical trials with a therapeutic (e.g. anti-IgE) or diagnostic (CD62L expression) approach in SLE patients. The success of the team is well documented in numerous high ranked publications, extensive fund raising, patents, clinical trials and contribution to a start-up.

For the next funding period the BMI group will evolve into the Laboratory of Immunopathology, Nephrology and Cell signalling (LINCS) but keep its main fields of action.

WP1 (Immunopathology) seeks to identify dysregulated immune pathways in patients with autoimmunity, and then goes back to experimental disease model to check whether similar dysregulations are present and have a functional impact on disease onset and disease progression. Several cohorts of patients will be studied including SLE, Sjögren's syndrome, MCTD, EGPA, ITP and sepsis with a focus on basophils and IgE. Novel methods like scRNAseq will be used to characterize potential basophil heterogeneity. The role of novel basophil regulators like a potential novel IgA receptor on basophils with negative regulatory function will be studied.

WP2 seeks to understand the underlying mechanisms of frequent disease regression in SLE patients and the role of mast cells in PD-induced peritoneal fibrosis. The newly recruited team member C. Cohen (MD / PhD) will take care of these questions. In addition, the role of mast cells will be studied in models of long- and short-term renal fibrosis with a special focus on mitochondria for mast cells regulation.

WP3 deals with cell signaling and seeks to investigate the role of mitochondria in regulation of mast cell numbers and functions. In addition, it seeks to understand the molecular mechanisms (e.g. fusion regulators) involved in degranulation and mediator release by mast cells. This may lead to new possibilities to interfere with mast cell biology in mice and humans.

The further plans of the group are nicely based on their scientific expertise, highly interconnected and a logical extension of their past work. The projects will increase our knowledge of immune dysfunctions in autoimmunity and have a high chance to reveal novel therapeutic targets.

RECOMMENDATIONS TO THE TEAM

1. Personnel composition of the group: Retirement of one PI and leaving of other researchers give the group the opportunity to hire new personnel and to bring in new competences. The joining of a new researcher seems to be a very good fit for the group, as he has a strong track record and interest for research in nephrology.

2. Mast cell biology in mice and patients is on the agenda of the group. The group needs to get research tools either from collaborators (as far as available) or generate own research tools as needed.

Team 3: Phagocytes and nadph-oxidases in inflammation

Name of the supervisor: Mr Jamel El Benna

THEMES OF THE TEAM

The team Phagocytes and NADPH-Oxidases in Inflammation focuses on the regulation of NOX expression and function in physiological and pathological situations (especially chronic inflammation), with an emphasis on NOX2 expression in phagocytes and NOX1 in colon epithelial cells. The team combines basic and translational research in the field of NOX regulation and neutrophil biology.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous recommendations were:

To maintain the excellent quality of basic research and increase research funding

To secure financial support to recruit post-doctoral scientists and consider the integration of a clinical researcher

To consider utilising existing mouse models to improve scientific projects, to focus aspects of the work based on a limited number of team members and to develop translational research projects using their molecular tools.

During the current period, the Team has maintained the quality of basic research and its capacity to offer an excellent training to PhD students.

The Team hosted three post-doctoral scientists and integrated one Inserm researcher (2022) who has brought her expertise in innate immunity in mouse models. However, the use of mouse models remains somewhat limited (despite the added value they could bring in terms of preclinical research), balanced by the development of original organoid models.

The Team has maintained the quality of translational research; no integration of clinician during the last period.

The number of research axis was maintained and the staff remained constant overall. New biochemistry expertise will be acquired with the integration of two researchers in 2025.

The strategy to identify new anti-inflammatory approaches remains poorly developed. As recommended in the previous report, translational research has been strengthened and will be further accentuated in the future project.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maitres de conférences et assimilés	2
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**9**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	6
Sous-total personnels non permanents en activité	**7**
Total personnels	**16**

EVALUATION

Overall assessment of the team

The Team has an internationally recognized expertise in the biology of NOX in phagocytes and inflammation. The scientific production and training are of high quality with strong national and international collaborations. The overall assessment is very good.

Strengths and possibilities linked to the context

The team has national and international recognition in the field of neutrophil biology and NOX regulation with focus on the mechanisms involved in NOX2 regulation in phagocytes (neutrophils, monocytes) and the understanding of the role of NOX1 in epithelial cells and NOX5 in monocytes and follows up both fundamental and translational aspects. The strategy relies mainly on cellular and molecular approaches that perfectly fit with the team's expertise. Among key scientific findings is the unravelling of a new mechanism of NOX2 regulation involving ROCK2 that is specific for monocytes (PNAS 2023). A novel function of p67PHOX as an unconventional regulator of p47phox-phosphorylation, a key process required for NOX2 activation, was analysed using neutrophils from patients with chronic granulomatous disease (Blood 2022). Furthermore, a new role of NOX1 of colon epithelial cells in mucosal immunity and inflammation via the regulation of production of lipocalin-2, a bacteriostatic protein with inflammatory properties (Mucosal Immunology 2019) was reported. The staff composition illustrates the team's objective of combining basic and translational research. The Team is composed of nine permanent staff including three researchers (2 DR and 1 CR, 2 emeritus researchers, 3 clinicians) and 1 engineer. Integration of a CRCH (Inserm) researcher in 2022 (CRCH, Inserm) will bring expertise in innate immunity and mouse models.

The Team trained twelve PhD (11 completed during the current period) and two visiting scientists. Most of the PhD students hosted during the last period came from abroad, thanks to long-standing and strong collaborations with Universities in Tunisia, Algeria and Lebanon (1-2 visiting scientists per year). Training of PhD students was excellent with at least two first author publications at the completion of their PhD. Team members teach in five different Master 2 courses.

Gender equality is respected. The organization of team life is classic, with weekly team meetings. Particular attention is paid to newly recruited members, who are given ad hoc training in safety rules and access to institutional training. The Team offers PhD scientists and visiting scientists appropriate working space.

Team members are involved in different national and international networks related to NOX and neutrophils (labex Inflamex, DHU-Fire, DHU-CARE, EU-COST, CNRS-GDR) and were involved in four congress organization committees (e.g. Neutrophil workshop at the Annual Meeting of the SFI), evaluation committees (ANR, FRM, GFRS, ECOS-NORD, UPC, International Swiss Science Foundation, Belgium FNRS, CGD Research Trust, etc.) and had editorial activities (J of Leukocyte Biology, Biochemical Pharmacology, Mediators of Inflammation, Frontiers in Immunology).

The Team has published 78 original peer-review articles, four book chapters and gave 21 conferences as invited speakers in national and international meetings. 26 articles were published in high-profile journals (Blood, J Exp Med, PNAS) and 35 were published in very good, peer-reviewed journals. 40 out of 78 publications were signed as 1st/last authors. Whenever possible, the team encourages publication of articles in open access journals.

The team has been funded by national agencies and charities (k€ 586) over the last period: one ANR, Inflamex and four contracts from charities/foundations), as well as k€ 75 from Inserm TRANSFERT (TTO of Inserm) and EFS. Valorisation activity of the team has been very good, in particular through licensing of tools generated for research. The team has filed one patent and licensed five antibodies (phospo p47 phox) with Merck Millipore.

Weaknesses and risks linked to the context

As underlined by the previous committee, the team appears predominantly supported by the labex.

There is a low number of publications in general journals as 1st/last authors and no contribution of research activities to society.

Analysis of the team's trajectory

In 2025, the team will be headed jointly by Dr Pham My-Chan Dang (DR2, CNRS) and Dr Margarita Hurtado-Nedelec (MCU-PH). The project of the Team, which will be entitled "Phagocytes, NOX and ROS in inflammation" (PNRI) is a continuation of the one developed during the current period, by capitalizing on their expertise and know-how, and by leveraging the tools generated to explore NOX activation pathways. Moreover, two new researches experts in glycosylation coming from Gouya team will be incorporated.

The research project is organized in three interconnected and integrated research programs aiming at deciphering the biology of NOX in phagocytes and colonic epithelial cells: (1) regulation of phagocytes and NOX2 in normal and pathological inflammatory context, (2) regulation and role of NOX1 in colonic epithelial cells in response to inflammatory mediators and microbiota and (3) identification of NOX1- and NOX2-derived ROS targets to better understand their impact in inflammatory processes and to discover new markers in inflammatory diseases.

These axes reflect the strengthening of translational research, with innovative approaches (3D models, organoids) based on the use samples from healthy subjects and patients (Crohn's disease, RA); this translational approach includes murine models (rat and mouse). The strategic choice to reinforce translational research is helped by the fact that the Team will be headed jointly by a researcher/clinician team management (Dr Pham My-Chan Dang (DR2, CNRS) and Dr Margarita Hurtado-Nedelec (MCU-PH)).

Team leaders must remain vigilant on the fact that the numbers of projects remain high relative to the staff. Moreover, the expertise of the new members must be incorporated in the projects based on a clear hypothesis and with long-term objectives.

RECOMMENDATIONS TO THE TEAM

The team should continue to deliver excellent research and is encouraged to publish in generalist journals. The team is encouraged to develop/foster international collaborations and should contribute to events for the general public (University open days, Fête de la science,…).

The team leaders are encouraged to integrate clinicians to foster translational research.

The team should implement a prioritization strategy to maximize its human resource potential with a limited number of personnel and seek more funding opportunities, particularly from national agencies.

The team is encouraged to collaborate with industries to identify/validate new therapies using their models. Moreover, the new members and their experience should be integrated in the research line based on a correct hypothesis and with a clear and structured long-term project.

Finally, the team is encouraged to recruit/integrate junior scientists.

Team 4: Heme and iron in oxidative stress and inflammation

Name of the supervisor: Mr Laurent Gouya

THEMES OF THE TEAM

The team is divided in three groups dedicated to the study of:

- **heme biosynthesis abnormalities**
- **iron metabolism** and
- **glycosylation abnormalities**

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous evaluation of the team was very positive and they were encouraged to continue with their productivity, activities and organization. They only were encouraged to increase the number of technical staff to support the projects.

However, they have not improved this situation given that they have gone from two technicians to one. In the report they mention that the LBMR provides a technician for methodological development. It is not clear whether this means that the group has finally two technicians or if it refers to the only technician of the group.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maitres de conférences et assimilés	5
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	7
Sous-total personnels permanents en activité	**17**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	4
Sous-total personnels non permanents en activité	**5**
Total personnels	**22**

EVALUATION

Overall assessment of the team

The HIROS team is an outstanding quality team for the publication record and the scientific recognition of the expertise of the team leaders.

Strengths and possibilities linked to the context

The team has unique expertise in studying heme and iron metabolisms and glycosylation mechanisms of proteins. The team has produced 130 publications with 59 publications in first, last or penultimate position. Including relevant works, such as a multicenter phase III clinical trial published in NEJM as last author, a study in American Journal of Human Genetics, a collaborative study in PNAS and Hepatology (first author). The team has relevant impact at the translational level at the national and international level. They have developed

methods transferred to the LBMR Porphyrias, a state-of-art method to measure hepcidin in human and mice samples (blood and urines) and a new treatment of congenital erythropoietic porphyria (CEP) by iron depletion.

The team is formed by members with complementary expertise performing both basic and translational research with international recognition. The team organized the international congress on porphyrins and porphyrias (ICPP) in 2017 and was involved in the scientific committee of the 2019 and 2020 editions. Team members have given 47 talks, including 12 invited participations 6 at international conferences (Gordon Newport 2018, ICPP Bordeaux 2017, ICPP Milan 2019, NCBI/NIH Iron Hac 2019, Belgian Society Internal Medicine Annual Conference L Hulpe 2019, ICPP 2022). They have also technological transfer activity. Methods developed in the research lab are transferred to the LBMR Porphyrias and the LBMR provides a technician for methodological development.

The team has trained five PhD students and hosted two visiting junior scientists. Moreover, the team was selected to coordinate a Phase three clinical trail using siRNA treatment for acute liver porphyria.

The team has benefited from a significant recurrent Inserm/UPC funding with an annual budget of about 70 k€. They have also obtained funding for a total of 1 103 k€ with 100 k€ of industrial grants, 599 k€ from ANRS, 284 k€ labex, 100 k€ FRM and 20 k€ idex.

Weaknesses and risks linked to the context

The structure and location of the team is going to change completely. In 2025 the part of the team dedicated to heme and iron metabolism will leave the CRI and will merge with Mariano Ostuni's team to create an Inserm unit on Necker site bringing together two teams with complementary themes, which already collaborate together, around anaemias and erythropoiesis.

The part of the team dedicated to glycosylation which joined the HIROS team in 2017 will be incorporated into the "Phagocytes, NOX and ROS in inflammation" team led by My-Chan PHam Dang and María Hurtado-Nedat.

Analysis of the team's trajectory

Not applicable

RECOMMENDATIONS TO THE TEAM

Not applicable

Team 5: Inflammatory and stress responses in chronic liver diseases

Name of the supervisors: Ms Sophie Lotersztajn & Ms Hélène Gilgenkrantz

THEMES OF THE TEAM

The main research themes are focusing on the understanding of the inflammatory mechanisms underlying alcoholic and non-alcoholic fatty liver disease (FDL) and its complications. Complementary, the team is focusing on the development of prognostic biomarkers and immunomodulation-based therapeutic strategies for FDL. The team emphasizes the development of novel translational approaches (bench to bedside) by integrating basic researchers and clinicians in the team. The research themes are a continuation of the topics presented during the last evaluation with changes in the organization of the leadership of the team. The team is now co-headed by Dr Gilgenkranz, the former co-leader Dr Rautou started his own team at the CRI.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Implemented recommendations:
The team addressed most recommendations of the previous reports. They maintained their excellent publication track record and improved their policy to publish in higher level generalist journals which recent publications in Nature Communications (2) and Science Translational Medicine (1). The team is actively collaborating with other CRI teams and emphasized the translational aspects of their research by integrating basic scientists and clinicians. The interaction between projects has been improved and addressed also by the reorganization of the team. The research on epithelial cells is continued as strong CRI collaboration with the team from Dr Rautou.

Pending implementations:
Vigilance about geographical separation between Bichat and Beaujon was recommended to maintain coherence of the team. This has not been elaborated very much in the auto-evaluation and remains a challenge and potential threat to the coherence of the team. However, the construction of Campus North end of the decade will attenuate this in a long term by gathering research and clinical parts of the team. Also, a relative low attractiveness to postdocs has been highlighted in the previous evaluation and remains a weakness of the team. Finally, a decrease in supporting staff (techs, IE) has been noted last time, a number which temporarily recovered between 2017-2021 but has decreased again to only one 'ingénieur d'étude' recently.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	11
Sous-total personnels permanents en activité	**19**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	2
Sous-total personnels non permanents en activité	**3**
Total personnels	**22**

EVALUATION

Overall assessment of the team

The team is delivering state-of-the-art translational research on the prediction and therapy of chronic liver disease with high international recognition and visibility. The team made major contributions to the field with an outstanding track record in top specialized and general journals, clinical studies and patents. The team has an outstanding capacity to secure funding and collaborating actively within the CRI and within research consortia.

Strengths and possibilities linked to the context

The team was a founding member of the CRI in 2014 and part of the labex Inflamex. It is currently headed by Dr Sophie Lotersztajn and co-headed by Dr Gilgenkrantz. The team is comprised of 11 permanent scientists (5 basic scientist Inserm/CNRS, 6 clinicians) and five non-permanent positions (2 PhD candidates, 2 master student, 1 engineer) (last update end 2022). The group is located at two sites: the wet lab research at the Bichat Medical faculty and clinicians at the Beaujon hospital. The team is performing state-of-the-art basic and translational research on the prediction and therapy of inflammatory chronic liver disease with high international recognition and visibility. Amongst the major contributions to the field have been (1) the identification of lipid metabolism as an immune-metabolic target, (2) the identification of a non-canonical form of autophagy as liver protective mechanism during inflammation and fibrosis, (3) the identification of MAIT cells as driver of liver fibrosis and putative therapeutic target, (4) identification of dysregulated of blood immune cells in during acute liver failure (ALF) (5) identified candidate biomarkers for metabolic and inflammatory response to disease and (6) developed novel therapeutic strategies and guidelines for cirrhotic patients with ALF. Since 2017 the team published 360 publications (284 original articles) in international, peer reviewed journals including first, senior and/or corresponding author in top specialized (i.e., Gut, Hepatology, JHep Rep., J Hepatol.), and general journals (Nat Comm., Sci Transl. Med., N Engl J Med.). Moreover, the team filed three patents, participated in the definition of new guidelines for patient care and partnered clinical studies. In the last five years the team secured external funding of 3.2 M EUR from national (labex, ANR, AFEF, FRM, French ministry of health, etc…) and international grants (i.e., H2020, EF-CLIF). Importantly, the team recently secured 6M funding as work package leader in a large translational SIRIC consortium sustaining their research for the next years. The team is actively collaborating with other CRI teams and is internationally visible in networks, associations, commissions and boards of the clinicians and the basic scientists. This includes a partnership with the Institute of Liver and Biliary Sciences in New Delhi, India. The group actively contributes to dissemination of their research and shaping the scientific field (Editorial board of Medicine & Science, HG; Declics dialog between researchers and school students, science festival, HG, ethic committees as the CMEIS CRI and the Comité d'éthique de la ligue contre le cancer HG). Moreover, they vulgarized their research to reach out to the public and the society in frame of educative movies (FRM) and by valorisation (proof-of-concept studies together with Inserm-Transfer and SATT to support, e.g., COPOC subvention).

Weaknesses and risks linked to the context

Despite five HDR of team members (3 HDR from basic scientists) the international visibility translates into attracting top students and PostDocs only in a limited fashion. Moreover, the local separation between wet lab and clinical researchers may pose a risk for the unity of the team. Even though a new joint Campus is in sight in the long term, no short-term measures are in place to strengthen team coherence.

Analysis of the team's trajectory

The main future research axis aims to develop:
1) Immune cell autophagy as therapeutic target. Collaboration with other CRI and international teams, using patient-derived immune cells and mouse models of chronic liver injury, fibrosis, and hepatic inflammation to evaluate if the previously identified metabolic pathway can be targeted. Two front runner compounds (TAT-beclin D11, autophagy-inducing peptide, and FcRn ligand) will be used to decipher the mechanism of action of the anti-fibrotic effect.

2) MAIT cells as candidate biomarker and therapeutic target. Study of patient blood, MAIT-deficient mouse models, precision-cut liver slices, liver regeneration mouse models. In collaboration with CRI teams and international collaborators the study of spatial transcriptomics and large-scale immunostaining in mouse models.

3) The validation of identified candidate biomarkers in large patient cohorts. Collaboration with a CRI team and international collaborators. Mechanistic studies of the role of albumin during immunomodulation. H2020 consortium funding (*DECISION*).

4) Novel therapeutic and predictive strategies. Involved in several clinical studies evaluating the effect of immune-modulation-based strategies and AI-based prediction model of bleeding during transplantation (H2020 funding, industry funding).

The future research presented by the team is a logical and important continuation of their previous and current research and outlines a new innovative allay (axis 4) which seems synergistic with axis 1-3. The big questions addressed by their research program are innovative and highly relevant to the field and are responding to urgent unmet medical need for reliable biomarkers to better stratify patients at risk and for novel concepts to treat chronic liver disease.

Weaknesses of the future program:
The future projects depend a lot on the mouse facility and the established models. The accessibility of the animal models paired with a lack of trained personnel could pose a potential threat.

RECOMMENDATIONS TO THE TEAM

The team should better translate its international visibility and reputation to enforce its attractivity for students and postdocs.

The team should remain vigilant about the geographical separation between Bichat and Beaujon and reinforce regular joint meetings and seminars between basic scientists and clinicians to strengthen the team spirit and coherence.

The team should provide an animal experimentation plan including animal training (concepteur, surgery, writing protocols for ethical) for scientists and supporting staff working with the animal models. The interaction with the animal facility should be formalized and incorporated in the experimental planning process if the team.

Team 6: Glomerulonephritis & immunoreceptors

Name of the supervisors: Mr Renato Monteiro & Mr Martin Flamant

THEMES OF THE TEAM

The team GLOMI is co-managed by Drs Monteiro and Flamant. The research programs aim at deciphering the role of Chronic Kidney diseases, especially IgA Nephropathy (IgAN) and its relationship to gut microbiota exploring the gut-kidney axis, by characterizing patient's microbiota, IgAN's relationship to autoimmunity, as well as mechanistical explorations of the CD89 and IgA-CARD9 axis in the microbiota dysbiosis. Furthermore, the team also studies Src as biomarker in autoimmune glomerulonephritis, and lately MAIT cells in COVID-19 infection. Altogether the team aims at defining distinct pathways in CKD with the goal to identify targets for new therapies.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

As recommended, the team focused and strengthened their work in IgAN, intracellular signaling and expression of immunoreceptors. Their previous work in podocyte and renal denervation research was not mentioned as part of their current scientific subjects. Furthermore, the team seems to have implemented paths to translate their basic findings into the clinical setting.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	5
Maitres de conférences et assimilés	2
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	7
Sous-total personnels permanents en activité	**15**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	2
Doctorants	4
Sous-total personnels non permanents en activité	**6**
Total personnels	**21**

EVALUATION

Overall assessment of the team

The team of GLOMI has an excellent to outstanding track record in basic and translational research on the immunopathology of chronic kidney disease with international recognition and visibility. The reviewer panel acknowledges the important contributions of the team to the CRI.

The overall assessment of the trajectory for the future INNALung team is very good, with potential to excellent.

Strengths and possibilities linked to the context

The team is co-led by two PIs and oriented to the understanding of immunoreceptors and kidney immunopathology. The team includes 22 members with eight permanent staff, seven PIs: one Inserm researcher, five professors, one associate professor, three consulting, three technicians, seven PhD students and two postdocs. The research strategy perfectly fits with their expertise and combines basic and translational research.

Key scientific findings obtained during the evaluation period report on mechanisms of immunoreceptor functions and in innate immune defenses as well as in renal immunopathology and have been published in top journals such as Nat Commun (2017), Cell Reports (2019), Nat Immunol (2021), Sci Rep (2022) and Kidney Int (2022) with team members (or the future PI of InnaLung) in key positions. During the evaluation period, the team published 300 original scientific articles, in top tier specialized and generalist journals.

The team is recognized for its expertise in the field of kidney immunopathology, with international and national visibility. The PI has been invited to lecture at 15 international congresses (WCN, ILBS, European / Brazilian Congress of Nephrology, FASEB, etc.), been involved in the organisation of two congresses (International IgA Nephropathy symposium, French Immunology Congress) and been president of the French Society of Immunology from 2017 to 2022.

At the national level, the team is part of the labex INFLAMEX, which is led by the team's PI and gathers several teams of the CRI into a research network on inflammation and inflammatory diseases. The team obtained the Fondation pour la Recherche Médicale (FRM) label, highlighting the excellence of their science and national recognition. From 2019 to 2022 the team procured ca. 1 500 k€ of total funding (50 k€/year internal, and 1 450 k€ external). The external funding includes agencies, charities, and pharma (4 ANR (3 as leaders), labex Inflamex (leader), FRM labelisation, four industrial contracts (Astra Zeneca, Selecta Bio, Moderna, etc.)). Aside to project funding the team procured ca. 200 k€ for personnel funds.

Furthermore, the team obtained two new Inserm patents (patent EP18306008 entitled USE OF ANTIBIOTICS FOR THE TREATMENT OF IMMUNOGLOBULIN A NEPHROPATHY; and patent EP2021/073742 entitled USE OF MAIT CELLS AS BIOMARKERS AND BIOTARGETS IN COVID-19). The PI of the team was the president of the French Society of Immunology (FSI) from 2017 until 2022, has participated at various TV programs and media journals to talk about immunology and inflammation notably during the COVID19 pandemic and co-organized with Kidney Foundation annual meetings for patient associations at the National Academy of Medicine. The team participates each year in the Day of Immunology program (FSI), as well as the Kidney Day organized by the French Kidney Foundation and the ITMO PMN.

Weaknesses and risks linked to the context

The team has secured funding and collaborates actively within the CRI and within French research consortia, yet with a good proportion of experienced and well recognized PIs, strategies for acquisition of large European funding could be evaluated at a single or multi-PI level. This would increase attractiveness for students, post docs, and scientists at the national and international level. Although there has been a noticeable improvement in the clinical translation of their findings, clinical cohort access is limited.

Analysis of the team's trajectory

The team will fuse with Team 1 of Inserm U1152 to create a new team called "Innate Immunity and Lung Inflammation" (acronym "InnaLUNG") and will be co-led by Luc de Chaisemartin and Pierre Launay. Luc de Chaisemartin is currently applying for a professorship at the Paris-Cite, he is immunologist and an expert in the role of neutrophil in lung pathophysiology. Altogether the team has expertise in lung immunology, and will integrate the expertise from Pierre Launay, a well-recognized myeloid cell expert.

The team proposes four work packages.

WP1 makes use of the COBRA cohort of asthma patients and will apply a wide spectrum of methods to immune-phenotype these patients. It is unclear which control groups will be included in the study. Apart from flow cytometry / spectral flow cytometry and spectral confocal microscopy, a multi-omic approach consisting scRNA-seq and in situ proteomics will be applied. Bioinformatic unsupervised analysis is supposed to reveal novel pathways of asthma-development, exacerbation susceptibility and treatment response. No power analysis has been performed to estimate the number of patients to be analyzed. Financial recourses seem to be the main limiting factor, even if only well characterized patients are planned to be recruited to reduce costs. Some of the identified pathways are then validated in mouse models of asthma. One topic will be the role of CD89 based on previous studies done by the group.

Apart from asthma some of the immunologic profiling will also be done in ICU patients with ARDS.

WP2 seeks to understand disease mechanisms in children with hyperacute asthma exacerbation treated in an ICU setting. Metabolomics and ELISA for specific mediators will be used to characterize the patients and to understand innate immune alterations. As control the same analysis will be performed in a follow-up visit after termination of the acute asthma attack.

WP3 deals with innate immunity (mainly mast cells and neutrophils) in primary graft dysfunction using a screening approach consisting in this case of spatial proteomic analysis and immunofluorescence. These studies are also planned in a subgroup of patients treated with plasma filtration to remove neutrophil derived NETs.

WP4 uses ex vivo and in vivo models (ex vivo perfusion of human lung explants, an orthotopic lung transplantation model in mice and a primary 3D air-liquid interface bronchial epithelial cells culture model) to study.

Many of the immunophenotyping methods are not established in the group itself but seem to be used in collaboration and performed by other groups. Also, the mouse lung transplant model is not yet established as well as the 3d culture model. The overall approach seems to be a very broad signal seeking study. It is not clear whether enough patients can be included in the study to obtain meaningful data. No power analysis has been performed and financial resources as well as time and personnel restrictions may prevent successful completion of all proposed projects. It remains unclear to what extent the group will only provide biomaterial for analysis by other groups or really aims to acquire the necessary competence in the own group.

RECOMMENDATIONS TO THE TEAM

InnaLUNG is recommended to focus on some of the screening methods and disease entities.

Team 7: From inflammation to cancer in digestive diseases

Name of the supervisors: Ms Valérie Paradis & Mr Alain Couvineau

THEMES OF THE TEAM

The team focuses on new mechanisms of initiation and progression of liver and pancreatic neoplasia. These include (i) assessing the contribution of the local environment including lipids and the crosstalks between adipocytes, endothelial cells and fibroblasts with epithelial cells in the progression of tissue damages and tumorigenesis in liver and pancreas (ii) exploring the mechanisms of preneoplastic lesion progression and tumor heterogeneity in liver and pancreatic cancer, (iii) providing new insights in the role of GPCR in digestive inflammation and cancers and new therapeutic targets.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has made efforts to **i**mplement previous recommendations:

- The set-up of a proteomic imaging platform (iMAP), ex vivo tissue culture models that preserve the 3D tissue environment, the team's expertise in ultralow input RNAseq using microdissected FFPE samples and multiplex IHC and image analysis and access to large patient cohorts have fostered collaborations with several other CRI teams (M. Le Gall, S. Lotersztajn, PE Rautou).

- The team has significantly increased the number of hosted PhD students (13 during the evaluation period), currently hosts three post-doctoral scientists and three to four M2 students per year.

- The translational activity of the team has resulted in eleven patents and several industrial contracts as well as a European Sanofi Innovation Award over the evaluation period.

- The team was encouraged to continue their efforts to ensure cohesion in view of working at two sites. This problem has not been solved and will continue during the next contract. However, an important change will be the reorganization of the team given that the liver cancer group (V. Paradis) will join the group led by R SInkus, and the axis focused on pancreatic cancer will constitute a new team lead by J Cros (PUPH) and C Haumaitre (CRCN Inserm).

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

Catégories de personnel	Effectifs
Professeurs et assimilés	13
Maitres de conférences et assimilés	3
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	10
Sous-total personnels permanents en activité	**29**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	3
Post-doctorants	3
Doctorants	6
Sous-total personnels non permanents en activité	**13**
Total personnels	**42**

EVALUATION

Overall assessment of the team

The group is outstanding and has made important contributions, published in specialized and generalized journals, on the mechanisms of preneoplastic lesion progression and tumor heterogeneity in liver and pancreatic cancer. The team has secured funding and collaborated actively within the CRI having implemented and shared with others teams different ex vivo experimental approaches based on human samples, a proteomic imaging platform (iMAP), an ultralow input RNAseq analytic pipeline from microdissected FFPE samples and histology-based AI models.

The trajectories of the Cros/Haumaitre and Sinkus teams are considered to be excellent.

Strengths and possibilities linked to the context

Scientifically the team has made very relevant contributions. In the liver axis it has demonstrated the prooncogenic effect of endothelial fatty acid binding protein 4, it has identified new tissue biomarkers in liver carcinogenesis through innovative technologies such as nanostring approach and mass spectrometry imaging and it has explored tissue heterogeneity via Precision-Cut-Tissue Slices and 3D co-cultures with organoids. In the pancreas axis, the team has contributed to demonstrate there is a great heterogeneity in the path to pancreatic tumors. It has shown the role of Hnf1b in pancreatic intraepithelial neoplasia and in MODY5/HNF1B, the impact of metabolic syndrome and obesity in the development of pancreatic precancerous lesions and characterized the role of OxA/OX1R system in PDAC.

Regarding reputation, two team members have received prizes, the "Chevalier de la Légion d'honneur", and the European Rising Star (UEG). Over 200 presentations at national and international conferences including presentations at International Liver Conference (ILC, EASL) were made. Several team members have been involved in the organization of national and international conferences (EASL, Internat. Assoc Pancreatology Meeting, etc.) and are members of editorial boards (Frontiers in Endocrinology, Discovery Medicine, Receptors, Journal of Molecular Science, etc.) and national/international advisory committees (European Society of Pathology, AFEF, CECED, Internatioal Liver Cancer Association, EASL, ENETS, etc.), institutional commissions (Inserm CSS3) and national agencies (ANR, INCA, ANRS).

The team has published more than 190 original papers and 60 reviews with many in excellent journals (30 in high-profile journals with 12 of these coordinated by team members). There are 33 joint publications with other CRI teams indicating good integration of the team within the CRI. Team members have been leaded authors on publication in high quality journals (Gut, Hepatology, J Hepatol…).

The team is coordinator of the FHU Mosaic and partner in two RHU (ca 4 M€). Other academic grant leverage originates from national organizations such as ANR, INCA, etc. (> 600 k€, 16 contracts 8 as leaders), partnership in two European H2020 consortia (2016 and 2017, ca 6 M€) and international grants (NETRF USA 300 k€, leader). Besides seven grants from charitable foundations (ARC, SNFGE, AFEF, GTE, FNAB total 1 380 k€ 6 of those as leaders), the team has been labelled by the "Ligue Nationale de Recherche Contre le Cancer" from 2016-2019.

Four industrial contracts have been obtained (Inserm Transfert, European iAward Sanofi, CC&C, Sanofi totalling ca 151 k€) and eleven patents been filed. Team members take part in the national "Declic" exchange, which consists of explaining one's profession to high school students, communicate in the press on behalf of the National Academy of Surgery, particularly on the news on pancreatic cancer, are involved in the French National Society of Gastroenterology (SFNGE), the Groupe d'Etude des Tumeurs Endocrine (GTE), are in close contact with patient associations and disseminate information on digestive diseases, their management, treatment, recommendations and scientific advances, including videos available on the SFGE website or on YouTube.

Weaknesses and risks linked to the context

The team will undergo a complete restructuration. For the next contract, the hepatic axis will join the new team ULTRA led by R Sinkus "From micro to macro in cancer development". The pancreatic axis will propose a new team "PATH" dedicated to the study of pancreatic carcinogenesis heterogeneity led by J. Cros (PU-PH, Pathologist) and C. Haumaitre (Inserm Researcher), structured along two main complementary axes: (i) the different paths of pancreatic carcinogenesis (ii) the heterogeneity of tumors to harvest their plasticity and develop new therapeutic approaches.

Analysis of the team's trajectory

Tracjectory of the Haumaitre/Cros team
The research for the next contract will be divided in two axis: 1. Heterogeneity of pancreatic preneoplasia initiation and 2 Pancreatic tumor heterogeneity & therapeutical approaches. More specifically using mouse and cellular models, and samples and data from patients, and based on their previous results, they will study the role of metabolic syndrome (MS) in promoting preneoplasia, the anti-inflammatory action of orexin in MS/pancreatitis, the mechanisms of IPMN formation, plasticity and progression, PDAC and NET (emerging topic) intratumoral heterogeneity and plasticity and the development of new therapeutic strategies.

To do so the team will be composed of three full-time researchers, seven clinicians/university faculty, five engineers (3 on a permanent position), six PhD students, one post-doc and several master students each year. Over the past 5-years term, Haumaitre and Cros raised more than 4 600 k€ in various national contracts. This includes funds available through the Siric 'InSiTu' and the RHU 'Operandi', two large projects running between 2022 and 2027. The publication records of the researchers demonstrate an ability to drive high level research projects (e.g. Journal of Clinical Oncology, Nature Communication) and participate to important clinical trials (e.g. Lancet Oncol, N Engl J Med, Annals of Oncology). C. Haumaitre is a young Inserm researcher who has joined the team relatively recently. She is an expert in preclinical research, while J. Cros is a pathologist PUPH, and is an accomplished clinical researcher. The combination of the two should be extremely complementary and warrants excellent feasibility for the project. With this new trajectory, this team will not be as focused as before on inflammation, but the team is very well cooperating with other teams from CRI (including R. Nicolle, L. Saveanu, B. Van Beers, and M. Le Gall), and its integration within the CRI is totally logical and efficient. Altogether, the team has demonstrated its ability to conduct high level research projets. The feasibility of the project is guaranteed by its continuity and the proven experience of the team.

Tracjectory of the Sinkus/Paradis team
The Paradis team has an expertise in inflammation, liver cancer, genetic signature, organoid/drug evaluation. Ralph Sinkus has developed MR-Elastography, including virtual evaluation of histological features, in vivo imaging as means to assess the response to drug, and to disentangle vascular from cellular alterations during carcinogenesis. R. Sinkus and V. Paradis are Co-PI of the imaging WP in the RHU project OPERANDI (improve PET-MR guided radiotherapy) and Co-PI of the imaging axis of the SIRIC project InSiTu. R. Sinkus will lead this new team. The future team project is organized around three axes: i) development of imaging-based biomarkers (using different imaging modalities) with special focus in the endothelial to mesenchymal transition (EndMT) recently described by the Paradis group, as a marker of early stages HCC ii) evaluation of the combination of genetics and imaging to improve the diagnosis and the therapeutic strategy, iii) development of ex vivo personalized tissue models, using organoids and liver tissue slices. The team is multidisciplinary, with one basic researcher in biophysics and several clinicians: pathology/molecular biology, oncology and novel therapeutic concepts, clinical imaging. Publication records of the co-PIs, on-going collaborations, and the background of the team members suggest that this team can successfully develop excellent research projects. The team will be composed of two basic researchers, six MDs with university positions (4 PUPH, 2 MCUPH), and two MDs with full clinical duty (PH). Three engineers (IE) are also mentioned. The integration within CRI appears very well planned, with proposed links with teams Crestani, Garteiser/Van Beers, Weiss/Gilgenkrantz, Rautou and the junior Nicolle ATIP-Avenir team. In particular, the proposed scientific project appears complementary to the one developed by Garteiser/Van Beers.

Overall, the ambition of the team is to develop methods and search for imaging biomarkers by exploring the links between clinical data obtained at the molecular and cellular scales, and clinical data obtained using MRI (in particular, elastography and diffusion, the details remaining to be explored). They will rely in part on collaborations with expert scientists in applied mathematics/artificial intelligence inside the CRI, and in part on collaboration with PR[AI]RIE, the AI research center in Paris. They will use data from existing patient cohorts and shall benefit from the recently funded RHU and SIRIC projects. This excellent interdisciplinary project should generate interesting data, and breakthrough results can be anticipated in the near future.

RECOMMENDATIONS TO THE TEAM

Cros/Haumaitre team: it is recommended to maintain the scientific productivity. The team should be vigilant about the number of projects and their possible dispersion. It is also recommended to promote the translational research and to keep in mind the interest of CRI in the relationship between inflammation and cancer potentiating for instance interactions with other CRI groups. The data analysis part, including the development of tools based on Artificial Intelligence could benefit of more developed collaborations with PR[AI]RIE (Paris Artificial Intelligence Research Institute).

Sinkus/Paradis team: This interdisciplinary team with a strong complementarity of expertises (biology/pathology/physics/imaging) will develop new strategies to capture global information from the micro- to the macro-cellular levels, transposable to clinical decisions. Since this expertise is quite unique, it is highly recommended to organize courses, masterclasses and symposiums to spread the knowledge to the scientific community. This might also further increase visibility and attractiveness. The final recommendation is to continue working hard in this innovative proposal.

Team 8: Plasticity of gastro-intestinal mucosa in nutritional pathologies and after surgery

Name of the supervisors: Ms Maude Le Gall & Mr André Bado

THEMES OF THE TEAM

Contribution of the gastrointestinal tract to nutritional pathologies.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team should aim to increase and reinforce the visibility, reputation and appeal of the team leaders (e.g. participating in international meeting, application to national and international calls…).
Observation: The team has addressed this point by having all members involved in societies and research steering bodies. The team has also an optima outreach plan, as MLG is member of "les expertes" that facilitates communications with journalists.

It is recommended that the team increases the number of PhD students and especially the number of post-doctoral scientists and a real strategy should be defined to achieve this goal.
Observation: The team has had 2 post-docs, 8 PhD students, and 19 M2 students during the 2017-2022 period. The team has addressed this previous recommendation.

The team is strongly recommended to increase the network of collaborations both inside and outside the CRI.
Observation: The team has addressed this point by having all members involved in societies and research steering bodies. One of the team members is the current president of SFNCM.

The team should increase and reinforce the connectivity between groups within the team. It is clear from the project description that the team leaders have taken this point into account but the high number of work packages do not appear to be scientifically justified.
Observation: The team has strengthened collaboration with the team led by Prof. Hugot. Still some issues in the connectivity within the same team.

There is a strong need for additional supporting personnel.
Observation: Still few personnel (only to full-time researchers)

The team is encouraged to focus on one or two projects and choose the most original and cutting edge scientific areas such as the plasticity of neuroendocrine cells or immunity/inflammation. This approach will facilitate strong collaborations with other CRI teams and better integration within the CRI.
Observation: The team has now focused on two main projects

The team is encouraged to develop connections and collaborations with industry as the projects have interesting translational aspects that may be of significant interest to industry.
Observation: The team has hosted a biotech company (Eukarys) and generated a start-up. They have also generated contracts with other companies (Tissium, Enterome, etc).

The team is encouraged to carefully consider their strategy for organoids development since, although it is of interest, there is some risk since numerous groups (national and international) have the same goal. The strategy and resources allocated to this objective merit thought and more information.
Observation: Organoids is a tool to address specific questions, therefore this as an issue. Moreover, there is a newly established organoid facility that might provide support to the team.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	5
Maitres de conférences et assimilés	6
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	1

Sous-total personnels permanents en activité	**14**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	1
Post-doctorants	1
Doctorants	3
Sous-total personnels non permanents en activité	**5**
Total personnels	**19**

EVALUATION

Overall assessment of the team

The team has a very cohesive and clear research program that will address a relevant question in the field. The team is evaluated as excellent to outstanding.

Strengths and possibilities linked to the context

This team led by Le Gall/Bado, tries to understand nutritional pathologies by focusing in the gastrointestinal tract function. The team combines clinical and experimental research to achieve its goals, such as tissue biopsies from patients undergoing bariatric surgery and the use of animal models (created by the team) of the same condition. Overall, the team focuses in exciting and timely scientific questions, which are highly relevant to the field and with implications beyond bariatric surgery (e.g. stem cells biology in the stomach). The team has made relevant contributions to the field, such as identifying functional changes in epithelial compartment after vertical sleeve gastrectomy (VSG), which was linked to the production of GLP-1 and GLUT1 (Nat comm, 2021; Gastroenterology, 2016). They have developed animal models in rat in which VSG and Roux-en-Y gastric bypass (RYGB) surgery can performed and that recapitulate the human features observed upon bariatric surgery. The team has published in specialised journals but also in general interest ones (Nature communications, 2021). The team has published over 130 publications (peer reviewed) among which several high-profile publications as lead authors, including Nature communications, Gastroenterology, among others. Publications seem to be evenly distributed among team members, suggesting good structure in project assignement and supervision. The team has established strong collaborations with other teams in the unit, in particular team 12 (Hugot).

Team members are regularly invited to numerous national and European meetings, are solicited as experts in European grant evaluation or peer review journals and are members of the SFNCM, SFN, AFERO, SOFCO and other organizations. Team members have been organizing e.g. the scientific program of the Journées Francophones de Nutrition since 2012 and participate in the selection of candidates for SFNCM or SFN scientific prizes. They have editorial functions (Journal of Clinical Medecine) and participate on scientific boards (ANR CE14, Inrae CSS Nutox) and institutional commissions (Inserm CSS3, CNU (section Physiology, Gastroenterology and Surgery)).

The team has obtained three national grants (ANR, Inca) for a total of 586 k€, obtained seven "prix de recherche " (SFNCM, SFD, Fondatin de l'Avenir for a total of 117 k€).

The team has close collaboration with the industry and obtained 281 k€ in five fee for service contracts (JellyNov, Tissium, Enterome, Ekarys, Takeda) in particular for its expertise of Ussing chambers. It is hosting a start-up company (Eukarys), and has generated a start-up (carembouche).

Members of the team (MLG) is member of "les expertes" to communicate directly with journalists, fight fake news, and increase women in science visibility.

Weaknesses and risks linked to the context

There is lack of large funding and European grants. There is no clear plan how to overcome this weakness.
There is no clear plan on how to recruit national and international talents into the team.

Analysis of the team's trajectory

This is a consolidated team mixing genders and experiences in the leadership. The team has made significant contributions in the field of bariatric surgery. Upon observations made in humans, the team developed experimental models enabling it to investigate causality. Importantly, the experimental model recapitulates the main observation made in humans.

The team has built a strong clinical research program, including the inclusion of relevant large cohorts of patients and clinicians. The above mentioned point is complemented with experimental models which makes the research program complete.

As per the transition, the team plans to investigate the mechanism of the stomach plasticity observed upon bariatric surgery. The team focuses on the epithelial and immune cell compartments and how the microbiome, bile acids, and nutrients modulate GI plasticity. The team will focuse on the "lactobiota" based on observation in SBS patients. The team will focus also on GLP2 analogues in collaboration with the industry. The team proposes to focus on innate and adaptive lymphocyte function. However, the expertise of the team in T and ILC biology is not clear.

For the future, the team plans to continue working on GI plasticity using patient cohorts and experimental models of obesity, SBS, and bariatric surgery. The team propose to study the crosstalk between immune cells and epithelial cells. It is not clear what systems will be used, and it would be recommendable to establish an organoid-immune cell co-culture system as per its relevance. The team is also establishing RNAseq datasets to get mechanistical insights.

Overall, the trajectory of the team is excellent and focused; generating new tools and becoming a strong team in the field.

RECOMMENDATIONS TO THE TEAM

The team should implement a strategy to identify and obtain large European funding that provides prestige and stability.

The team do not have a clear plan on how to attract young talents students/postdocs. Organizing international courses and symposiums is recommendable.

The team should implement a clear plan to favour gender equality.

The team proposed to study the cross talk between immune cells, and the epithelium. Establishing organoid immune cells co-culture using human cells would be recommendable.

The team should clarify the expertise for then analysis of RNAseq datasets.

The team has developed new preclinical models, in which bypass surgeries are performed. This expertise is quite unique. It is highly recommended to organize courses and symposiums to spread the knowledge to the scientific community. This might also increase visibility and attractiveness.

Team 9: Vessels in liver diseases

Name of the supervisor: Mr Pierre-Emmanuel Rautou (ATIP avenir)

THEMES OF THE TEAM

The team currently led by Pierre-Emmanuel Rautou conducts studies dealing with:
-Extracellular vesicles (EV) as vectors of information in alcoholic liver cirrhosis and other chronic liver diseases. This comprises basic and translational studies, and a contribution to the creation of the EV core facility in CRI.
-Defects in endothelial autophagy in MASH (Metabolic dysfunction-associated steatohepatitis) progression
-Coagulation (defects) in liver diseases
-Porto-sinusoidal vascular disorder, which is a rare disease, defined as portal hypertension with bleeding but no cirrhosis. The team has also contributed to the implementation of Fibroscan or Computed Tomography (CT) for diagnosis.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

- Improve / increase the public outreach: this issue has been addressed and efficiently solved, since the team has now designed its own website (Rautoulab.com), regularly posts scientific information on Youtube and Twitter, and is involved in press releases.

- Stop the decrease in the number of permanent positions, i.e. increase attractiveness: this is not solved, but the team leader is aware that this issue is a weakness and might become a threat to the development of the team. However, no strategy is proposed to improve attractiveness at this stage.

- Concerning the project's part dealing with extracellular vesicles characterization: the previous report raised substantial concerns on the fact that the composition of these EVs remains unknown; analyses should be performed to postulate functionality and validate their utility as biomarkers, specially using animal models. This point raised has been solved, with a PhD student has won a Lopez-Loreta prize (1 M EUR, 3-years position) to achieve this characterization, and ongoing high-throughput proteomic analyses of EVs, soon to be published. The translation toward clinical application of these analyses is now financially secured, with a "France 2030 RHU" 10 M€ funding (LIVER-TRACK, coordination of 9 teams by PE Rautou).

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

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maitres de conférences et assimilés	1
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	0
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	5
Post-doctorants	1
Doctorants	3
Sous-total personnels non permanents en activité	**10**
Total personnels	**13**

EVALUATION

Overall assessment of the team

The team has an outstanding track record in basic and translational research, an outstanding national and international visibility, and raise an impressive amount of funding to sustain their research including a recent France 2030 RHU 10 M€ grant as coordinator for the future research program. It has an outstanding collaborative network within the CRI developing innovative and original research on vascularization in liver diseases. It provided proof-of-concept for EVs as candidate biomarkers for liver (dys)functions, that are now translatable to clinical applications.

Strengths and possibilities linked to the context

The team leader is by himself a strength to his team. Indeed, he has an internationally recognized expertise on the link between vascularization and liver diseases (such as cirrhosis, NAFLD, NASH). He has been awarded in 2018 with the EASL Emerging leader, and with an ATIP-Avenir financial support in 2019. Since then, he contributed to the writing of four EASL guidelines, and has been extremely successful at raising funds to reach and maintain top level quality research. The team is composed of people with a vast diversity of profiles, which increases the emergence of new concepts and ideas.

The team has an outstanding track record in basic and translational research, an excellent national and international visibility, and raised an impressive amount of funding (5.2 M€ : 3 PHRC for 1,6 M€ total, ATIP Avenir 390 k€, 2 ANR for 622 k€ total, idex 40 k€, Inserm Transfert 40 k€, RHU Quid Nash 250 k€, Mairie de Paris 210 k€, APHP 100 k€, ARC 220 k€, H2020 as a partner, 352 k€) to sustain their research. It has an excellent collaboration network within the CRI, developing innovative and original research on vascularization in liver diseases. It provided proof-of-concept for EVs as candidate biomarkers for liver (dys)functions. This has led to a total of 159 publications in high-profile specialised and general journals (PNAS, Hepatology, JHep, J Clin Invest, Lancet Gastroenterol Hepatol, Gut, Nature Commun, Gastroenterology, etc) and to the creation of a core facility at the CRI. On the past mandate, one student defended her PhD, and three students are currently in thesis. On the next mandate, two post-docs will work in the team.

The team leader is a recognized expert in the field of vascularization in liver (inflammatory) diseases, with international and national visibility. He has been contributing to meeting organizations, masterclasses, guidelines of EASL.

The team also has excellent skills for technology transfer, with close interactions with private companies and patent registration (6 licensed patents, partnership with Grifolds, Terra Firma for budgets still under negotiation). The research on EV is a rapidly moving field, with great opportunities to raise new concepts and settle novel disease biomarkers. This is a strength for the team, but may be as well as a threat (see below). Actions towards general public include yearly participation at the "Apprentis chercheurs" program, videos dedicated to general public (including via PUMS channel, almost 1 000 000 view) and patients' events (with AMVF and ELPA).

Weaknesses and risks linked to the context

There is no senior scientist specialized in cell biology in the team, and the current expertise in all fields reported in the past and future activities of the team is only held in full by the team leader. This might constitute a threat for the next mandate and for the future development and potential extension of the team, and also for the future supervision of students and should be consolidated. This might create a bottleneck for students due to a lack of HDR holders in the team.

Analysis of the team's trajectory

The team led by Pierre-Emmanuel Rautou has been funded in 2019, when the team leader received his ATIP-Avenir funding.

Since then, it has evolved in an extremely favourable and dynamic manner, with substantial amounts of fundings raised in the last five years, supporting breakthrough strategies, novel concepts and bleeding-edge technologies.

The human resources of the team are adapted to the projects proposed, and each part of the projects are financially supported (either by academic or industrial fundings, or by prizes).

The team develops innovative and original research, linking vascularization to liver (dys)functions, coagulation to liver diseases, endothelial senescence to liver immunity and consequences on bacterial infections. A fourth axis of research proposes to study how fatty liver (in the context of NAFLD, NASH) could play a role in cardiac remodelling post-infarction.

The team relies on patient cohorts to gain *in vivo* information, and develops strong links with patient associations. The team's trajectory is therefore extremely positive, ascending and dynamic with is also reflected by a recently awarded RHU grant that is coordinated by the team leader and which further sustain the teams' cutting-edge translational research.

RECOMMENDATIONS TO THE TEAM

Attractiveness toward basic science researchers and students should be improved, and the strategy in doing so explicitly presented. Strategic international collaborations should be reinforced to consolidate the teams positioning in the fast moving field. The EV composition analyses should be pursued, and published in order to settle the team as a key player in the field of EVs, and more specifically of EVs as biomarkers of liver diseases.

Team 10: Antigen presentation to T cells

Name of the supervisors: Ms Loredana Saveanu & Mr Pierre Guermonprez

THEMES OF THE TEAM

The team Antigen presentation to T cells is co-managed by Drs Saveanu and Guermonprez. The research programs aim 1) to decipher the role of endocytic trafficking in antigen presentation and immune receptors signaling (PI: LS), 2) to characterize the phenotype and functions of dendritic cell (DC) subsets in T cell activation (PI: PG) and, 3) to develop of new vaccine strategies (mainly against bacteria).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The main recommendations were:

The Team should continue to deliver outstanding research.

The Team leaders are encouraged to develop international collaborative networks.

The Team is encouraged to consider developing translational work in the future.

The Team leaders are encouraged to develop collaborative synergistic projects.

During the current period, the Team has maintained a very high quality of research as illustrated by articles published in top quality journals (Nat Immunol. 2017; 2 Nat Commun. 2020; Immunity. 2020) and has established strong and productive collaborations, at the local, national and international levels (Nat Commun, 2017; Cell Rep, 2018; Science Transl Med, 2020; Immunity, 2022; Cell 2022).

During the current period, the Team has also developed a translational research program focused on a new antimicrobial vaccine strategy; the initiation of this project was accompanied by the integration of new collaborators in the Team.

Except a scientific publication in Nat Commun and reviews that are co-signed by the two leaders, the Team leaders did not develop long-term synergistic projects.
Overall, most of the recommendations made in the previous report have been followed and implemented. The departure of the co-leader has led to a new scientific strategy based, on the one hand, on the expertise of L. Saveanu's group (immune receptor signaling) and, on the other, on a stronger commitment to translational research.

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

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

EVALUATION

Overall assessment of the team

The Team has a unique and exceptional recognized expertise in the biology of dendritic cells and in immune receptor signaling. The scientific production and training are of high quality with strong national and international collaborations. The Team has strengthened the translational aspect in its strategy, in line with CRI objectives.
The overall assessment is excellent / outstanding.

Strengths and possibilities linked to the context

The team investigates the cellular and molecular mechanisms by which dendritic cells (DC) activate T cells, with a focus on intracellular trafficking in both DCs and T cells. The team has described a new population of DCs (DC3) able to generate TRM (Immunity 2020), a specific endosomal population which regulates innate immune response of myeloid cells (DCs and Mj) (Nat Immunol, 2017) and controls phagosome maturation and antigen presentation (Cell Rep, 2018). It also demonstrated that IRAP, the main protein signature of these endosomes, is a pivotal actor in endocytic signaling platforms of TCR (Nat Commun, 2020) and FcgR) (iScience, 2023).

During the current period, the team has initiated a thematic repositioning, with a focus on receptor signalling. Results revealed (i) a pivotal role of PI3Kg in FcgR-mediated antigen presentation probably by regulating phagosome maturation and ROS production, (ii) that internalized FcgR recruit signaling partners in endosomes, controlling cytokine secretion and ADCC. Finally, the team has set up an approach allowing to discriminate plasma membrane versus endocytic signaling platforms relying on protein biotinylation by APEX2. This original strategy will allow to identify timely and spatially the transient protein interactions involved in immune receptor signaling. Of note, these projects allowed to initiate internal collaboration.

The team is composed of sixteen members, including four PI (3 directors of research, including 1 emeritus, and 1 associate Prof). Between 2017 and 2022, the team hosted three research assistants, seven PhD students and six post-doctoral scientists. The staff is roughly constant (15-20 members). A PI is scientific coordinator of the ImaCRI platform and developed a technical plateau dedicated to the production of genetically modified cells.

The team has an excellent capacity to secure funding, notably in highly competitive national calls (ANR, INCa). Over the current period, the total budget was around 2 500 k€, including » 2 000 k€ from national (8 x ANR, 2 x INCa and 1 x idex) and international agencies (Swiss National Fund) and from national (ARC, LNCC, FRM) and international charities (EFE, Spain).

Thanks to their internationally recognized expertise, the team leaders are involved in different national and international networks related to IRAP and DC biology and are invited to present at national and international congresses/meetings.

The team trained eight PhD including three who completed their PhD during the current period and published at least one article as 1st author in top quality journals.

Integration of senior scientists (in the field of immune receptor signaling and of vaccine strategies) during the current contract or who will integrate the team at the beginning of the next period.

Gender equality is respected. The organization of team life is classic, with weekly team meetings.

During the current period, the Team has published twenty original peer-reviewed scientific articles, including articles in top-quality journals (Nat Immunol, Nat Commun, Immunity) as 1st and senior authors, and eleven reviews or editorials. Team members gave 21 conferences as invited speakers in national and international meetings.

Following a thematic repositioning consecutive to the departure of one of the team co-leaders, the team has integrated scientists who bring (or will bring) their expertise in the fields of immune receptor signaling, vaccine strategies and translational research. The research program dedicated to vaccine development is developed in collaboration with a recently created biotech company.

Weaknesses and risks linked to the context

The staff composition remained stable over the last period, with no recruitment of junior scientists. Most of the technical staff is recruited on short-term contracts, which could have an impact on long-term know-how. The departure of the co-leader may affect the fund-raising capacity of the team.

Limited technology transfer and IP activity.

Limited contribution of research activities to a *large public*.

Analysis of the team's trajectory

For the future period, one of the PIs will lead a new group entitled "Immune signaling in cancer and infections" (IMAGE) which will be joined by two researchers who will bring their expertise in immune receptor signaling and functions. The project is a continuation of the current project and is organized in three complementary axes.

Axis 1 aims to understand the cross-talk between ITAM-coupled receptors and IL-12 signalling with a fine characterization of signaling partners using a supervised (STAM molecules) and non-supervised (APEX2) approach. Axis 2 aims to investigate host-pathogen interactions in the context of Chlamydia and Pseudomonas infections and to develop new vaccines. One major objective is to characterize, at the molecular level (APEX2-based approach), the microbe-containing endosomes (project granted). The second objective aims to characterize the immune response induced by vaccine candidate developed by the company BCV Care. Axis 3 aims to improve existing protocols of cell therapy (CAR-T cells) to increase TCR antigen sensitivity, TCR signalling, cytokine production and T cell persistence by targeting endosomal signalling.

This project is well-focused and relies on the expertise of the team. In addition to a basic research approach, the team has integrated a translational approach, fitting with the overall objectives of the CRI. The feasibility relies on existing collaborations at the local, national and international levels collaborations. Funding have been secured.

RECOMMENDATIONS TO THE TEAM

Recommendations on scientific production and activities

The team should continue to deliver excellent research.

The team must continue to integrate a translational perspective into their projects.

The team should contribute to events for the general public (University open days, Fête de la science,…).

Recommendations on the global strategy

The team should clarify the strategic and IP issues with the company BCV Care.

Team 11: Laboratory of imaging biomarkers

Name of the supervisor: Mr Bernard Van Beers

THEMES OF THE TEAM

The LBI team is a multidisciplinary team working in translational biomedical imaging research. It develops and evaluates new diagnostic and prognostic imaging biomarkers to characterize inflammatory and cancerous diseases in the abdomen. Currently, two research axes are followed:

i) development of new quantitative MRI imaging approaches, at the preclinical (small animal models of abdominal disease) and clinical levels. This research also relies on the use of phantoms and human tissues samples and on the use of biophysical modelling.

ii) imaging biomarkers in patient cohorts. In the context of preclinical and clinical studies, the team integrates image-derived information with clinical and biological data.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

1) Production and scientific activities

There is no sign that the team increased its public outreach activity. The LBI team however mentions several lectures in the Master 2 ('Biomedical Engineering', 'Physics for Bioimaging' and 'Biocoeur'), the DES of Radiology, and at Bachelor level, in line with previous recommendations. Collaborations with academic and industrial partners (e.g. participation to pharma-led clinical trials) was pursued, as recommended.

2) Team's organization and life

The number of permanent members went from eight in 2019 to nine in 2022. There is however one professor less and two additional staff members. The work as platform is not described in the document but there are a few collaborative studies with other teams of CRI involving the MRI facility, as recommended. Regarding the concentration of activity on one site, the document mentions a solid plan. Regarding the addition of PET or metabolomics, this was not addressed. The LBI team collaborates with other CRI teams at the preclinical and clinical levels. There is however no collaboration with the 'renal' teams, as suggested.

3) Scientific strategy and projects

The LBI team performed both methodological developments and application studies. NASH was one of the focuses of the team (thanks to the support of the RHU QUID-NASH), as recommended. No ultrafast ultrasounds were used yet (but ultrasounds were used in several studies of the LBI team).

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

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maitres de conférences et assimilés	1
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**9**
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	**11**

EVALUATION

Overall assessment of the team

This interdisciplinary team has national and international recognition, with an outstanding fund raising, an excellent publication record and solid research projects at the interface between clinical studies and imaging methods. The group manages an in vivo imaging platform, labelled at the national level, and collaborates with several teams of the CRI. Regarding weaknesses, the group size and production is slightly smaller than that of the previous term and the collaboration at the preclinical level with other CRI teams remains too small. Overall, this is an excellent to outstanding team.

Strengths and possibilities linked to the context

The LBI team is focused on medical imaging, primarily on MRI but also uses other clinical imaging modalities such as PET and ultrasound. It is mainly composed of radiologists, some with an outstanding track record, and hosts one Inserm researcher and one Inserm research Engineer.

About 3.8 M€ were raised over the past period (i.e. more than the 3.1 M€ raised during the previous period). Funds came from research networks such as DHU "Unity", the FHU "Mosaic", the SIRIC "InSiTu". LBI members were workpackage leaders or coordinators for one international grant "Force", EU H2020) and for several national programs ("QuidNASH", ANR RHU), "PairPanc", ARC / La Ligue / InCa), "StediNASH", ANR AAPG), BPI France. This includes three finances via PIA (899 kE, one as leader). The team also manages the Paris-Center hub of the "France Life Imaging" (FLI) network (ANR INBS), a national network of imaging research platforms.

Several abstracts presented by PhD students and postdocs of the LBI team at international and national meetings received an award (ISMRM, ESGAR, EMRMB,etc). Publications were made in the best journals of the field (Radiology and European Radiology for clinical radiology; JMRI and NMR in Biomed for MRI methods; clinical: clinical: lancet Oncol, to name a few). Among the 165 publications reported, 106 (64%) were signed as last or first author. Overall, the publication record is excellent.

Students presented their work in national and international meetings with 10 invited presentations (ESMRMB, International Society of Magentic Resonance in Medicine, International Tissue Elasticity Conference, etc.) .

The team members are involved in international scientific societies, in the organization of national scientific meetings (SFRMBM, CNIV, France Life Imaging Paris Hubs Conference, etc.), and in the evaluation of research projects (e.g. ANR, Hcéres, CSS Inserm). It hosted three visiting scientists over the evaluated period. One PUPH joined the team during the period and another one is joining the team for the next term. This demonstrates that the team is attractive, a good sign for the future.

P. Garteiser will take the lead of the team for next term, in association with B. Van Beers. This means to anticipate the retirement of B. Van Beers is well appreciated. Finally, the team make a special effort on open science, with a practice of sharing data/code, and on renewable research, with an involvement in a CRI committee.

Regarding the inclusion in society, the activity from the LBI team also led to two patents and one software translated as an industrial product (Myrian from Intrasense). The team also conducted and/or participated to several clinical trials and is involved in teaching, in particular in the field of methods for in vivo imaging.

Weaknesses and risks linked to the context

Regarding attractivity, the team size appears slightly smaller than that of the previous term (1 researcher less).

Regarding the production over the evaluated period, the team raised more funds (3.8 M€ instead of 3.1 M€) but published slightly less (173 instead of 198) than during the previous mandate. The number of PhD students (6 over 5 years), given the number of researchers with an HDR (4 in the team), is not optimal.

Regarding collaborations within CRI at the preclinical level, there are six papers involving collaboration but most of them are driven by the team. One collaboration not driven by the team involved MRI to measure a tumor volume, but did not make use of the expertise of the team. The role of platform, useful for other teams of CRI and labelled at a national level, could be further developed. This is explained in part by the limited number of staff scientist at the preclinical level. There is no collaboration with teams from the renal department.

Regarding method developments, the collaborations with other laboratories is not developed enough: for example, the help from other physicists and/or mathematicians could help leverage the expertise of the team and accelerate methods development.

Regarding the team organization, the work on two distant sites (clinical at one site and preclinical at the other) does not facilitate the development of collaborations.

Analysis of the team's trajectory

The structure and the general scientific direction of the team does not change for the next mandate. The main event to come is the departure of B. Van Bers, which is well prepared. At this stage, P. Garteiser (HDR authorized and scheduled early 2024) already appear as a collaborator with MDs of the team. The links should be reinforced with the announced move into a new building. The strategy to recruit a second researcher in biophysics is timely. There is also a need to reinforce the staff supporting the imaging platform. There is a mention of an involvement of the team in the "data science" and "imaging" CRI.3 research axes, but we don't know whether this contributes to support the projects of the team.

Three sound scientific projects are briefly described: "LiverSynth": the methodological development of 3D multifrequency MRE, DWI, fat quantification and relaxometry from the cellular scale to the patient scale (coll. Leuven and Valencia; arrival of a new researcher in the team; coll team Rautou at CRI), "Mistra-XL": preclinical and clinical evaluation of pancreatic ductal adenocarcinomas (PDAC) (coll. Team Haumaitre/Cros and Paradis/Sinkus at CRI; coll. Charité) and "AbdoMapper.AI": a methodological project which proposed to include physics information to constraint AI. Looks conceptual at this stage and no preliminary results are mentioned here.

Altogether, these projects are excellent and well adapted to the expertise of the team and to its environment. Several collaborations are mentioned, which will contribute and amplify the proposed methodological development. The ambition to place a special focus on tissue sample, using a tabletop MRI system with a gradient coil capable of reach high gradient strength, is a smart move that will help develop the link between basic scientists and clinicians. The third project appears more conceptual at this stage than the two others, and therefore more at risk, but is ambitious and would yield to major improvements in image analysis if successful. The collaboration with R. Sinkus, who also performs methodological research in the field of imaging and seek links between data at molecular/cellular scale and imaging data, will come in support of this project. Project are already partly funded. The recently obtained RHU projects (in particular Liver-track, PI: P.E. Rautou) is also an opportunity to value the contributions of the team.

RECOMMENDATIONS TO THE TEAM

Pursue your effort to reinforce the biophysics side, as planned. Plan to reinforce the support for the imaging facility.

Start with the team co-direction (Garteiser/Van Beers) as soon as possible, possibly before 2027. Pay special attention to value the contribution of P. Garteiser as co-leader, e.g. by signing papers as senior author.

Set-up an organization (e.g. recurrent meetings at the hospital) to secure links between P. Garteiser and all the clinicians of the team.

Evaluate whether the analysis of tissue samples can generate further collaborations with CRI teams.

Develop additional collaborations with physicists/mathematicians to further leverage the proposed methodological developments, for example with PR[AI]RIE, and value the already rich activities at the preclinical and clinical levels

Team 12: Host-environment interface in inflammatory disorders

Name of the supervisor: Mr Jean-Pierre Hugot

THEMES OF THE TEAM

The team led by Jean-Pierre Hugot is composed by seventeen members including clinicians, basic researchers, and students among others. The goal of the team is to gain insight into the etiology of inflammatory bowel diseases (IBD) with a current focus on trying to understand how aberrant host-microbiome interactions may lead to the chronic inflammation observed in IBD.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

A – Recommendations on scientific production and activities: The team should develop a strategy to reinforce publication of their work in high impact journals especially for experimental papers. The team should intensify efforts to apply for competitive grant funding (ANR, ERC…) for the sustainability of their resources. Increasing industrial contracts could help.
Observation: Unfortunately, this recommendation had not been addressed.

The team should aim to increase the recruitment of PhD students and post-doctoral scientists especially in view of the retirement of one of two full-time researchers of the team.
Observation: The team has three engineers, four postdocs, six PhD students and thirteen master students during the 2017-2022, which seems more than optimal.

Younger researchers should be supported as they begin to acquire independence. The team should consider adopting a more efficient search for industrial contracts.
Observation: Although there was not a clear plan written, the team clearly supports young scientists as seen by the new leaders who have been supported all the way through. The new leaders have a plan to support PhD and postdocs to the next step.

The team should display a clear policy regarding gender balance.
Observation: This recommendation has not been properly addressed. There is still no clear policy regarding gender balance

The team needs to present a more rational and rigorous scientific presentation of the background and aims of the projects to improve understanding of the future scientific strategy.
Observation: The team has distributed their aims in three major WPs. These WP are cohesive and connected, still independent to each other. The team has addressed this issue.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	7
Maitres 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	**14**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	2
Sous-total personnels non permanents en activité	**3**
Total personnels	**17**

EVALUATION

Overall assessment of the team

This team is excellent to outstanding.

Strengths and possibilities linked to the context

The team is trying to understand a very ambitious question, which is what are the genetic factors and/or environmental factors leading to inflammatory bowel diseases. For example, the team has utilized AI and genetic polymorphisms to discriminate Crohn's Disease (CD) patients and healthy individuals (Sc Rep, 2019). Similarly, using large cohorts of patients, the team identified association between industrialized food and low intake of Zinc with IBD (Am J Gastro., 2020). The team will focus on stool sample analysis from IBD patient cohorts, and experimental models of colitis. The team is well connected in the IBD network and count with relevant collaborations, such S. Lotersztajn and PE Ratou labs (Liver disorders), and with teams specialized in the microbiome among others.

The team has been highly productive, as seen by over 150 publications, including publication in specialized journals in the field, including CMGH. JCC, etc., three patents and building two start-ups (Inception IBD and Thabor Therapeutics). Scientific production is proportional with contribution of all staff members.

Team members are highly involved in national and international societies (eg ECCO, UEGW), IBD patient associations (eg AFA), coordinate networks for rare digestive (MARDi) and pediatric rheumatological disorders (RAISE) and are heading departments of gastroenterology, pediatric gastroenterology, surgery or pathology.

The team had developed and made available a platform for microbiome analysis and built up the Mikinautes cohort based on the links with the IBD patient association AFA.

The team is well funded, including funding from the European Commission (1x Marie Curie, 2x ANR as leader, PIA: Inflamex partner, TRAILS as leader, 3x contracts from caritative foundations (FRM, LNCC)), rising over 2 M€ in the past five years. The team has achieved three promotions/tenure positions, including two engineers and one senior researcher.

The team seems to attract young talents from all over the globe, as seen by the recruitment of five postdocs of which four were foreigners. The team mentioned having two PhD students per year/PI/.

The team has organized several scientific annual meetings (ERNICA workshop on Hirschprung Disease, Séminaire annuel maladies rares digestives, SOFREMI, GETAID) and members are regularly invited to national and international conferences (aprox 20/year).

Weaknesses and risks linked to the context

The team partially depends on funding from INFLAMEX, and plans in case of discontinued funding from INFLAMEX has not been discussed.

Although the team is highly productive (50 publications per year in average) it lacks high impact publication. This may reflect breadth at the cost of depth.

The team will focus on the study of the microbiota, however there is no clear bioinformatic skills to analyze the microbiome in the team.

Somehow, the projects descriptions are rather superficial and it is difficult to evaluate novelty. It seems that the team will follow up or reproduce already known concepts in the field. For example, in "outer" is is not clear how from stool sample analysis, the team will identify dietary/environmental factors leading to IBD. These studies at last will provide associations, in "interface" the experimental plan is not clear therefore it is difficult to evaluate feasibility.

Analysis of the team's trajectory

The team has focused on trying to understand the causes of IBD. During the previous period, the team has achieved the proposed aims and have published original articles, patents and created two start-ups. The team has associated IBD with low intake of zinc, additives in food, and others that have been published in good journals. The team has also investigated the mechanisms behind extraintestinal manifestation in IBD, such as the connection between intestinal permeability and arthritis.

As part of the transition period the team recruited a researcher who is an expert in host-microbiome interaction. In addition, this researcher was promoted, securing expertise in extraintestinal manifestation of intestinal inflammation.

For the next five years, the team will recruit PhD students and postdocs to work on three main projects: outer, interface, and inner. These projects aim to better understand the environmental factors involved in IBD (outer), the role of micro-RNA in the lumen (interface), and how deregulation in the intestinal "interface" impact distant organs.

The future program is ambitious and tries to resolve major questions in the field. The team research program would benefit of more focused aims and in-depth description of the experimental plan and methodologies.

The team has two new young leaders who are highly engaged with the project and well prepared to lead this ambitious research program.

RECOMMENDATIONS TO THE TEAM

The team heavily relies on collaborations for the epidemiological and microbiome analysis. It is recommended to include a bioinformatician in the team with expertise in metagenomics analysis.

The team should develop its research program in more detail, indicating specific questions and methodologies to be used. For example, how exactly the team will identify dietary/environmental factors associated with flares?

The team should move into causality studies in the first project might help to increase the impact/relevance of the team's publications/research.

Team 13: Inflammation and fibrosis in lung diseases

Name of the supervisors: Mr Bruno Crestani & Mr Arnaud Mailleux

THEMES OF THE TEAM

The team is focused in understanding the immune mechanisms involved in the development of idiopathic and non-idiopathic forms of pulmonary fibrosis. The scientific agenda proposed for the team for the next five years is organized in 4 main themes, first the maintenance of the profibrotic phenotype of lung fibroblasts, second immune mechanisms in Pulmonary Fibrosis, pathway overlaps between lung cancer and IPF, and last genetics of lung fibrosis.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

N/A

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

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

EVALUATION

Overall assessment of the team

The overall assessment of the team, taking into account their trajectory and future plans promise an excellent integration within the CRI.

Strengths and possibilities linked to the context

The team, currently at Inserm 1152, will be joining the CRI. It has a long-standing trajectory in investigating pulmonary fibrosis, the team has made several important contributions to the field.

The team is multidisciplinary, structured in a collaborative fashion, with a strong clinical foundation in the area of pulmonary, rheumatology, pathology, radiology, intensive care, as well as more basic areas, as genetics and immunology. The team is well networked at the national and international level, which give them access to national and international cohorts. The projects cover a variety of key aspects from basic, translational and clinical angle. The research environment within the CRI, and the recent recruitment of a junior professor of immunology will strengthen their immunology work, for example in the areas of immune controls of fibrosis, as MAIT and immune checkpoint work packages, that are also ongoing areas in other CRI teams.

The addition of the team to the CRI will bring bilateral benefit. So far, the CRI covers research areas mainly focused on the involvement of gastrointestinal organs, kidney, lacking the immune regulation of lung diseases. Some of the projects have already secured funding, which ensure feasibility.

Weaknesses and risks linked to the context

The lines of research proposed by the team required significant wet-lab, in the current structure of the lab there is a personal imbalance in regard of clinicians/researchers and postdoc/technicians/ students, additional personnel as e.g. technical assistant, engineer would be helpful for balancing the wet-lab work and ensure feasibility. A structured plan for students and postdoc recruitment, should be stablished. Here will be advantageous that the team creates strategies to increase their attractiveness for recruitment of international students and scientists, given their international visibility.

Analysis of the team's trajectory

In terms of trajectory, the team has a structured plan on their leadership, it will be co-led by Crestani and Mailleux, until Crestani's retirement in 2029. Multidisciplinary recruitment at the professor level, as well as collaborations in line with the future scientific themes, are planned.

Regarding the scientific trajectory, the team has vast experience in the pathological regulation of fibrosis. For example, the team recently demonstrated in the identification of PRRX1, a mesenchymal transcription factor upregulated in IPF. Modulation of PRRX1 with an antisense oligonucleotide attenuated fibrosis and might be a therapeutic target with antifibrotic effects (bioRxiv 2021, in preparation). Furthermore, the team has contributing in defining the role of developmental pathways e.g. fibroblast growth factors (FGF) in lung fibrosis. FGF-9 has an antifibrotic effect in vivo models of fibrosis (Am J Physiol 2017), endocrine FGF 19 and 21 have a role on lung repair (Am J Respir Cell Mol Biol 2022). Through the anti-apoptotic effect of FGF19, mice are protected from bleomycin-induced fibrosis. This protective effect occurs independently of FGFR4, the main receptor for FGF19 (manuscript in preparation).

The recent recruitment of a junior professor of immunology will generate and structure the research efforts in immune mechanisms in Pulmonary Fibrosis. Specifically, the team aims to resolve the role of the collagen receptor leukocyte- associated immunoglobulin-like receptor-1 (LAIR-1), as key regulatory immune checkpoint. Funding is already granted from Roche. Furthermore, the team will expand and explore the role of Mucosal-Associated Invariant T cells (MAIT) in IPF, characterizing their role and function in initiation and progression of PF, and addressing their crosstalk with lung microbiota and the temporal relationship between MAIT activation, lung dysbiosis, inflammation and fibrosis.

In the area of the genetics of RA-ILD, the team have had major contributions (Eur Respir J 2017, NEJM 2018) and identified the MUC5B promoter variant rs35705950 as main risk factor for RA-ILD. This demonstrates the national and international collaboration network. The team will address the role of PARN deficiency, one of the most frequent TRG mutation in their cohort.

Regarding previous funding, the team was able to obtain funding from different sources, for instance al the European level (co-coordinator of RARE-ILD, an EJPRD 2019 project-200 k€), at the national level from French public funding (3 PHRC national-2 000 k€, 1 PRTK-550 k€, 1 ANR as coordinator and 2 ANR as collaborators-205 k€), from private foundations (587 k€) and pharma companies (620 k€).

RECOMMENDATIONS TO THE TEAM

The team should continue to deliver excellent research and integrate through collaborations within the CRI network to enhance and strength their immunology angle. The team must continue to enhance an immunology-basic/translational perspective into their projects. The team should ensure a structured transition leadership for the time of retirement of B. Crestani to Mallieux. The team should continue enhancing attractiveness toward basic science researchers and students, that will help ensuring students/scientist recruitments. The team should enhance young talents in the team 3rd party funding procurement at the national, European, and international level.

CONDUCT OF THE INTERVIEWS

Dates

Start: 11 December 2023 at 08:00

End: 12 December 2023 at 18:00

Interview conducted: on-site

INTERVIEW SCHEDULE

December 11th

8:40-9:30	Administrative and Scientific presentation of the Unit
9:30-9:50	Debriefing committee and break *(closed door meeting)*
9:50-10:30	*Team "Basophils, mast cells and immunopathology"*
10:30-11:10	*Team "Antigen presentation to T cells"*
11:10-11:25	Debriefing committee and break *(closed door meeting)*
11:25-12:05	*Team "Phagocytes and NADPH oxidase in inflammation"*
12:05-12h45	*Team "From micro- to macro in cancer development"*
12:45h-14h	Lunch Break (plateau) *(closed door meeting)*
14:00-14:40	*Team "From inflammation to cancer in digestive diseases"*
14:40-15:00	*Team "Inflammation and fibrosis in lung diseases"*
15:00-15:40	*Team "Inflammatory and stress responses in chronic liver diseases"*
15:40-16:00	Debriefing committee *(closed door meeting)*
16:00-16:40	*Team "Laboratory of imaging biomarkers"*
16:40-17:20	*Team "Innate immunity and lung inflammation"*
17:20-17:45	*Team "Heme and iron in oxidative stress and inflammation"*
17:45-18:00	Debriefing committee *(closed door meeting)*

December 12th

8:30-9:10	*Team "Vessels in liver diseases" (currently ATIP/Avenir)*
9:10-9:50	*Team "Physiopathology and treatment of viral Hepatitis"*
9:50-10:30	*Team "Plasticity of gastro-intestinal mucosa in nutritional pathologies and after surgery"*
10:30-11:10	*Team "Host environment interface in inflammatory disorders"*
11:10-11:30	Debriefing committee and break *(closed door meeting)*
	Meeting with personnel, will be organized in parallel
11:30-12:10	Meeting with ITAs (in French)
	In the absence of any managing staff
11:30-12:10	Meeting with researchers
	In the absence of any managing staff
11:30-12:10	Meeting with post-docs and students
	In the absence of any managing staff
13:10-13:40	Meeting with institution representatives *(closed door meeting)*
13:40-14:10	Debriefing committee and break *(closed door meeting)*
14:10-14:45	Meeting with the Management Team of the Unit *(closed door meeting)*
14:45-18:00	Redaction of the final report *(closed door meeting)*

PARTICULAR POINT TO BE MENTIONED

Mr Renato Ostuni, San Raffaele Scientific Institute, Italy has withdrawn from the evaluation for private reasons on Dec 12th 2023.

GENERAL OBSERVATIONS OF THE SUPERVISORS

Université Paris Cité

Le Président

Paris, le 4 mars 2024

HCERES
2 rue Albert Einstein
75013 Paris

Objet : Rapport d'évaluation de l'unité **DER-PUR250024166 - CRI - Centre de recherche sur l'inflammation.**

Madame, Monsieur,

L'université Paris Cité (UPCité) a pris connaissance du rapport d'évaluation de l'Unité de Recherche **CRI - Centre de recherche sur l'inflammation.**

Ce rapport a été lu avec attention par le vice-doyen Recherche et le doyen de la Faculté de Santé d'UPCité, qui signalent l'omission du nom de la présidente du comité des experts (Madame Nathalie Vergnolle) sur la première page du rapport, par la direction de l'unité, de la part de laquelle vous trouverez deux courriers joints qui signalent des erreurs factuelles à corriger et apportent des réponses au comité, par la vice-présidente Recherche d'UPCité et par moi-même.

Le doyen de la Faculté de Santé et moi même souhaitons indiquer que le CRI est un centre de recherche d'excellence sur l'inflammation, unique au sein de l'université, alliant à la fois recherche fondamentale, préclinique et clinique. La recherche translationnelle qui y est menée est un atout dans cette thématique avec un adossement hospitalier très fort. Avec l'appui d'un scientific advisory board (SAB) international, le CRI se restructure au prochain plan quinquennal avec la venue de nouvelles équipes et un changement de direction, ce qui insuffle une nouvelle dynamique. Cette évolution se fait avec le soutien et un accompagnement des tutelles (Inserm, CNRS, UPCité).

Je vous remercie pour la qualité de ce travail d'évaluation et vous prie d'agréer, Madame, Monsieur, l'expression de ma considération distinguée.

Édouard Kaminski

Présidence

Référence
Pr/DGDRIVE/2023

Affaire suivie par
Christine Debydeal - DGDRIVE

Adresse
85 boulevard St-Germain
75006 - Paris

www.u-paris.fr

Paris, February 14, 2024

We thank the HCERES visiting committee for their evaluation.
Please find our reply to the comment raised by the committee

Weaknesses and risks linked to the context
The outlay of the future management structure is unclear at the time of writing. The unit should clarify the representation of the different classes of personnel in the steering committee as soon as possible.

The duration of election of steering committee members needs further clarification (2 years?). Unit decisions will be formally approved by a center council (meeting every 3 months) gathering the executive committee, all the team leaders and elected representatives of each professional's staff. The precise composition of the council remains to be defined at this stage.

Reply
Reorganization of the operational management for the next contract is currently under process, and we aim to improve and facilitate interactions between all team members and platforms. We have started to rewrite our internal regulations' document which will define the structure of the different committees, their missions and the rules for their constitution (number of members according to the different classes of personnel, mandate duration, etc). The operational management will include

- *An executive committee* (monthly meetings), composed of 7 members [Director (V Paradis), Deputy director (S Lotersztajn), the general administrative manager (M Berthelot)), and 4 elected team leaders representative of the different research axes (2 representatives for axis (1) 1 for axis (2) and 1 for axis (3)). The executive committee will be renewed once during the contract. The representatives are elected by the team leaders of their respective axis for 2.5 years.

- A *steering committee* (every 2 months) composed of team leaders, volunteers PI researchers, volunteers technical staff (engineer/technicians). The steering committee will discuss scientific strategy, budget policy regarding specific operational actions (equipment acquisition, recruitment, internal calls for projects). It will also be responsible for overseeing matters concerning parity, inclusiveness, and ethics, and it will prepare the center council agenda. All the proposed actions will have to be validated by the CRI.3 center council.

- CRI.3 decisions will be formally approved by a *center council* (meeting every 3 months) gathering the Director (V Paradis), Deputy director (S Lotersztajn), the general administrative manager (M Berthelot), each team leader and elected representative members of each professional's staff (2 researchers and teacher researchers, 3 technical and administrative support, 2 Post-docs and docs). The members of the center council will be renewed once during the contract The representatives are elected by the respective staff for 2.5 years.

V Paradis, S Loterstazjn, R Monteiro

Paradis

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

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