Research evaluation

EVALUATION REPORT OF THE UNIT

CRC – Centre de recherche des cordeliers

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

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

EVALUATION CAMPAIGN 2023-2024

GROUP D

Rapport publié le 24/04/2024

High Council for evaluation of research and hignter education

In the name of the expert committee[1] :

Philippe-Paul Juin, Chairman

For the Hcéres[2] :

Stéphane Le Bouler, acting president

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

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Christine Guillard: Université Paris Cité (UPCITE)
Edouard Kaminski: President Université Paris Cité; Michel Vidal, Dean of Research, Faculty of Health, Université Paris Cité

CHARACTERISATION OF THE UNIT

- Name: Centre de Recherche des Cordeliers
- Acronym: CRC
- Label and number: UMRS1138
- Composition of the executive team:
  Directrice Jessica Zucman, Directeurs Adjoints Guido Kroemer, Pierre-Laurent Puig

SCIENTIFIC PANELS OF THE UNIT

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

THEMES OF THE UNIT

The 'Centre de Recherche les Cordeliers' (CRC) is a multi-thematic unit dedicated to fundamental research in biology and human health. During the last mandate, it comprised three departments: 'Physiology and Metabolism', 'Immunology and Cancer' and 'Genome and Cancer', each composed of 6, five and 6 teams respectively (17 teams altogether). The main scientific themes of teams in the 'Physiology and Metabolism' department were: eye disease (Team 1), kidney and ion homeostasis (Team 3), bacteriology, antibiotic resistance (Team 14), oral physiology (Team 15), diabetes, metabolism (Team 16) and inflammation (Team 18), 'Immunology and Cancer' department: cancer, immunity, immunotherapies (Team 4), autoimmune disease (team 8, 10), cellular stress, onco-immunology (team 9), and statistical modelling in health (team 19); 'Genome and cancer' department: liver cancer (team 2 & 6), liver steatosis (team 6), digestive, lung, gynecological cancers, personalised medicine (team 11), chronic lymphocytic leukemia, genomic abnormalities (team 12), functional genomics, tumour heterogeneity (team 13), medical ethics, informed consent (team 17).

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The CRC is located on the historic Cordeliers campus in the 6th arrondissement of Paris, and is owned by the Paris City Council since 1875. The site has been occupied by the Paris Faculty of Medicine since 1872, and is still home to the 'Paris-Cité' University medical school. The CRC was created in 2007 with the aim of bringing together biology and health teams from this site. The creation of an 'Unite Mixte de Recherche en Science' (UMRS 872) in 2009 formalised the creation of the center. This UMRS was renewed in 2014 and again in 2019 (UMRS 1138), and brings together laboratories and core facilities on a single site.

RESEARCH ENVIRONMENT OF THE UNIT

The CRC is hosted by the Sorbonne Université (Science & Engineering Faculty), with the Université Paris Cité (Faculty of Health) and the 'Institut National de la Santé et de la Recherche Médicale' (INSERM) as its main other supervisors. The Centre National de la Recherche Scientifique (CNRS) (Team 3) is an associate supervisor. In keeping with the center's aim of creating a strong link between bench and bedside, the CRC is associated with the University-Hospital Group Paris Centre and a network of 39 hospitals of the 'Assistance Publique — Hôpitaux de Paris' (AP-HP). CRC is a member of the SIRIC CARPEM (Sites of Integrated research in Cancer, Cancer Research for Personalised medicine), which is accredited as a comprehensive research center by the Organisation of European Cancer Institutes (OECI) at AP-HP. The CRC also contributes to the CURAMUS site for integrated cancer research (SiRIC), labelled in 2018 by the National Cancer Institute (INCa) and supported by the AP-HP Hospital Group. CRC coordinates two 'Future Investment programs-France 2030': The Labex Immuno-Oncology, and EquipEx Onco-Pheno-Screen. The CRC technology platforms CEF, CGB and CHIC are ISO 9001: v2015 and NFX 50–900 certified. CEF and CHIC were awarded the IBISA (Infrastructure en Biologie Santé et Agronomie) label. The unit is affiliated with eighteen doctoral schools from the Universities of Paris and the Paris region.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	64
Maîtres de conférences et assimilés	37
Directeurs de recherche et assimilés	25
Chargés de recherche et assimilés	27
Personnels d'appui à la recherche	99
Sous-total personnels permanents en activité	**252**
Enseignants-chercheurs et chercheurs non permanents et assimilés	53 (including 25 PhD)
Personnels d'appui non permanents	41
Post-doctorants	40
Doctorants	127
Sous-total personnels non permanents en activité	**261**
Total personnels	**513**

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

Nom de l'employeur	EC	C	PAR
UNIVERSITÉ PARIS-CITÉ	67	0	18
INSERM	0	40	40
AUTRES	8	3	13
SORBONNE UNIVERSITÉ	26	0	22
CNRS	0	9	6
Total personnels	**101**	**52**	**99**

GLOBAL ASSESSMENT

The Centre de Recherche des Cordeliers (CRC), located on the historic Cordeliers campus in the 6th arrondissement of Paris, is under the supervision of Sorbonne Université (Science & Engineering Faculty), Université Paris Cité (Faculty of Health), 'Institut National de la Santé et de la Recherche Médicale' (INSERM) and Centre National de la Recherche Scientifique (CNRS, for Team 3).

CRC stands as a distinguished research center in France, holding the impressive 17th rank in France (427th in the world) in the Scimago 2022 rankings, resulting from the direction's adept utilisation of unique expertise and strong clinical affiliations within top-tier teams. The center operates at the intersection of immunology, oncology, and metabolism, employing integrated approaches and cutting-edge 'omics' methodologies to unveil genetic and environmental factors influencing cancer and chronic disease development and define precision medicine tools. Significant findings have been made regarding: i) the role of immunogenic cell death in cancer and infectious diseases, and the importance of immunity in cancer prognosis, classification and treatment (e.g. breast cancer and sarcoma); ii) the association between mutational profiles and cancer subtypes (in hepatocellular carcinoma and colon cancer); iii) mechanisms of macular edema; iv) risks associated with and sarcoma); ii) the association between mutational profiles and cancer subtypes (in hepatocellular carcinoma and colorectal cancer); iii) mechanisms of macular edema; iv) risks associated with hepatic and non-hepatic complications in cirrhotic patients; v) gene therapy in the presence of anti-AAV neutralising antibodies; vi) genetics and function of the kidney in human health and disease, among others.

Notably, CRC and its17 teams has made significant major contributions to Oncology, Immunology, Cell Biology, Physiology & Nephrology, Gastroenterology & Hepatology and Hematology with groundbreaking concepts published in prestigious journals: Nat Rev Immun, Cell, Nat Rev Clin Oncol, Cell Research, Lancet, Nat Rev Cancer (x2), Nature, Nat Rev Dis Primer, J HEP, prog ret eye research, JNCI, Gastroenterology, Nature Med, Nat Rev Nephr… Overall, the level of publication is outstanding in relation to the size and financial resources of the unit. CRC members published 5965 original articles over the 2017–2022 period. More than 40% of articles were signed as first, co-first, corresponding or co-corresponding authors. 863 publications were in the TOP 10% most cited publications according to the bibliometric analysis provided by INSERM. Eight researchers are among the 'highly cited researchers' in 2022, according to Clarivate.

CRC's excellence includes remarkable fundraising capabilities (in particular European and international calls), securing substantial support globally, and attracting diverse research talents into competitive programs. Over the period approximately 90% of funding was obtained through competitive calls for a total of 99M€. CRC members obtained 621 contracts, 72% as PIs. These include 28 international contracts outside Europe, 51 European contracts (18 as PIs, including an advanced ERC, a consolidator ERC, a Junior ERC, an EU Mission on Cancer project, an ETN and others), 248 national contracts (36 in the framework of PIA; SIRIC CARPEM and CURAMUS, 43 INCa (22 as PI, including 3 PRTK and 16 PLBIO); 96 ANR, including as PIs 24 PRC, 3 PRCE, 5 PHRC, 2 PRCI, 4 JCJC and others), 29 regional contracts and 190 contracts from national associations and foundations (such as ARC, 'Ligue contre le cancer', FRM…). Five teams were labelled by the 'Ligue Contre le Cancer', one by Foundation ARC and three by FRM.
Unit members were attributed over 130 national and international awards (e.g. European inventor award, Albert 1er de Monaco Prize, Baillet Latour…), further highlighting its international reputation. The Unit's attractiveness is also evident in its successful recruitment of staff (integration of 5 CRCN and 4 MCU/PU/PUPH, including 1 'chaire d'excellence', attracting a new team following an international call). Training is excellent, with numerous theses (183) and post-doctoral fellowships (112). The CRC's platforms, certified and labelled, maintain strong connections with leading universities.

The center's industry engagement is outstanding, marked by 75 industrial contracts over the period (GERCOR, SANOFI DASSAULT systems, Pierre Fabre, Pfizer, ALhist…), 129 patents, and the establishment of 9 start-ups. Communication efforts, both in research dissemination and societal engagement, are noteworthy, involving national media and active participation in public debates.

The center could attain its full potential by reinforcing a participatory approach, disseminating newly set objectives, and enhancing internal communication. The upcoming mandate is pivotal to consolidate the multidisciplinary scientific approach, emphasising cross-fertilisation between fields. Keeping the balance between research on cancer, metabolic and inflammatory diseases, basic/translational/valorisation projects will contribute to affirming the identity of CRC in its ecosystem (i.e. cancer centers). The implementation of a participative and interactive organisational model will maximise the impact of this distinctive strategy.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

CRC has implemented corrective actions in response to the recommendations made in the previous HCERES report, as detailed in the following section. 1/ Development of inter-team, multidisciplinary collaborations: several projects between at least two CRC teams were submitted and funded (INCa, ANR, CARPEM, Labex...), and over 100 publications are co-authored by members of different teams. 2/ Setting up 'in-house' intellectual property management: one full-time person now coordinates intellectual property in conjunction with 'INSERM transfert'; One hundred and twenty-nine patents were filed and fourteen start-ups created, representing an increase of 16% and 280% respectively; 3/ Extending CRC's international communication/visibility: recruitment of a communication director, creation of a new website, promotion of numerous events and scientific animations; 4/ Including teacher researchers in the executive committee in charge of training: the CRC chose to place teaching and training under the responsibility of several people. It sets up scientific clubs on bioinformatics, organoids and imaging; 5/ Implementing of CODIR committee: all team leaders are present, three retreats have been organised; 6/ Expansion and refurbishment of platforms supported by management: renovations are underway, more than ten new instruments have been acquired and more than a million euros has been earmarked for platforms. Technicians and engineers are also being recruited for the platforms; 7/ Ensuring a balance between the CRC's three departments: the CRC has encouraged the development of collaborations between teams of the different departments. Two teams working in the field of metabolism are moving to INEM and ICAN; Paris odontology teams are regrouping at Montrouge (UPCité). Medical biostatistics is joining INRIA at PCS. MICROB. RESIST team will join a research unit in the field of microbiology and chemistry and biophysics applied to biology (future LBM/PASTEUR unit). 8/ Establishing a bioinformatics platform: recruitment of a 'chair of excellence' in bioinformatics in Oncology and emergence of a research team and a bioinformatics platform; 9/ Creation of a team dedicated to bioethics: CRC and Université 'Paris Cité' have created a team called 'ETRES'.

B – EVALUATION AREAS

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

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

Assessment on the scientific objectives of the unit

The direction has capitalised on the remarkable expertise and links to the clinic of leading teams in their fields and it implemented high-level technological platforms. As a consequence, CRC is equipped and organised to study the origins and physio pathological causes of human cancer and chronic diseases in a highly competitive manner. CRC occupies an outstanding position as a multidisciplinary research center of excellence (ranked 17th in France in the Scimago 2022 rankings) working at the interface between immunology, oncology and metabolism.

Assessment on the unit's resources

The ability of CRC teams to raise funding (in particular in Europe and worldwide), to recruit research players of all categories and to work on competitive research programs, is outstanding.

Assessment on the functioning of the unit

The unit is built on an excellent, rational and pragmatic organisation to promote parity (note that it is remarkably applied to team management) and career development with respect for diversity. The health and safety functioning are very good. Consolidating a participative mode of functioning, informing on the newly implemented objectives and structuring internal communication to clarify the decision-making process will allow them to fully exploit the Center's potential.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The Unit has excelled in harnessing the expertise of individual teams in basic research. Its proficiency in securing competitive funding, leveraging mutualised core facilities, and establishing robust connections with clinical research has further enhanced its reputation in immunology, oncology, metabolism, physiopathology, bioinformatics, and biostatistics. Through this comprehensive approach, the Unit has achieved a notable position in both national and international rankings, including the Scimago ranking.

Significant findings have been made regarding: i) the role of immunogenic cell death in cancer and infectious diseases and the importance of immunity in cancer prognosis, classification and treatment (e.g. colorectal & hepatocellular carcinomas, and sarcoma); ii) the association between mutational profiles and cancer subtypes (in hepatocellular carcinoma and colorectal cancer); iii) mechanisms of macular edema; iv) risks associated with hepatic and non-hepatic complications in cirrhotic patients; v) gene therapy in the presence of anti-AAV neutralising antibodies; vi) genetics and function of the kidney in human health and disease, among others.

Weaknesses and risks linked to the context

A potential concern is a decrease in technological development (which may be harmful in the constantly evolving field of healthcare research) due to a decrease of new and young PI's. This may in the long-term limit the dynamics of scientific innovation.

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

As of December 31, 2022, the CRC had a staff of 550, including 49 INSERM or CNRS researchers, 131 professors or lecturers, 146 research support staff (including 70 on fixed-term contracts), 178 PhD students, 45 post-docs and around 60 trainees per year (from BTS to Master). Over the period of the contract, the total number of doctoral students was 305 (including 183 theses defended) and 112 post-doctoral students. Thirty-two researchers joined the CRC for twelve departures. For the new contract, the CRC will welcome two new teams (1 senior and 1 junior) following an international call.

The CRC has an annual operating budget excluding payroll: 18.9 M€/year) of around 12.5 to 20.7 M€/year (with the exception of 2022, which was characterised by the award of major contracts (Equipex, European and RHU) and a marked increase in the budget to 40.1 M€). On average, 9.4% (3.9% to 14.88% depending on the year) of this budget comes from grants from the supervisory bodies (Sorbonne Université, Université Paris Cité, INSERM and CNRS), 78.4% (61.12% to 94.63%) from local, national, European or international project calls, and 12.2% (1.47% to 24%) from collaborations with industry.

Teams were very successful in raising financial support (9 to 18 M€ per year between 2017 and 2021 and 37 M€ in 2022 alone, with Equipex, RHU and European funding. Own resources relied on European funding and other international, national (ANR and INCa, PIA), and regional contracts, industrial partnerships, and caritative associations and foundations. Nine teams are labelled by Foundation ARC, 'Ligue contre le cancer' or FRM.

Recruitment is dynamic, despite staff turnover. The CRC has been able to recruit permanent staff to maintain its research activities in a tight budgetary context. Recruitment of PhD students and post-docs has remained extremely dynamic. Overall, CRC's teams have an excellent fundraising capacity, enabling them to develop their research programs.

Weaknesses and risks linked to the context

Despite the efforts made in terms of intellectual property and some major successes with the industry, there seems to be limited, if any, financial return to the unit over the contract ever since 2019. This may restrain the ability of the unit's direction to fund incentive transversal actions and/or to allocate resources to the platforms, insofar as the endowment from the supervisory authorities are the main means to implement a scientific policy. Providing manpower for a mutualised Bioinformatics platform, in addition to securing and upgrading laboratory space will be key actions to consolidate CRC visibility and attractiveness.

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

In terms of human resources, CRC is composed of 61% of women and 39% of men. The scientific advisory board is composed of 6 men and three women. A committee ensures parity and provides information on legislation and actions to be taken. It also promotes diversity, with more than 35 nationalities represented and eleven people with disabilities integrated into teams. An internal mobility campaign is conducted annually, and a twelve-member committee representing all staff category analyses and ranks CRC promotion applications before forwarding them to the supervisory authorities. Job requests and their distribution within teams are analysed twice a year by the CODIR and the Laboratory Council.
Servers and IT security are being upgraded in coordination with INSERM and university departments.
An engineer reporting to management (100% full-time) is in charge of coordinating accident prevention at CRC. A single document is drawn up each year, and corrective action is taken in response to incidents. Regulatory training is provided every year (autoclave, etc.). For each team, a referent is present for hygiene and safety. In-house health and safety training is provided, as are preventive measures to deal with psychosocial risks.
In 2021, CRC began to take environmental impact into account, at the instigation of Sorbonne University. CRC's first actions were to take into account the environmental impact of its activities (greenhouse gas balance), and a 4-person committee was set up at the end of 2022 to reduce this impact.

Weaknesses and risks linked to the context
None

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

CRC is one of France's leading research centers. Its dynamism in shaping the European and international research landscape is remarkable. The CRC staff has won over 130 national and international prizes (European inventor award, Albert 1er de Monaco Prize, Baillet Latour…). Recruitment at the CRC is very good (integration of 5 CR and 4 MCU/PU/PUPH, including 1 'chaire d'excellence'), to excellent (integration of two new teams following an international call). Training is good (183 theses defended) to excellent (112 post-doctoral fellows). Fundraising capacity is remarkable, with more than €99M (621 contracts, ¾ of which as leader) raised at the international and national level. The CRC platforms are recognised by their certification and labelling. Their links with the joint centers of Paris Sorbonne and Paris Cité universities are also excellent.

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

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

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

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

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

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

The CRC is one of the leading research institutes in France. Members obtained 28 international contracts outside Europe (among them Kidneeds C3G, Hadassah (X3), Diabetes UK) 51 European contracts (18 as PIs, including an advanced ERC, a consolidator ERC, a Junior ERC, an EU Mission on Cancer project, an ETN and others). It plays a leading role in shaping the international research landscape by organising 127 international conferences, including highly prestigious ones (ESMA European Cancer Research, AACR on tumour immunology and liver cancer) and 205 local conferences with internationally renowned speakers. CRC members were

invited to 800 international meetings. A total of 1369 oral communications and 401 posters were presented at these meetings. CRC Sixteen members are editors of international journals (Frontiers in immunology, journal of hepatology, JHEP, Cell & molecular immunology…). CRC members participate in 199 steering committees or expert evaluation panels (European Council, HCERES, CNU, CS & CSSs INSERM, university research/scientific councils, INCa, ANR, IUF), members of foundations or associations (ESMO, SNFDT, FITC, Vaincre le cancer…) or members of SABs (Sobi, Takera...). CRC researchers have won more than 130 prizes and awards (Gallien Prize, Inserm Innovation Prize, European Inventor Prize, Albert 1er de Monaco Prize, Baillet Latour...) and two have been awarded honorary doctorates by foreign universities (University of Louvain, Belgium and Rome ter Vergata, Italy). CRC Twenty researchers have spent one or more periods abroad (as a researcher, 'en détachement', visiting professor/scientist, etc.).

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

During this contract, the CRC recruited five INSERM research fellows following competitive calls, and 4 MCU or PUPH fellows (including one Chair of Excellence, Université Paris Cité). The net balance of arrivals is positive, with 32 arrivals for twelve departures. The CRC will also be welcoming a senior team (32 people) and a young team following a competitive bidding process. CRC Teams share 50% of CRC's recurrent budget, with the remaining 50% going to infrastructure and platforms. Newcomers receive training in ethics, health and safety, management, etc.

Fifty-two researchers and 38 staff members were promoted (change of grade or department). Twenty-five have obtained the HDR, and 42 are holders of the PES or the PEDR. At least 52 visiting scientists were hosted by CRC.

Three hundred and five doctoral students were hosted and 183 defended their thesis during the period (110 for 162 HDR Researcher/lecturers supervised thesis students). Four students abandoned their PhD training. The average thesis duration is 41 months (median = 39), and 21 theses (10%) lasted more than 50 months. One hundred and twelve post-doctoral fellows were hosted, and a large number of students, including over 300 Master's students.

Two researchers are in charge of the doctoral school, and teaching staff teach at Université Paris Cité and Sorbonne Université.

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

Approximately 90% of funding is competitive (excluding payroll), for a total of 99M€. CRC obtained 621 contracts, 248 national contracts, including 36 funded by the PIA, 75 industrial contracts, 29 regional contracts and 190 contracts from national associations and foundations. More specifically, the CRC was awarded 449 contracts as a leader: 24 governmental international contracts (Indo-French center for the promotion of advanced research, Hadassah (x3), KIDNEEDS, International Waldenstrom's Macroglobulinemia Foundation, Fibrolamellar Cancer Fundation, etc.– ; Eleven international private contracts (Sidra Medecine, NPRP, SAMSARA, OSASUNA, Bioverativ, Bayer award (x2), etc.), eighteen European contracts (ERC advanced grants (x1), ERC Starting Grant (x1), ITN Marie Curie (x3), etc..).

National contracts included 36 in the framework of PIA (IDEX (x11), 1 labex ImmunuOncology, Equipex Onco-Pheno-Screen, 1 PPR antibioresistance, 1 IHU iCAN), SIRIC CARPEM (x10) and CURAMUS (x4), 43 INCa 22 as PI (including 3 PRTK, 16 PLBIO), 96 ANR, 36 as PI including 24 PRC, 3 PRCE, 5 PHRC, 2 PRCI, 4 JCJC), 'Agence de la biomédecine', etc.), 73 private funding (SATT, GERCOR, SANOFI DASSAULT systems, Pierre Fabre, Pfizer, ALhist…), twenty local (IDF region, university, AP-HP, Pasteur institute, city of Paris...), 175 from associations and foundations (Fondation ARC, "Ligue contre le cancer", SFNDT, association Laurette Fugain, FRM, SFCE, Gefluc, COMETH, etc). Five teams are labelled by the 'Ligue Contre le Cancer', one Fondation ARC and three by FRM.

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

The CRC has a core facility which manages the technological platforms. This core facility received €1.5 million in public and industrial funding over the course of the contract. Fifty percent of the recurrent funding of CRC is devoted to the 4 platforms.

1) The animal facility (Functional Exploration Center, CEF) consists of a team of twelve people (including 2 fixed-term contracts). It has supported some 200 researchers on 158 projects. It provides functional exploration in ophthalmology, immunology, metabolism and an imaging platform. During the contract, and a mouse 'functional metabolic phenotyping' platform was created. Imaging equipment within this facility has been renewed to include two ultrasound scanners, one IVIS Lumina, one echograph and instruments dedicated to ophthalmology. This facility is part of the animal facility network of Paris Sorbonne University (called RRPA) and Paris Cite University (called Anima 75).

2) The 'Genotyping and Biochemical facilities' (CGB) platform has 4 dedicated staff. It is particularly active in genotyping (cell, tissue, human, mice…). Instruments include quantitative PCR equipment (Taqman 7900, Biorad QX200 Droplet Digital PCR, Prism6 Stilla (2021); a nucleic acid analyser, LabChip GX; an Applied Biosystems™ 3500xL sequencer and a capillary electrophoresis protein analysis system (Jess, Bio-techne). It is part of Sorbonne University's OMICS network.

3) The Histology, Imaging, Cytometry Center (CHIC) has a staff of three and a PhD student for around 200 users, 2/3 of whom are external. It comprises a histology platform (2 automated slide staining systems, AS48L DAKO

and Bond RX Leica, 1 slide scanner Axioscan Z1; 1 multispectral imaging microscope (Vectra, PerkinElmer); One multispectral slide scanner PhenoImager HT (Polaris, Akoya) one HistoCore Spectra (Leica); One cytometry platform (two cytometers for sorting and two analysers); One spatial imaging platform: GeoMx Digital Spatial Profiler associated to an nCounter Flex Analysis System (Nanostring) and a Visium CytAssist (10x Genomics). The platform also develops artificial intelligence tools in collaboration with industry and hosts a PhD for technological developments. It is part of the LUMIC network at Sorbonne University.
4) A L2 and L3 technical platforms. The L3 is designed for hazardous virological, bacteriological and human cancer cell line experiments.
All four platforms are Iso9001 & NFX-50-900 certified. The CEF & CHIC platforms are IBISA certified. A bioinformatics platform is under development.

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

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.

Changes in administration and financial management difficulties following the COVID period strongly affected the various coordinating groups and associations (for example, PhD student groups). This had lasting consequences for the coherence of actions, doctoral student training, feedback and communication within the unit. For instance, only 25% of PhD students were able to take part in international congresses outside the CRC.

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

The CGB (Genotyping and Biochemical facilities) platform is in difficulty due to the limited number of staff. L2 and L3 are relatively small compared to the size of the unit.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

CRC is to be credited with an exceptionally outstanding scientific production, with several new concepts unravelled in the field of Oncology, Immunology, Cell biology, gastroenterology & Hepatology, Physiology & Nephrology and Hematology, and published in high-profile journals: Nat Rev Immun, Cell, Nat Rev Clin Oncol, Cell Research, Lancet, Nat Rev Cancer (x2), Nature, Nat Rev Dis Primer, J HEP, prog ret eye research, JNCI, Gastroenterology, Nature Med, Nat Rev Nephr.

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

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

CRC researchers were associated with 5965 original articles over the 2017–2022 period and have produced 130 written communications through other media (books, book chapters, expert reports, software…). The bibliometric analysis provided by CRC and INSERM over the period 2017–2022 shows that 266 researchers

published 5109 publications over this period, including 3478 original articles. Seven percent of articles were published in non-English-language journals. Forty percent of articles were signed as first, co-first, corresponding or co-corresponding authors) by at least one CRC researcher. For original articles, 78,336 citations were recorded, and 863 publications were excellent journals. CRC Eight researchers are among the 'highly cited researchers' (Clarivate). Many of CRC's most-cited publications are in high-profile journals (Nat Rev Immun, Cell, Nat Rev Clin Oncol, Cell Research, Lancet, Nat Rev Cancer (x2), Nature, Nat Rev Dis Primer, J HEP, prog ret eye research, JNCI, Gastroenterology, Nature Med, Nat Rev Nephr).

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

Publications from the CRC reflect its main research axes: Oncology, Immunology, Cell biology, gastroenterology & Hepatology, and Hematology. On average, the center's teams have published 350 publications per team (median = 334), with wide variations between teams: the minimum is 30 publications and the maximum 1030. 6 of the seventeen teams (approx. 35%) account for more than 60% of publications. These variations can be explained by team themes (more fundamental or more clinical), funding, and team size. CRC encourages teams to publish in high-profile journals. It also encourages young researchers to share scientific leadership by defending HDRs (25 over the period). 93.4% of PhD students have at least one first-author publication (and an average of 5.3 publications per thesis) and were invited to present their work as posters or oral communications at international conferences. The rules governing publications and the position of authors in publications are the subject of training courses accessible to all staff. The contribution of each author is discussed within the research teams, according to the work carried out.

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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.

CRC has a proactive policy in terms of integrity and ethics, through staff training at dedicated seminars. It also implements data traceability tools (lab notebook). Plagiarism is systematically analysed by software for reports and papers submitted. Open access publication of articles is encouraged (within the limits of financial sustainability), and publications are also accessible on public repository platforms such as HAL. Data is also accessible through public repositories within the limits imposed by the RGPD (patient anonymity, confidential data).

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

The number of publications signed by more than one CRC team seems to be relatively low.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The ability of CRC to translate its activity towards industry is outstanding, as judged by the securing of more than 70 industrial contracts, 129 patents and by the creation of 9 start-ups. CRC has a remarkable action to communicate its research to the general public, in particular via national media and to contribute to debates in society.

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

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

The CRC has developed numerous interactions with non-academic partners. In addition to welcoming students for internships, it also welcomes pupils from primary to secondary schools to take part in research-related cultural activities during the Fête de la Science. It has also welcomed high-school students through various programs designed to help them enter the workforce or raise their awareness of research (discovery internships in junior high schools, apprentice research program, 'l'envol' program). CRC members also take part in the executive committees of learned societies, expert appraisals for various public bodies and public or private scientific committees. The unit also communicates via the national media (newspapers (Le Monde, Libération, Le Point), radio (France Culture, Europe 1), television (BFM, France 5). In addition to interacting with the general public, CRC members also participate in management committees/boards of directors as members (x59), secretaries (x7), vice-presidents (x8) or presidents (x13), scientific councils/research commissions as members (x45), vice-presidents (x1) or presidents (x5), industrial scientific advisory board members (x 12) and experts (x14). Interaction with the private sector is also demonstrated by the center's ability to attract funding from socio-economic players (75 industrial contracts and 11 CIFRE theses).

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

In conjunction with INSERM Transfert, CRC is actively developing a transfer activity towards industry, supported by the recruitment of staff dedicated to commercialisation. The CRC has secured 75 industrial contracts (Daiichi Sankyo, Bayer, Sparks Therapeutics, Grifols, Topas, AstraZeneca, Janssen, Poxel, Jacquemier, ABBOTT, Sanofi, CEMKA, eXystat, Pierre Fabre, Dassault Systèmes, Pfizer, Gercor, etc.), eleven CIFRE theses, 129 patents and 9 start-ups (14 since 2008). CRC members also participate in science advisory boards for industrial companies (Bayer, OctA 101, Sanofi, Sobi [x3], Takeda, Novonordisk, 4DMT, Alexion Pharmaceuticals, Abbvie, Institut Danone).

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

Through their academic communication activities (courses) and the hosting of numerous interns, CRC members help to disseminate knowledge to the general public. Knowledge is also disseminated through conferences and seminars either organised by the CRC, or attended by CRC members. The CRC also organises events aimed at the general public, such as the Fête de la Science, where visitors can tour the laboratories and take part in small-scale science-related activities. It is also developing programs to welcome young students for short periods of time, in order to stimulate their interest in science. CRC is also active through its website, and particularly active on LinkedIn (1100 followers, 95 posts), X (ex Twitter) (750 followers, 1318 tweets), YouTube (broadcast '360 degrés', INSERM, CNRS and foundation blogs (FRM)). And participation in interviews with traditional media (press, radio, television) or the internet (blogs on the websites of charitable foundations (FRM) and institutional (INSERM, CNRS…).

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

No weaknesses

ANALYSIS OF THE UNIT'S TRAJECTORY

In the next mandate, the unit aims to develop and integrate multiscale analysis to characterise the origins and physio-pathological causes of human diseases (and of cancers in particular). To address this, the unit has formulated a strategy centred on the team restructuring, implementing a new organisational framework, and fostering the development of new technologies. Importantly, this strategy is the result of consultation with external experts (3 times with SAB), consultation between research actors of the unit (two retreats involving team leaders), and a dialog with supervisory bodies (1/2-day meeting).
Reorganisation of the CRC will lead to the departure for other research units of the two teams working on diabetes (teams16 and 18) and the microbiology team (team 14, led by a new director). Moreover, following the retirement of the team leader, members of team 15 will either move to another research unit or join team 1. Finally, team 17 will integrate team 11. To enforce its activity in the priority fields of immunology, oncology, metabolism or bioinformatics, the unit launched (accompanied by its SAB) a call for proposals which led to the creation of a new team (team 7, dedicated to genomic alterations and metabolic errors in rare cancers), and the emergence from team 11 of team 5, dedicated to new methods of omic data analysis. The complementarity of these new teams with other teams of the Unit, and their potential input for the development of mutualised techniques, are major assets.
The Unit will modify its organisation in departments (encompassing individual teams) to implement transversal axes (in the form of 'Integrated Research Projects' IRP on which teams will work together). Three IRP (Metabolism and immunology, environment, exposome and genome, Therapeutic innovation and precision medicine) aim to develop common explorations, while a fourth one (Ethics, Research and Society) is more dedicated to the development of a common culture.
This organisation should be very useful in promoting further interactions between teams, so it will be important to give it concrete objectives and indicators of success, and to find ways of stimulating it (for example, through internal calls…).
The Unit will maintain its effort in implementing new technologies by hosting an onco-pheno screen platform (Equipex 2030, in collaboration with Institut Curie and IGR), investing in spatial biology and by mounting a Bioinformatics platform. This Unit will pursue translating its discoveries to the clinics.
As a whole, the Unit's project is thus well designed, and supported by the current leaders and new recruits. The project is to evolve from a unit dedicated to specific disciplines (e.g. in physiology) to a more interfaced research structure, wherein integrated approaches and the development of 'omics' methodologies will cross-fertilise immunology, oncology and metabolism, characterise the influence of environmental factors in the genesis of cancers and other chronic diseases and develop precision medicine tools.

RECOMMENDATIONS TO THE UNIT

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

Following discussions with various interest groups during the site visit, the committee suggests implementing the following measures to enhance the organisation and dynamics within the unit. It is important to emphasise that these changes necessitate the collective effort of all interest groups (and requires that they position themselves as proposition forces) and cannot be solely executed by the leadership team, although their complete support is indispensable for the successful implementation.

The leading team (internal steering committee) needs to increase transparency related to their decision-making and communicate decisions by increasing the number of Center councils per year and setting up a rigorous system of agenda announcements and accessible reports. The creation of committees composed of team representatives and dedicated to logistics issues, communication, etc. might be beneficial. Strengthening the unit's administrative pole by opening a permanent position will be instrumental.

Integrated research programs (IRP) and thematic clubs have the potential to promote synergy between teams and foster interactions between actors. The unit should consolidate them with clear missions and propose funding for collaborative programs and/or the use of platforms to generate a leverage effect. Responsibilities of IRP leaders must be made explicit, and a regular reporting system should be implemented to help transversal actions evolve in the most agile way possible. Indicators of success will be, for instance, to note that all teams working in liver physiopathology collaborate with each other.

There is a clear need to mutualise an activity related to Bioinformatic analysis. The creation of an additional permanent engineer position is a priority to allow the creation of a related platform, and clearly separate its activity from that of the future bioinformatics research team (whose objectives will be distinct).

The establishment of self-organised interest groups for PhD and postdoctoral fellows, led by elected representatives serving on rotating terms, is essential. This initiative might be backed by a modest flexible budget to facilitate regular activities that foster a shared identity within the unit, transcending individual team boundaries. This could be done through the organisation of events such as PhD student science days. In addition, the unit should ensure that each doctoral student is able to attend at least one international conference, as this is crucial for their career development.

It seemed to the committee that there is an absence of a well-defined reporting structure that would allow the systematic identification, monitoring, and resolution of bullying or harassment issues. Similarly, there seems to be a lack of a visible framework dedicated to psycho-social risks. It is crucial to identify unit members responsible for addressing matters related to these subjects. These individuals should be readily identifiable and entrusted by the bodies with the responsibility of handling reports from those who have witnessed or experienced situations of suffering in the workplace.

Recommendations regarding the Evaluation Area 2: Attractiveness

To fully exploit the potential of the CRC and maintain its dynamics of excellence over time, there is a clear need to anticipate the renewal of PI's, to identify strategies to maintain a research topic in case of a PI retirement, to favour emergence, and to recruit young tenured scientists.

With, for instance, the opening of a 'Chaire Professeur Junior' announced in 2024, the Committee suggests that the CRC base its recruitment policy for new PIs on an explanation of its key milestones and scientific vision. Defining ideal scientific profile(s) of the future PIs might slightly decrease the number of applications; yet it should encourage support from the supervisory bodies whose policy is often driven by a programmatic and macroscopic vision of investments. Strategies to identify lab/office spaces for new teams should be carefully anticipated and considered as a valuable attractiveness factor. Implementing an overt policy to recruit and attract young tenured scientists based on mentoring and supporting actions (facilitated access to the unit's platforms, for instance) is also recommended. Finally, to enhance the sense of belonging among CRC members, it might be beneficial to create a dedicated structure for socialising and to create an Alumni association.

Recommendations regarding Evaluation Area 3: Scientific Production

No specific recommendations on the scientific production which is outstanding.

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

The committee congratulates the unit for the contribution of its research activities to society. It would suggest organising the interactions with the general public at Unit level if a member of the unit could take on the responsibility of 'relationship manager'.

TEAM-BY-TEAM OR THEME ASSESSMENT

Team 1: Physiopathologie des maladies oculaires : Innovations thérapeutiques

Name of the supervisor: BEHAR-COHEN Francine

THEMES OF THE TEAM

The main focus of the team is basic and translational research in the broader field of neurosciences, specifically ophthalmology and vision sciences. Their research axes focus on common forms of vision loss (age-related macular degeneration, glaucoma, retinal detachment) but there is also an interest in rare eye diseases. Apart from pathophysiological research, their research deals with innovative treatments for eye diseases, such as non-viral gene therapy and neuroprotection.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team addressed recommendations from the previous evaluation:

1) They attracted EU contracts to their overall grant portfolio (7 M€ over a period of 5 years). The team has an excellent international visibility testified by international collaborations.
2) It was recommended to improve the diversity of the team with non-clinical students and to improve the senior/junior balance of the team. The team composition shows that apart from part-time researchers (0.2-0.33 devoted to research) there are also eight permanent staff members that have a full-time research mandate. Although the team has many senior profiles with four emeriti, there are at least ten team members with more junior (early- to mid-career) profiles. Apart from two post-docs, there are six PhD students (15 when taking into account the defended ones).
3) The team has invested in the development of innovative therapies in less studied areas (e.g. non-viral gene therapy).

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	9
Maîtres de conférences et assimilés	4
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	6
Sous-total personnels permanents en activité	**23**
Enseignants-chercheurs et chercheurs non permanents et assimilés	4
Personnels d'appui non permanents	1
Post-doctorants	4
Doctorants	6
Sous-total personnels non permanents en activité	**13**
Total personnels	**38**

EVALUATION

Overall assessment of the team

The scientific output of the team is excellent to outstanding: 152 publications as PI in outstanding journals in the discipline (Am J ophthalmology, ocular surface, Invest. Ophthalmol. Vis. Sci…) and multidisciplinary journals (Nat Commun). Attractiveness is outstanding: ~7 M€ over five years including two EU funding as partner, and eight ANR as leader, Prix European Association for Vision and Eye Research 2019. The team shows a high degree of entrepreneurship, fostering academic-industrial interactions. The PI founded three companies (Ammtek, Eyevensys, Earlysight). Societal impact is outstanding: Anses report on the effect of LEDs on health, spin-off company Eyevensys.

Strengths and possibilities linked to the context

The team consists of seventeen part-time researchers, 4 emeriti, and eight permanent staff members that have a full-time research mandate (13.1 FTE research time in total). During the evaluation period, two post-docs and 21 PhD students were trained (15 completed their PhD). At least ten team members have early- to mid-career profiles.
Scientific production includes 352 original articles (152 in leading position) mainly in the fields of ophthalmology, oncology, medicine, pharmacology, genetics/molecular biology and multidisciplinary sciences. Nineteen percent of these are top 10% papers in their respective fields, and one third of these are 'primary' articles as PI, for a total of 6% PI papers in the top 10%.

The team was highly successful in fundraising: ~7 M€ over five years, including two EU funding (as partner), eight ANR as leader (4 PRC, 2 PRCE, 1 JCJC, 1 PHRC), twelve contracts obtained from charitable foundations (Fondation Katz, AFM, FRM…), donations (Novartis). The PI was awarded prestigious prizes (Inserm Award for Innovation Prize 2021, Prix European Association for Vision and Eye Research 2019). Key studies include the effect of mineralocorticoid receptor antagonism on choroidal neovascularization and neovascular age-related macular degeneration (Nat Commun), and neurotoxicity of iron in retinal detachment and of neuroprotection of transferrin (published in Int J. Mol Sci., a top multidisciplinary journal). Tight links with the clinic and their access to patient-derived and donor biological samples are a strongpoint. The team has an excellent international visibility, with 115 presentations and 39 posters at meetings during the assessment period.
The team hosted fifteen PhD students (9 theses defended). These include two CIFRE and five international theses (2x Israel, USA, Turkey, China). Sixteen members have an HDR.

The team participated in the report for Anses on the effect of LED on vision, emphasising the societal impact of the team's activities. Its translational research is highlighted by the development of innovative therapies for eye diseases. The PI founded three companies (Ammtek, Eyevensys, Earlysight) dedicated to various aspects of ocular disease detection and therapy. It obtained 440K€ in industrial contracts and two CIFRE theses.

Members of the team are president and treasurer of the patient association 'Tous Unis pour la vision' that support eye research and gives information to patients about eye diseases.

Weaknesses and risks linked to the context

The ratio of thesis defended (9) to HDR (16) is low.

Analysis of the team's trajectory

The team will mainly be active in pillar three of the CRC unit, namely therapeutic innovations & precision medicine. With a team of ca forty people will invest in unifying themes of neurogenic and neuroinflammatory regulations in the pathogenesis of ocular blinding diseases such as age-related macular degeneration, glaucoma, retinal detachment but also of rare eye diseases, supported by the EU Restore Vision project. Their angle is original, studying iron metabolism, and gluco- and mineralo-corticoid pathways. Apart from pathophysiological research, their research deals with innovative treatments for eye diseases, such as non-viral gene therapy and neuroprotection. The projects range from molecular targets to human proof of concept studies. For most of their projects, IP is secured by patents. Specifically, they will study: (i) the effect of mineralocorticoid receptor antagonism on choroidal neovascularization and neovascular age-related macular degeneration, and research on the neurotoxicity of iron in retinal detachment and of neuroprotection of transferrin. An original technology used is electroporation. Funding (ANR price) has been secured for this research; (ii) the role of steroids in corneal transparency, and neuro-immune crosstalk; (iii) the role of YAP in the cytoskeleton, a recent research line that relates to myopia, a hot topic in ophthalmology research. The team developed a system to elongate cells, putting them in a unique position. Working with organoids may help answer this question.
Omics work (multi-omics, single-cell omics) will be done in collaboration with the Cordeliers Bioinformatics Center (CBC) led by Aurélien de Reynies, with whom the team applied for a large joint grant.

RECOMMENDATIONS TO THE TEAM

The committee applauds the team for clearly promoting clinician-scientists in translational research. The committee encourages the team to continue their innovative and translational research activities and projects. The team is encouraged to further apply for international/EU funding (ERC Advanced grant for the PI), and foster academic-industrial collaborations whenever relevant.

Team 2: ONCOLIV: Fonctions oncogéniques de la signalisation de la β-caténine dans le foie

Name of the supervisor: COLNOT Sabine

THEMES OF THE TEAM

Research carried out by the team stems from the original observation of a functional role for beta-catenin signalling in liver embryogenesis, regeneration and pathogenesis, in a genetically-modified mouse model developed by the PI. Since then, the team has been studying the pathogenesis of beta-catenin-HCC (hepato-cellular carcinoma), which is characterised by resistance to immunotherapy thereby defining an important clinical issue for liver cancer treatment. Over the contract period, the team developed four clearly-defined research projects: metabolic reprogramming; interactions between epigenetics, chromatin and transcription; development of relevant preclinical murine models using CRISPR-Cas9; and assessment of new therapies for this subclass of HCC resistant to immunotherapy.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team followed most of the recommendations from the previous evaluation. Notably, they applied to ERC synergy grants and were selected for the next phase. Additionally, they applied to grants offered by the pharmaceutical industry in order to increase their interaction with the private sector.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
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	1
Post-doctorants	1
Doctorants	2
Sous-total personnels non permanents en activité	**4**
Total personnels	**8**

EVALUATION

Overall assessment of the team

The research activity and scientific production of the team are excellent, as attested by publications in journals of the highest reputation in their domain (Gastroenterol 2019, Gut 2019, J Hepatol 2022). The attractiveness is also excellent for the size of the team: two INCa, one ANR, one prestigious Ligue labelling. The interaction with the non-academic sector is very good to excellent: one patent in liver cancer and yearly outreach activities (e.g. Fête de la Science).

Strengths and possibilities linked to the context

The organisation of the team is fully coherent at the quantitative and qualitative levels, with staff scientists (3 INSERM researchers), staff engineers (1 engineer), postdocs and PhD students (4). During the contract, the team

maintained a very good balance between senior staff scientists and young researchers, with an average of two post-docs and two PhD students per year.

This team was very successful in securing competitive national funding. As examples, the team obtained two INCa PLBIO (2021) and a young researcher ANR grant as PIs (2018), Emergence INCa funding, one prestigious team label 'Ligue contre le cancer' (2019) and one team label 'Ligue Childhood Cancer' (2022), for a total of sixteen national grants, among which 9 as coordinators. The project is clearly innovative, highly relevant to the clinic, including children's cancers, and may lead to new therapies in liver cancer.
The team published 34 papers: 24 research articles and ten reviews. Eight original research articles were signed in first or senior position and published in journals of the highest reputation in their speciality (Gastroenterol 2019, Gut 2019, J. Hepatol 2022). Of note, they reported two seminal papers on reprogramming tumour metabolism in HCC (addiction of beta-cat-HCC to dietary choline, Gastroenterol 2019; and fatty acids as energetic fuel, Gut 2019), and the oncogenic cooperation of the chromatin-associated protein ARID1A with beta-catenin in HCC (Elife). In addition, they reported relevant new murine models showing beta-catenin driver mutations in HCC and HB carcinogenesis (J Hepatol), highlighting the fruitful collaboration with team 13 of CRC.
The team's work is internationally well recognised in their domain, as attested by invitations to meetings in the respective speciality (13 conferences and symposia in the last period, including the invitation to the HCC summit in 2018). The team was very successful in attracting young scientists (7 PhD students and 2 foreign post-docs). Five students defended their thesis with papers in first author position (one is in revision). PhD students received several awards, with the notable example of the prestigious L'Oréal-UNESCO for Women in Science Awards in 2018.
The team is very active in their participation in European scholarly societies (EASL, ILCA) and the national society AFEF. Team members acted as editorial board members of very good journals of their speciality (e.g. World J. Hepatol). They were involved in national grant evaluation (Ligue contre le Cancer, INCa, ANR) and international research organisation (e.g. AFEF, National Science Centre Poland), and reviewed articles in prestigious journals (e.g. Nat Metabolism, J. Hepatol). The team is also active in communicating their findings and knowledge to the public (e.g. 'la Fête de la Science', 'ma thèse en 180 sec').
The team deposited one European patent in 2022 reporting a new regulatory element of beta-cat HCC, which constitutes a therapeutic strategy of interest.

Weaknesses and risks linked to the context

Although the team developed clinical research collaborations, there is no clear integration of clinicians in the team that would further enhance this activity.
The team did not capitalise on its research activity and network via European research projects.
The translational potential of the research activity is not demonstrated by sufficient patent filing or industrial contracts.

Analysis of the team's trajectory

The team project is a continuation of the study of beta-catenin-dependent liver cancers, with a specific emphasis on tumour metabolism, tumour microenvironment and hepatoblastoma liver cancers. These parts of the project are innovative and highly relevant to clinical research, including children's cancers, potentially leading to new therapies. The overall project is well designed, fully credible and well supported by the current manpower and secured funding. The team is also well integrated in the identified axes of the CRC for the next contract, and ongoing PIAs (e.g. SIRIC). Finally, the collaborative aspect of the project, notably in clinical research, is an important strength of the proposal.

RECOMMENDATIONS TO THE TEAM

The committee recommends the team to continue their excellent research activity and projects with their current staff. The team is encouraged to apply for international funding, foster interactions with the private sector whenever possible and envisage recruiting a clinician or a new scientist to consolidate the team during the next contract.

Team 3: Physiologie rénale et tubulopathies (PRET)

Name of the supervisor: CRAMBERT Gilles

THEMES OF THE TEAM

The PRET team studies how the kidney contributes to the regulation of ion transport and the related minerals homeostasis in various physiological and pathophysiological contexts. To achieve these goals, the team has developed a unique expertise combining basic science techniques, animal models, and translational/clinical approaches. Over the contract period, the team developed three different research projects: i) identification of novel kidney pathologies; ii) evaluation of the physiological consequences of various perturbations on kidney function and iii) development of novel concepts for renal physiology and tubulopathies. Team 3 is the ERL8228 ('équipe de recherche labélisée, Métabolisme et physiologie rénales') identified by the CNRS.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team followed most of the recommendations from the previous evaluation: it developed interactions with other teams of the CRC as attested by significant joint publications and successfully integrated newly recruited clinicians in different aspects of their research projects.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	4
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**12**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	2
Sous-total personnels non permanents en activité	**4**
Total personnels	**16**

EVALUATION

Overall assessment of the team

The scientific production of the team is excellent: 158 original articles (63 in leading position), many published in top-ranked journals of the speciality (JASN, Kidney Int., Clin. JASN, AJP) as well as in more generalist journals (JCI, Scientific Rep., EMBO Rep.). The attractiveness of the team is excellent (4 ANRs, 2 PHRC, 1 FRM as PI), in terms of funding and excellent in terms of communications at meetings (63), students lectures, and recruitment (1 MCU-PH recently joined the team); team members coordinate or participate otherwise in national reference centers (for example, rare renal diseases) and steering/scientific committees of learning societies (SBPI, SFNDT….). Public outreach is very good to excellent: participation in the program 'apprenti-chercheur', public conferences, and scientific debates through social networks.

Strengths and possibilities linked to the context

Team 3 is organised in a rational and clear structure with a unique combination of fundamental researchers (1 DR CNRS, 1 CRHC CNRS, 1 CR INSERM, 1 MCU) and clinicians (1 PUPH and 3 MCUPH from SU or UPC). The team also includes five engineers (CNRS, SU, GR), one technician and one assistant. Over the last period, the team trained 7 PhD students (5 defended and 2 are still in progress), thirteen master students, and recruited a young clinician (MCU-PH, UPC).
The team develops three main themes of research: i/Identifications of novel pathological entities linked to kidney diseases. The team showed that mutations in the ASICs 2b channel cause a pathological Na+ reabsorption and water retention resulting in oedema in a context of idiopathic nephrotic syndrome (Fila et al., JCI insight 2021). They also demonstrated that autoantibodies targeting proteins of the tight junction (claudin 16/19) alter Mg2+ reabsorption, causing hypomagnesemia with hypercalciuria. (Figueres el al. JASN 2022), and the involvement of ER in the pathogenesis of Bartter syndrome related to NKCC2 mutation; ii/ consequences of chronic perturbations on kidney function. The team explored the relation between chronic kidney disease and pathological hyperkalemia (Walter et al. Sci. Rep 2021). They also show that specific polymorphisms of the angiotensin converting enzyme are associated with an increased risk of death in patients with type 1 diabetes (Abouleka et al. Diabetes Care 2021). The team also demonstrated the correlation between lithium nephropathy and the presence of microcysts, allowing the identification of radiomics signatures; iii/ development of novel fundamental concepts in renal physiology. They demonstrated that K+ retention through a specific H+/K+ transporter is essential to maintain normal blood pressure (Walter et al. AJP 2020), and the unique role of the GDF15 growth factor in cell proliferation. These research projects are supported by the availability of cohorts of patients suffering from various kidney diseases to identify new pathogenic genes (Hureau et al. Kidney int. 2019).
The team displays a unique and rare expertise to micro dissect different segments of the nephron and to explore kidney proteins functions, organised in a technical facility (specific equipment/technologies and highly skilled technical assistance) accessible to CRC teams and other national collaborators.
Team funding is excellent with 6 ANRs (4 as PI), two national PHRC (PI), one FRM (PI) and other grants obtained from various foundations/associations as P1 (SFNDT, Fondation Lefoulon-Delalande).

Team 3 is internationally well recognised in the domain of nephrology, kidney transport and physiology as attested by the high numbers of invitations and communications (63) to national and international meetings (SFNDT, SBPI, IUPS). Members of Team 3 organised every year a workshop on renal physiologies regrouping most of the local teams (~50 participants). Members of the team are also involved in various learned societies/foundations as members of the scientific (SBPI) or administrative committees (SFNDT) and in the organisation of various congresses (Eur. Soc. of Clinical Science, kinin2020). Two PUPH of the team participated actively as coordinator or members of national reference centers (rare renal diseases and calcium/phosphate-related rare diseases). Members of the team participate in teaching in different specialities at different levels (more than 60 lectures in license/master programs). Int J. Mol Sci.
The team welcomes young students through the program 'apprenti-chercheur', and participates in the 'Fête de la Science' and public conferences such as 'Pint of Science' and 'graine de chercheurs'. The team participates is scientific debates through social networks (@et-rein) which is followed by>560 people.

Weaknesses and risks linked to the context

Team 3 is not involved in technology transfer and patenting.

Analysis of the team's trajectory

The team's projects for the next period are coherent with the expertise of the team and correspond to direct extension of the previous investigations. The three main themes developed in this project are perfectly fitting with the new strategy of the CRC to develop transversal projects, and in particular 'exposome, genome and chronic diseases'. Briefly, the three main themes are focusing on 1/Cellular stress and development of tubulopathies, 2/Renal adaptation to environmental stress and 3/functional and cellular heterogeneity.

RECOMMENDATIONS TO THE TEAM

As several experienced researchers/clinicians will soon be retiring, the committee recommends that the team should consider renewing its staff with talented young researchers/clinicians for future recruitment (INSERM, CNRS and/or clinicians…).
The number of PhD students should be increased, and postdoc recruitment should be improved
The team is encouraged to continue to apply to European grants and networks as coordinator or partner.
The team is encouraged to promote collaboration with other CRC teams through the organisation of a 'kidney club'.
The team will have to be attentive to its future scientific orientation following the reorganisation of the CRC into IRP (integrated research projects).

Team 4: InC2: Inflammation, Complement and Cancer

Name of the supervisor: CREMER Isabelle

THEMES OF THE TEAM

The InC2 team aims to better characterise the microenvironment composition in solid tumours, the microenvironment of renal disease, and the involvement of the complement system in these pathologies.
three main research themes were developed: 1) Inflammation and cancer, which analysed the heterogeneity TME and its impact on the immune system (respiratory viral infections, TLR7, autophagy TLR7 dependent pathway, B cell subset, induction of immunogenic cell death by cold-atmospheric plasma treatment); 2) Immunotherapy and cancer, which analysed B cells and tertiary lymphoid structures as biomarkers of response for survival and response to immunotherapy; and 3) Complement and diseases, which studied the role of the complement system in renal diseases (rhabdomyolysis-induced acute kidney injury, sickle cell disease, C3 Glomerulopathy and Post Infectious Glomerulonephritis, Monoclonal Gammopathy and thrombotic microangiopathies) and the intracellular role of complement in cancer.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

As recommended by the previous committee, the team has developed its search for funding outside France, with an international contract as leader (USA), and has also been a partner in 6 European contracts. The team signed industrial contracts with Roche, CSL Behring (2x) and Commit Bio for a total of 620 k€. Additionally, one contract was signed with Aztrazeneca for 165 k€. New industrial contracts were signed since 2018 with Roche, CSL Behring (2x) and Commit Bio for a total of 620 k€ and one is under negotiation with Appelis.

The previous committee recommended recruitment of basic scientists experienced in writing publications and raising funds, in order to ensure smooth transition at a time when senior top scientists will be retiring: A senior Inserm researcher joined the team in 2021 (CRHC), from the College de France. A basic scientist is coming to the lab after five years postdoc in NIH USA with the objective to apply for an Inserm CR position to strengthen the complement and cancer research topic.

The team was encouraged to use data-mining approaches (meta-analysis of well annotated public datasets and data from clinical trials run by members of the unit) to test novel hypotheses with experimental work pending outcome: This strategy was implemented in soft tissue sarcoma leading to a publication in Nature 2020 (Petitprez et al.) and is part of the RHU CONDOR program. Spatial transcriptomics and hyperplex imaging data are shared between team members to address different scientific questions. This generates pressure and the need for research assistants with bioinformatics expertise.

The previous committee also recommended increased use of bioinformatics approaches to refine biological hypotheses upstream of bench work in the context of the planned investment in bioinformatics resources for the CRC: This was done in renal cell cancer to demonstrate the in-situ generation of anti-tumour B cell responses inside TLS (Meylan et al., Immunity 2022). Bioinformatics approaches are now largely used for all the projects developed in the team.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maîtres de conférences et assimilés	5
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**13**
Enseignants-chercheurs et chercheurs non permanents et assimilés	5
Personnels d'appui non permanents	8
Post-doctorants	2
Doctorants	9
Sous-total personnels non permanents en activité	**24**
Total personnels	**37**

EVALUATION

Overall assessment of the team

The team's scientific production is excellent as shown by their publication record: 180 articles published as leader (123 original contributions and 57 review articles), 21 of these in journals of the highest ranking (Nature, Nature Medicine, Immunity, Nature Cancer, Nat Rev Cancer, etc.). Their attractiveness is excellent, with strong international visibility in their field as shown by invited presentations at international meetings such as AACR, EACR, ICIC and ESMO. Fundraising is outstanding: 12.7 M€ for the period including six European Union grants as partner, three ANR and four INCa grants as leader. The contribution to society is excellent: ten contracts with industrial partners (Astrazeneca, SCL Behring, Roche, Novartis), three patent applications filed, 4 clinical trials initiated.

Strengths and possibilities linked to the context

Team InC2 is organised in a rational and clear structure with a unique combination of fundamental researchers (1 INSERM DR, 2 INSERM scientists, 2 PU, 2 MCU) and clinicians (5 PUPH, 3 MCU-PH and 3 physicians) dedicated to the exploration of immunology, complement system, oncology, biochemistry, cellular and molecular biology, vascular biology, genetics, pre-clinical experimental models and bioinformatics. The team also includes three engineers, eight contractual engineers and two post-docs.

Team 4 published 180 articles published as leader (123 original contributions and 57 review articles), 21 of these in journals of the highest ranking (Nature, Nature Medicine, Immunity, Nature Cancer, Nat Rev Cancer, etc.).
The ability of Team 4 to raise funds is outstanding with a total budget of 12.7 M€ for the period including six European Union grants as partner, four ANR (3 as PI), six INCa (4 as PI) and additional contracts from private foundations/associations as PI (FRM, ARC, CARPEM …).

Team 4 is internationally well recognised as attested by the high numbers of communications (over 20 invitations per year) to national and international conferences (AACR, EACR, ICIC and ESMO).
Team members received over 25 awards and distinctions (ESMO, Cancer Immunotherapy Association, and the International Society for Biological Therapy of Cancer). They organized three ESCI conferences and have responsibility in national scientific societies, such as the Fédération des Industries Technologiques du Cancer and the Société Francophone de Néphrologie Dialyse et Transplantation. The team has established numerous national collaborations (Cochin and George Pompidou hospitals in Paris, Bergonié Hospital in Bordeaux) to work on human samples, and international ones (National Taiwan University Cancer Center, MD Anderson Cancer Center) for clinical studies on sarcomas. Over the assessment period, the team recruited one senior INSERM researcher. 23 PhD students, 7 Master 2 students and 2 post-docs were trained, and two visiting scientists were hosted.
Team members filed three patent applications with INSERM Transfert, and secured ten contracts with national and international industrial partners (AstraZeneca, CSL Behring, Roche, Novartis, Invectys for a total amount of 1.8 M€). Team 4 actively participates in teaching and student/general public information or transmission.

Weaknesses and risks linked to the context

The number of postdocs and engineers is limited. The Immunotherapy and Cancer Group leaders may soon retire

Analysis of the team's trajectory

The team projects for the next period are coherent with the expertise of the team and correspond to a direct extension of the previous investigations. The following aims have been established for the next mandate:

1) Explore the role of intratumoral microbes on cancer progression and response to treatment; explore mechanisms involved in therapeutic resistance and then identify targets to recover sensibility to chemotherapy.
2) Identify mechanisms inducing the absence or lack of response to immunotherapy of TLS positive patients.
3) Analyse the biological relevance and the role of intracellular complement proteins, and the pathways leading to glomerular, vascular and tubular injury; analyse the role of complement in tumour progression.

They will use cutting-edge technologies, applied on molecular, cellular and animal models of disease, and on patient cohorts. They will include integrated functional exploration, multi-omics approaches (spatial transcriptomics, scRNAseq, and ultra-highly multiplexed imaging, etc.). Computational analysis will be applied to molecular, cellular and animal models of disease and patient's cohorts.

RECOMMENDATIONS TO THE TEAM

The number of postdocs and permanent engineers should be increased. The team is encouraged to improve the technology transfer activities based on its excellent scientific activity. The emergence of young scientists is recommended in order to maintain expertise in cancer immunotherapy.

Team 5: MUST: Multi-scale and SpatioTemporal modelling in oncology

Name of the supervisor: de REYNIES Aurélien

THEMES OF THE TEAM

This emerging team will be co-led by a member of team 11 and a member of team 19. Its aim is to combine medical informatics and bioinformatics approaches to develop methods to improve cancer diagnosis, patient stratification, and post-treatment monitoring. The proposal to integrate multi-layered and multi-modal data is coherent with the expertise of the two leaders. At the core of the team's strategy is the adoption of a spatiotemporal perspective, departing from conventional bulk, single-time experimental designs.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Not applicable; this is a new team

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Not applicable; this is a new team

EVALUATION

Overall assessment of the team

This emerging team will be created in 2025 and co-led by former members of teams 11 and 19; members of both teams will join this new group. The past scientific production of the two co-PIs is excellent (Genome Med, 2020; J Am Med Inform Assoc, 2021). The two co-PIs are involved in research and hospital organisations regarding data management and start-ups (Minos, OncoDiag, MethysDX). The societal impact is therefore excellent.

Strengths and possibilities linked to the context

The goals of the team are very timely. The two co-PIs are highly competent in their respective field and have complementary skills allowing them to develop their joint research program. The combination of molecular and patient/clinical levels of data as well as the strong integration with the clinic is a promising strategy that leverages on CRC existing strengths. These elements will attract future recruits, and young talents to help meet the ambitious objectives. There is a strong commitment from clinicians in different specialities (oncology, surgery, pathology) to join the future team, and collaborations to access annoted data from clinical sample are in place.

Weaknesses and risks linked to the context

Following his 2–3 year stay in team 11, one of the co-PIs may encounter difficulties in reconciling his new role with his role in the bioinformatics core platform created under his scientific supervision. While his continued role on the platform may provide opportunities to identify new projects/partnerships, there is also a risk that this may become a source of distraction, and that innovative developments made through the platform may not be fully attributed to his role as a team leader. There is also a further risk that people joining the new team 5 from teams 11 and 19 may find themselves acting as personnel for the bioinformatics platform in the absence of dedicated recruitment on this platform in the very near future.
As a purely computational group, the team may encounter difficulties to emerge as a truly independent research team.

Analysis of the team's trajectory

The team's future project is built on its solid expertise in functional genomic data analysis and medical informatics. This expertise relies on a continuing collaboration with Team 11. The most appealing, high risk-high high-gain axis of the future trajectory is the integration of medical informatics and bioinformatics to investigate tumour heterogeneity at multiple levels and time points. This is a very ambitious and timely perspective, and its success would lead to strong visibility.
The team's plan to access data, identify promising biological molecules or mechanisms, and validate these through collaboration with experimentalists is a viable strategy.

RECOMMENDATIONS TO THE TEAM

The Committee suggests that particular attention should be paid to the clear separation of work carried out in the context of the bioinformatics platform from work developed in the context of collaboration with Team 5.
The Committee recommends that the specific diseases on which efforts will be focused should be further defined. Finally, to be evaluated by Inserm, CSS2 might not be the easiest choice given the very methodological nature of the project. CSS6 or CSS7 could be more appropriate and relevant.

Team 6: Instabilité génomique, métabolisme, immunité et tumorigenèse hépatique : GENOMETABIMM

Name of the supervisor: DESDOUETS Chantal

THEMES OF THE TEAM

The team is dedicated to basic and translational research in the field of liver physiopathology, and notably investigates the role of ploidy, metabolic and inflammatory responses in the initiation and progression of hepatic diseases in both animal models and human samples. Research is structured around different areas of expertise: liver pathophysiology, cell cycle/ploidy, metabolism and immune microenvironment.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

As previously recommended, the team has developed collaborations with other CRC teams, in particular with teams 2, 9 and 13 (common publications).
The previous HCERES committee also recommended the recruitment of post-doctoral fellows and/or permanent researchers with a strong expertise in metabolism. Team 6 has developed a collaboration with team 9 for metabolic studies, and plans to recruit a former PhD student currently in postdoctoral training on a permanent position as researcher.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

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

EVALUATION

Overall assessment of the team

The scientific production of the team is excellent with publications in the highly reputed specialised (Hepatol 2019, Gut 2020, J. Hepatol 2021) and more generalist journals (Dev Cell 2022). The team's attractiveness is excellent. It is recognised at the international level as evidenced by the invitations to international conferences (e.g., EASL, AACR, EMBO, CSHAsia), and was successful in grant funding (ANR, INCa PLBIO, FRM, ARC).
Contribution to society is excellent. The team is involved in public outreach activities, and the PI is largely involved in student training as Head of the Doctoral School of Paris Cité university.

Strengths and possibilities linked to the context

The team is organised in a quantitatively and qualitatively coherent way, with scientists (2 INSERM permanent researchers with 1 DR and 1 CR, 1 PR and 1 MCU-PH), technicians/engineers (1 university engineer and 2 contract engineers), one post-doc and five PhD students. Over the course of the contract, the team maintained a very good balance between senior scientists and young researchers, and trained twelve PhD students (6 defended), two post-docs and nineteen undergraduates (including students from the ERASMUS program).
The PI is a leader in the field of hepatic division/polyploidisation under physiological and pathological conditions. The team conducts basic and clinical research aimed at understanding how polyploidy, the DNA damage response and immunosurveillance influence hepatocyte cell division and transformation leading to the

emergence and progression of hepatocellular carcinoma (HCC), particularly in the context of non-alcoholic steatohepatitis (NASH).
The team is highly successful in securing competitive funding: 33 national grants were obtained for a total of 3 million euros directly allocated to the team (total amount 5 million euros). Twenty-nine grants involved team members as principal investigators, including three ANR, two INCa PLBIO, one PRTK. Funding from charities included two prestigious labels: 'Team Fondation pour la Recherche Médicale' (3 years contract in 2019) and 'Team Ligue contre le cancer' (5 years contract in 2023).
Since 2017, the team has generated 63 publications: 38 original research articles and 24 reviews/commentaries. Thirty-nine of these were signed as first, last or corresponding and published in highly reputed journals in their speciality (Hepatol 2019, Gut 2020, J. Hepatol 2021) or more generalist (Dev Cell 2022). Highlights include the quantification of cellular and nuclear ploidy spectra as a powerful test for HCC prognosis (2 publications in Gut and Cancers), the demonstration that steatotic hepatocytes show evidence of replication stress due to nucleotide pool imbalance in NAFLD livers (Dev Cell 2022), and the identification of an NKG2DL-related immunosurveillance escape mechanism during beta-catenin-dependent liver tumorigenesis and its association with tumour aggressiveness (J. Hepatol 2021).
The team's research work is internationally recognised in the field of hepatic division/polyploidisation processes, as evidenced by invitations to international conferences (e.g., EASL, AACR, EMBO, CSHAsia). This has attracted Masters students, PhD students and postdocs from several countries (UK, Spain, Lebanon, China). Twelve PhD students and two post-docs were recruited over the period. Graduate students won numerous prizes at national and international meetings (EASL and FASEB meetings). On average, students are co-authors of 4.3 publications, with one first-author publication of experimental work per candidate. All postdocs and students have found positions to pursue their careers (for example, senior scientist at Sanofi, clinical trial manager or scientific coordinator of SIRIC CARPEM or Labex Inflamex). Attractiveness is mainly due to the PIs' involvement with the university: the team leader is director of the ED 562-Université Paris Cité doctoral School, the PR is director of the Master 2 in immuno-oncology (Université Paris-Cité) and the MCU/PH is director of medical courses at Sorbonne Université. The international visibility of the team has allowed them to attract foreign students and postdocs from several countries (UK, Spain, Lebanon, China).

The team is very active in organising national meetings (n=7, Symposium "Tumour Microenvironment and Immunity" Plan Cancer, Congrès AFEF, etc...). Team members sit on several international (EASL, ILCA) and national (AFEF) scientific councils. The team leader has editorial responsibility for JHEP reports. All principal investigators are referees for various prestigious journals (JCI, Nature Communications, Dev Cell, J of Hepatology, Hepatology, Gut, Gastroenterology, JHEP Reports), and for national/international funding agencies (e.g. EASL PhD fellowship program, German Cancer Research, Israel Science Foundation, LNCC, ANR, AFEF). The team leader is involved in steering research: Scientific Director of the ANR CE14 committee (2019–2021) and co-chair of the call (2018-2017), Director of the ED562 Université Paris Cité doctoral School (670 PhD students), Co-Director of the Genetics and Cancer department at CRC (since 2019), and proposed as Deputy Director of CRC for the next contract. All team members are active in communicating their results and knowledge to the public (e.g. 'la fête de la science', debates on science, open access conferences on tumour immunology, …).
The team has created its own platform for isolation of murine primary hepatocytes and cell sorting of immune populations. It is involved in translational research, but not in its valorisation through patents or industrial partnerships.

Weaknesses and risks linked to the context

The team has not capitalised on its research activity and network through European research projects. In spite of its excellent funding capacity and its international recognition in the field of liver pathologies, the team has no European or international funding.
The translational potential of the research activity is not reflected in patent applications or industrial contracts.

Analysis of the team's trajectory

The team's project is in line with current research on liver tumorigenesis, DNA integrity, metabolism and the immune microenvironment. The future project aims to describe how altered genome integrity, metabolic activity and the immune microenvironment contribute independently or in concert to the emergence and progression of HCC, particularly in the context of NASH. It is organised into four axes, from basic to translational research (3 axes in the continuum of their works and based on their expertise with unique mouse models and one translational axis focused on human NAFLD and HCC). The overall project is well conceived, fully credible and well supported by current manpower and funding. It is also innovative and highly relevant to clinical research, and may lead to the identification of new targets and novel therapies.

RECOMMENDATIONS TO THE TEAM

The committee recommends that the team continue its excellent research activity and projects. Despite its excellent capacity to fund its projects and its international recognition in the field of liver pathologies, the team has not fully capitalised on its research activity and network through European research projects.
The translational potential of the research activity has not been translated into patent applications or industrial contracts.

Team 7: Génétique et Métabolisme des Cancers Rares

Name of the supervisor: FAVIER Judith

THEMES OF THE TEAM

The team is evaluated by its current unit, PARCC, but asked to be auditioned by CRC

The team focuses on Pheochromocytomas/Paragangliomas (PPGL) and rare forms of renal cell carcinomas (RCCs). They investigate fundamental mechanisms that link genetic alterations to metabolism, epigenetic and carcinogenesis in these tumours, with a major interest in oncogenic pathways associated with metabolic alterations and mitochondrial dysfunctions of succinate dehydrogenase (SDH). The group develops solid patient-oriented research based on human genetic studies, biomarkers and the identification of new therapeutics. The team is currently extending its research to the identification of genetic and somatic biomarkers in PPGL and RCC, the exploration of the metabolic consequences of SDH deficiency dysfunctions, the study of the environmental impact on PPGL, and the impact of SDH-deficiency on the tumour microenvironment.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team is currently located at the CRC, evaluated by PARCC

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

The team is currently located at the CRC, evaluated by PARCC

EVALUATION

Overall assessment of the team

The scientific production of the team is excellent, with 128 articles, 58 as first, last or corresponding author in generalist journals (Cancer Res. Cell Reports, Clin Cancer Res), and this production is outstanding in the field of specialty (2 Nat Rev Endocrinology).
The attractiveness is excellent to outstanding: the team obtained €2.6 million of funding as PI (INCa-PLBIO, ANSES, European grants from the Swedish Paradifference Foundation). The team attracted four Postdocs, six PhD students and obtained two MCU-PH positions. Team members have major responsibilities in National and European Adrenal Tumors networks (Cancéropole, Réseau Comete, PRESSOR, ENS@T).
The impact on society is excellent: team members contribute to European decision-making in the clinical management of PPGL (international consensus, routine diagnostic, SDHB variant Databases and WHO recommendations). The team is a partner of two clinical trials on targeted therapies for PPGL (FIRSTMAPPP and JUMMPP). The team has also communicated in the media (Press and TV) regarding the health risk associated with the use of SDH inhibitors. The team is strongly connected to Swedish and French patients' organisations.

Strengths and possibilities linked to the context

The team is composed of 6 PUPH, two MCUPH and a DR. Its basic scientific manpower will be reinforced with an Inserm engineer and DR starting January 2025.
The team has an excellent track record with 128 articles (58 as first or last author). Publications include original research articles (62), reviews (32) and clinical publications (34) that highlight its pluridisciplinarity. One fourth of the published work is in top quality journals (Clin Cancer Res, Cancer Res, Cell Rep), including two invited reviews in Nat Rev Endocrinol and a Cancer Res article that received two awards for best paper of the year in 2021 (ENSAT and SFE). The team focuses on PPGL and rare forms of kidney cancer. Between 2017 and 2022, the team identified the tumour suppressor role of SLC25A11 (Cancer Res 2018), the role of telomerase promoter or ATRX gene somatic mutations as a risk factor for PPGL metastasis (Clin Can Res 2019). They developed a new NGS panel to detect rare genetic events in PPGL patients and refined the biological and metabolic action driven by SDH-deficiency in PPGL and demonstrated the role of succinate in promoting metastatic transformation (Cell Rep 2020).
The team has secured fifteen national grants with €2.6 million to the team as coordinator (INCa-PLBIO, ANSES, La Ligue Contre le Cancer) and European funding from the Swedish Paradifference Foundation (539K€). In addition, all master and PhD students have obtained fellowships from funding agencies (ARC, FRM, Plan Cancer, La Ligue, MESR).
During the period the team hosted five PhDs and 4 Postdocs. Two PhD students have obtained their MCU-PH position in the team to conduct their research. The team has also communicated in the media (Press and TV) regarding the health risk associated with the use of SDH inhibitors.

The team is a leading force in national and international PGL research networks. Members are involved in the national teaching program (Paris Univ.) and summer school (ESE Berlin 2018)). The team is strongly connected to

Swedish and French patients' organisations and has major responsibilities in PRESSOR (Pheochromocytoma Research Support Organization) and ENS@T (European Network for the Study of Adrenal Tumors). Members contribute to European decision-making in the clinical management of PPGL (International consensus, SDHB variant Databases) are frequently invited at major conferences (ECE, EACR, EMBO….), and two team members participated in the writing of the 5th edition of the WHO Endocrine and Neuroendocrine Tumors Book.
The team has contributed to developing novel routines to diagnose PPGL and immuno-histochemical tools that have been applied in pathology departments worldwide. The team has also contributed to developing an MRI-based detection of succinate for PGGL patients named SUCCES. Finally, the Team is involved as a partner in two clinical trials on targeted therapies for PPGL (FIRSTMAPPP and JUMMPP).

Weaknesses and risks linked to the context

The physical integration at CRC may impact the productivity of the team and create a competitive context with other CRC teams. This could limit both student recruitment and funding opportunities and ultimately reduce the scientific productivity of the team.
Visibility of the team on rare renal cancers is not as clear as for PPGLs. The team's track record and research publication on the topic are rather limited for a project started 6 years ago (i.e. 2017). The existence of ongoing funding on RCC projects is not clear. No leader is identified within the team to lead this specific research.
So far the team has not managed to recruit young INSERM or CNRS permanent researchers to further support its fundamental research axis.
The team appears to be more focused on the clinical valorisation of their research and translating their discoveries into clinical practice. The economic and industrial valorisation driven by the team is lagging behind due to a lack of patents or incubation of start-up companies during the period under review. The group owns a single international patent to predict metastatic potential of SDHB-mutated paraganglioma (EP18306527.5) while opportunities have possibly been missed improving the valorisation of their work.
Team's interactions with the economic world remain limited, due to the reduced interest of pharmaceutical companies in the field of rare cancers.

Analysis of the team's trajectory

The team will move from PARCC, where it is located since 2009, to join CRC, a decision driven by the evolution of the group thematics towards the field of cancer research and their broader interest in cancer genomics, oncometabolism, and oncoimmunology. At the CRC, the team proposes to pursue the research they developed on PPGL and push forward their projects into 4 main axes covering: the use of new technologies for identification/characterisation of novel biomarkers for PPGL and RCCs, the study of SDH metabolic dysfunctions in oncogenesis, the impact of the environment on the onset of PPGL, and the connection between the tumour microenvironment and PPGL-tumour cells.
The integration of the team at CRC has been anticipated as the head of the team will lead the 'Environment, Exposome and Genome' axis of the CRC project. 350m2 of space has already been allocated to the team, but questions remain whether the renovation of this space will be available at the beginning of the new contract.
The team leader's position as Deputy Director of the 2023-renewed CARPEM-SIRIC will foster interactions with CRC research teams and should facilitate collaboration opportunities. Increased manpower has also been anticipated with the addition of two members with leading expertise in the field of mitochondria (1 DRE CNRS and 1 IR Inserm). The team's 4 research axes are integrated within three IRPs of the CRC, and its experimental strategy is based on mastered approaches that will benefit from technological expertise available through CRC-core facilities (spatial omics and metabolomics, single-cell sequencing and multiplex immunohistochemistry).
Team projects rely on solid preliminary data (available markers identified through the COMETE-TACTIC project, validation of the 13 C-glucose fluxomics approach in mice, environmental role of SDHi…). Part of the proposed research relies on identified or existing collaborations, some of which are already funded (COMETE-TACTIC, COMETE-CARE, PGL/EXPO, …).
The move to CRC could result in a number of challenges. In addition to potential delays in the renovation of lab and office spaces, the team should not underestimate the extent to which the competitive CRC environment may impact its productivity. The team will need to define a solid strategy to secure the recruitment of young scientists and increase in size to carry out its ambitious projects. Likewise, the use of a single cell and spatial – omics approaches that are proposed may require the recruitment of a bioinformatician in the group to overcome the possible saturation of the new bioinformatics platform at CRC.

RECOMMENDATIONS TO THE TEAM

The committee congratulates the team for the achieved work and major contribution to the field of endocrinology and rare diseases. The committee recommends the team to maintain its unique and outstanding international work and visibility in the field of Pheochromocytomas/Paragangliomas (PPGL). The team leader should therefore consider applying to ERC funding. The decision to extend the research to rare RCC is a good decision that should contribute to the growth of the team at CRC. The committee recommends fully exploiting the unit in terms of collaborative opportunities. The balance between fundamental and clinical research should be maintained through a well-defined plan of permanent researcher recruitment and scientific research strategy.

Team 8: Laboratory of Integrative Cancer Immunology

Name of the supervisor: GALON Jérôme

THEMES OF THE TEAM

The team has conducted basic and clinical research aimed at understanding the molecular mechanisms that control the interaction between tumour and host immune response during cancer development. It also developed computational pathology tools to classify cancer patients and predict treatment outcomes, and to improve anti-tumoral immunotherapy protocols. The team also develops tools to help clinicians make the adequate treatment decisions based on scoring of the immune context following analysis of immune components present in the tumour microenvironment. The current team projects aim to combine integrative biology and bioinformatics to understand tumour progression and the immune response to cancer, from precancerous lesions to metastasis, based on the analysis of pre-existing immunity and its modulation.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

One concern for the previous committee was the potential impact of the team leader's extensive involvement in valorisation activities on the academic research quality. However, this concern appears to be unfounded given the impressive number of publications and patents over the evaluated period.
Another concern was the low number of PhD students in the team (2 over the past evaluation period). In light of the multiple activities of the team leader, it was recommended that the team recruit researchers to reinforce the management of the team and the supervision of students. The last recruitment of a researcher took place in 2017.
Concerning scientific strategy, a main recommendation was to extend the Immunoscore concept to other cancers and validate its use, in particular for hematological malignancies. The team recently established the prediction of a response to immunotherapy by immune contexture parameters, including Immunoscore, in large B-cell lymphoma (Nature Medicine, 2022).

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

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

EVALUATION

Overall assessment of the team

The team has an outstanding scientific production in the field of immuno-oncology with remarkable publications as leading authors in Nature, Cell, Nature Medicine, Lancet, etc. The team has been very successful in obtaining funding: 23 international (including H2020) and national (INCa, ARC, LNCC) grants (20 as PI) for a total budget of 5000K€. The team is exceptionally well known at the international level (Duquesne Prize from La Ligue Contre le Cancer, Galien Prize, European inventor Award, and more than 300 invitations to international congresses). It is also attractive for post-doctoral fellows (7 over the assessment period). The team is outstanding in terms of valorisation: 73 patents and development of biotechs (HalioDx). Overall the team is outstanding.

Strengths and possibilities linked to the context

The organisation of the team is coherent at the quantitative and qualitative levels, with scientist researchers (2 INSERM researchers and 1 non-permanent), university researchers (1 PU/PH and 1 MCU/PH), one clinician, 4 technician/engineers. Since 2018, the team has hosted 7 post-doctoral fellows, 4 of whom were recruited on a permanent position in a private company. Three PhDs defended their thesis.
This is an internationally recognised team that provided an impressive contribution in the field of tumour immunology with innovative and groundbreaking basic and translational research. They defined the immune contexture as immune parameters associated with patient survival, and determined the Immunoscore based on immune contexture analysis. Building on these breakthrough concepts, they deciphered the mechanisms of immune evasion and metastasis evolution (Cell, 2018 and Nature 2019). More recently, they demonstrated that the tumour immune contexture is a determinant of anti-CD19 CAR T-cell efficacy in large B-cell lymphoma (Nature Medicine 2022).

The team is outstanding in obtaining funding: 23 international, European and national grants over the period for a total budget of 5000K€, including twenty as the principal investigator and three as participants: two international grants from private societies (Sidra Medecine-Qatar and NPRP-Qatar, total 260 K€), two H2020 European grants (1 as coordinator), several national academic grants (IDEX UP Covid-19, LABEX LabEx-Immuno Oncology, INCa), and charity grants (ARC, LNCC). The PI was awarded prestigious prizes (Duquesne Prize from La Ligue Contre le Cancer, Galien Prize, European inventor Award…) and some postdocs and PhD students were also awarded prizes for their work.

The scientific production of the team is outstanding with a strong visibility in both scientific and clinical communities: 83 articles during this period, including 61 original articles of which 22 as PI (Nature, Cell, Nature Medicine, Lancet…). The team holds a prominent presence in the scientific community. The PI was invited to numerous international meetings and delivered more than 380 lectures at seminars and international congresses.
The PI is the inventor of 73 patents between 2017 and 2022. Three products derived from these patents have been developed, Immunosign®, Immunoscore-IC® and Immunoscore®, and received EMA approval as CD-IVD assay. The PI is cofounder and CSO of HalioDx, recently acquired by Veracyte. The team was awarded several industrial research grants (ImCheck Therapeutics, HalioDx…).

Weaknesses and risks linked to the context

No weakness

Analysis of the team's trajectory

The objective of the team for the next term is to maintain its leading position in the national and international scientific field of tumour immunology. Based on their findings and expertise, they will develop three axes to better understand the relationship between tumours and the immune compartment:

- Integrative analysis of the tumour microenvironment in human cancers, based on the analysis of immune contexture of different types of tumours (hot, cold, excluded, primary or metastases) with the goal of discovering novel mechanisms that may lead to new or improved treatments.
- Integrative analysis of the immune microenvironment in adenoma, based on the analysis of immune contexture in precancerous lesions. The objective here is to understand the mechanistic behind the immune control of cancer progression.
- Analysis of the impact of environmental/lifestyle factors on cancer development, especially the impact of host microbiome and senescence on the development of cancer and on shaping the host immune responses.

These projects require expertise in basic immunology, oncology and bioinformatics, all of which are well represented in the team. Clinical activities related to these projects are already being developed by the team. The team is well supported by the current manpower and funding.

RECOMMENDATIONS TO THE TEAM

The committee recommends that the team continues its outstanding and remarkable research activity and projects.

Team 9: Metabolism, Cancer & Immunity

Name of the supervisor: KROEMER Guido

THEMES OF THE TEAM

The team has developed exceptionally original, innovative and internationally competitive programs regarding stress signals and regulation in the domains of cell death, longevity, immunity and cancer. The overall goal is to follow a continuum from the basic biology of cell stress, aging and death to translational and applied research, focusing on aging and age-associated, socio-economically relevant diseases (such as prevalent cancer types, heart failure, obesity). The team is particularly interested in the role of immunogenic cell death (ICD) in cancer, the identification of new ICD inducers and new factors controlling cancer immunosurveillance, and the identification of molecular partners involved in the modulation of autophagy and in the mechanisms of human aging and obesity.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The only recommendation made by the previous committee was to increase the number of researchers with HDR in the team (3 only) given the large number of PhD students (20). The number of HDRs increased to 5 for 38 PhD students (25 defended and 13 ongoing).

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	2+
Chargés de recherche et assimilés	6
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**12**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	6
Post-doctorants	15
Doctorants	16
Sous-total personnels non permanents en activité	**38**
Total personnels	**50**

EVALUATION

Overall assessment of the team

The team's scientific production is outstanding in the field of cell death, longevity, immunity and cancer (129 articles as PI in the top scientific journals, such as Nature Commun, Cell Metabolism, Cell Death Differ). International recognition and attractiveness are exceptional, with an impressive number of PhD students and postdoctoral fellows recruited. The team has been extremely successful in grant funding (2 ERCs, RHU, Labex, 30M€), patents (14 total, of which 4 licensed) and 4 industrial partnerships. The general organisation of the team, including its scientific animation, training, and communication, is remarkable and is fully adequate to the exceptional productivity. The overall assessment of the team is outstanding.

Strengths and possibilities linked to the context

This is a large research team composed of one PUPH (the team leader), 6 senior researchers (2 DR and 4 CR Inserm), two visiting researchers, ten engineers (6 with permanent position), one permanent technician and an impressive number of postdocs (14) and PhD students (13) located on two sites, the Cordeliers Research Institute (CRC, Paris) and Gustave Roussy (GR, Villejuif). Since 2018, the team has hosted 30 post-doctoral fellows and 38 PhD students (25 have defended their thesis). The team appears to be particularly well organised benefiting from a deputy director and has also a well-balanced women/men ratio among team scientists, while the women/men ratio among postdocs and PhD students is in favour of women reflecting the gender ratio in biological science in France.

The team is internationally recognised and provided an impressive contribution in the field of cell death, immunity and cancer with innovative and breakthrough basic and translational research. The production of the team in terms of publication is outstanding with a strong visibility. The team published more than 530 articles over the period with 129 as PI. They showed that ICD impacts the therapeutic success of anti-cancer chemotherapy, radiotherapy and targeted therapies (Cell Death Differ 2017 and 2021, Nat Commun2019). They also identified new factors controlling cancer immunosurveillance such as FPR1 (Cancer Discov. 2021) and intestinal microbiota (Science 2018, Nat Med 2020 and Science 2023). Also, they identified acyl coenzyme A-binding protein (ACBP), as an extracellular autophagy-inhibitory factor and appetite stimulator that is elevated in human aging and obesity, associated with features of metabolic syndrome (Cell Metab. 2019, Cell Death Dis. 2020 and PNAS 2022).

The team has an outstanding funding power for a total budget of 30 M€ over the period. It obtained two ERC Advanced Investigator awards (2013–2018 and 2023–2027 of 2.5 M€ each), four EU grants as partner, several major French state grants (including a 14.7 M€ Labex coordinated by the PI and the coordination of two RHU grants, as well as 4 ANRs and 4 INCa grants as PI. The team is also labelled by the French League against cancer. Research contracts have been signed with private partners of the biotech/pharma industry (Sanofi, Osasuna Therapeutics, Samsara Therapeutics…). The PI was awarded by prestigious prizes (Baillet Latour Health Prize (EUR 250,000), Prize for Cancer Research (CHF 100,000), International Prize 'Lombardy & Research' (EUR 1 million)) and some postdocs and PhD students were also awarded by prizes for their work.

The team has a high visibility in the scientific community, the PI is listed as Highly Cited Researchers. Among his works, published during 2017–2022, some have already been highly cited: Science 2018 cited 2480 times, Cell 2018 cited 1078. The PI is often invited to international meetings (FEBS congress, ESMO, AACR) and he is the president or member of the scientific boards of many societies (for example President of European Academy of Tumor Immunology from 2011 to 2022, member of the German Academy of Sciences from 2007) and also is the director of the LabEx Immuno-Oncology, and the director of the Equipex Onco-Pheno-Screen.
Over the past five years the team filed fourteen patents, among which 4 were licensed to industrial partners such as Osasuna Therapeutics, PharmaMar, Samsara Therapeutics, and Therafast Bio. The team has also developed three software applications and the PI created three biotech companies.

Weaknesses and risks linked to the context

No Weaknesses

Analysis of the team's trajectory

In the forthcoming period, the team plans to continue its research on the triangulation between metabolism, cancer and immunity. The team wants to take advantage of its location on two major research campuses to benefit from the development of a series of high-tech approaches in the area of metabolism (with spatially resolved mass spectrometric metabolomics down to single-cell resolution), cancer cell biology (with chemical genetic engineering for the creation of 'synthetic' signalling systems) and immunology (with the development of 3D imaging of tumours).
Based on their expertise and with the innovative approaches to which they will have access, they will develop three main axes in the continuum of their current works:

- Deciphering cell stress and death mechanisms involved in cancer biology and the identification of ICD inducers and enhancers.
- Study of metabolism alterations and impact on cancer immunosurveillance.
- Autophagy, aging and identification of novel nontoxic autophagy inducers.

This program is well supported by the current manpower and the obtained funding.

RECOMMENDATIONS TO THE TEAM

The committee encourages the team to pursue research at this outstanding level.

The exceptional visibility and recognition of the team are mainly due to the head of the team. It is recommended that other PIs of the team increase their visibility and recognition.

Team 10: Immunopathologie et immuno-intervention thérapeutique : IMMUNOHEM

Name of the supervisor: LACROIX-DESMAZES Sébastien

THEMES OF THE TEAM

The team is focused on three main areas of research: 1) the creation of new therapeutic antibodies; 2) the development of innovative immunotherapeutic methods to regulate undesired immune responses; and 3) medical investigation of autoimmune diseases – especially thrombotic thrombocytopenic purpuras. Studies rely on both fundamental research and clinical assessments associated with original studies assessing endogenous or therapeutic proteins targeted by the immune system.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous HCERES report recommended that the team focus on priority topics in order to increase the impact of publications and reduce the number of participation in meetings organised by pharmaceutical companies. It also recommended increasing the number of permanent staff. Regarding PhD training, it proposed moving the students between the different laboratories with which the team collaborates, using exchange programs such as Marie-Curie grants.
The report also recommended an increase in the level of interdisciplinarity such as using phage libraries instead of the random generation of human monoclonal antibodies, the analysis of glycosylation, collaboration with groups having routine animal models of autoimmune diseases and genomics when appropriate, as for example, in studying the interactions of IVIg with autophagy.

The team successfully increased the level of publications (Nat Med). Collaboration with groups routinely using animal models of autoimmune diseases and genomics was not identified during the presentation of the team.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	3
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**9**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	3
Doctorants	3
Sous-total personnels non permanents en activité	**6**
Total personnels	**15**

EVALUATION

Overall assessment of the team

The scientific production of the team is excellent, with publications as leader in journals with the highest reputation (Nature Medicine, Science Immunology).
The attractiveness is outstanding, with the funding of 5.8 million euros including a H2020 ERC starting grant.
The societal impact is excellent with 4 patents and 6 private contracts representing 513 k€ (8.9% of their budget) with Bayer, Sanofi, Spark therapeutics, Topas or Grifols.
Scientific outreach is excellent: TEDx presentation, student outreach programs.

Strengths and possibilities linked to the context

The permanent staff is composed of three directors of research (2 CNRS and 1 INSERM promoted recently), one associated researcher from INSERM recruited in the team in 2011, one clinical professor, two clinical associated professors and one associate professor. The team also includes one engineer INSERM, one deputy manager INSERM and one administrative manager. The team was divided into three groups with few details regarding their composition and focus.

The team benefits from numerous financial resources, including ongoing support from INSERM (amounting to 360 k€ over a 5-year period) and non-recurrent funding exceeding 4,600 k€ during this period as the main lead/main applicant. The team secured an ERC starting grant (2016–2023).

Additional funding is either national (2 PHRC as PI, 5 ANR, including one as PI, for a total of 1.8M€) or international (1 H2020 ERC starting grants for 2.9 M€, three additional EU grants, of which 2 as PI).
The team has a high level of scientific productivity reflected in the number of papers published across a spectrum of journals, with 138 as first, last or corresponding author in generalist publications such as Nat Med, Blood and Haematologica, and more specialised ones such as Annals of Biochemistry, Trends in Immunology, and Autophagy.
Over the assessment period, the team successfully recruited and nurtured a total of fifteen PhD students and eight post-doctoral fellows. Team members were invited to give more than one hundred seminars or oral talks to international meetings and organised international meetings such as ISTH in 2020.
One member of the team has editorial functions to Frontiers in Immunology
The team deposited five patent applications, none granted so far.
Research contracts were signed with private companies (513 k€, 8.9% of budget): Bayer, Sanofi, Spark therapeutics, Topas or Grifols.

Team members are involved in teaching for scientific and medical universities (License, Master, PhD, MD, …), outreach activities towards patients' associations (French association of hemophilia [AFH], European hemophilia consortium, …). They host high school students in the context of the 'chercheur en herbe' project, as well as students from unfavored social background (BTS in Biotechnology, lycée Galilée, Gennevilliers). The PI contributed a TEDx presentation (Rencontres MOVE 2019), and one member participated in the Forum métier, collège St Exupéry, Andrésy.

Weaknesses and risks linked to the context

Funding declined over the assessment period, jeopardising the development of future projects.
The Nat Med paper (IgG-cleaving endopeptidase enables in vivo gene therapy in the presence of anti-AAV neutralising antibodies. Nat Med. 2020;26(7):1096-101) is the result of a collaboration published by 22 authors including the co-last and co-corresponding author, but only three authors come from the team.
The Blood paper (A regimen with caplacizumab, immunosuppression, and plasma exchange prevents unfavourable outcomes in immune-mediated TTP. Blood. 2021;137 (6):733-42) is the result of an international clinical trial without evidence of a direct contribution from the INSERM structure.

Analysis of the team's trajectory

The objectives set for the upcoming five years are both logical and ambitious. While the groups pursue distinct research directions, the alignment of these endeavours with the team's overarching developmental strategy will be upheld. The prospects for IMMUNOHEM are undoubtedly promising.
The project is not detailed but the main topics are described within a structure divided in 4 groups working on the following topics:

1) immunogenicity of protein therapeutics in general, and in particular factor VIII in continuation of the Haematologica 2019 paper;
2) canonical and non-canonical functions of immunoglobulins;
3) thrombotic thrombocytopenic purpura, and 4) systemic autoimmune diseases, especially systemic sclerosis and vasculitis.

RECOMMENDATIONS TO THE TEAM

The team is focused on improving the function of antibodies, and studying the clinical impact of auto-antibodies. The team may benefit from a better description of the expected clinical outcomes, especially regarding the thrombotic thrombocytopenic purpura project.
The team should also better define the relationship between the 4 groups, especially regarding the synergistic potential between them.

Team 11: Médecine personnalisée, pharmacogénomique, optimisation thérapeutique : MEPPOT

Name of the supervisor: LAURENT-PUIG Pierre

THEMES OF THE TEAM

The MEPPOT team works on personalised medicine, pharmacogenomics and therapeutic optimisation. It investigates tumour heterogeneity and therapeutic optimisation in the field of solid cancers, most notably digestive (colon, pancreas, gastric), lung, gynecologic (ovary, endometrial) and urological. The team has developed a solid expertise in pharmacogenomics and cancer treatment, allowing it to tackle the issue of resistance to anti-cancer agents and their toxicity.
The team strategy integrates competitive technological developments to achieve its biomedical objectives. This includes bioinformatics pipelines to detect or identify various new biomarkers: transcriptomic signatures, cfDNAs, miRNAs. MEPPOT relies on well-annotated tumour biobanks and omics analytic tools to decipher tumour heterogeneity.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous evaluation recommended that, given its strong focus on genomic technologies, the team develop internal capabilities in bioinformatics and data analysis. This point has been addressed, in particular through the recruitment in 2021 of a highly experienced bioinformatician in cancer genomics with whom the team was already collaborating. His venue fostered several new developments as well as the training of several team members to perform basic bioinformatic analyses autonomously.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	13
Maîtres de conférences et assimilés	4
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	7
Sous-total personnels permanents en activité	**27**
Enseignants-chercheurs et chercheurs non permanents et assimilés	3
Personnels d'appui non permanents	6
Post-doctorants	2
Doctorants	9
Sous-total personnels non permanents en activité	**20**
Total personnels	**47**

EVALUATION

Overall assessment of the team

The scientific production of the team is excellent. Of the 873 original papers produced by the team, 300 are signed as first or last author. Five percent of these are in the top 10%. Key papers appeared in Clin. Cancer Res. And Br. J. Cancer 2021.
The attractiveness is excellent. The team obtained three European Grants as partner. As PI, the team obtained two ANR, two contacts with biomedicine agency, two ITMO cancer grants and 6 SIRIC CARPEM grants. The team recruited several permanent staff, including an MCF and a PHU. Team members contribute to the definition of international and national clinical practice guidelines in different cancer types and are expert for regulatory agencies (ANSES, ANSM, Agence de Biomédecine).

The societal impact is excellent to outstanding (3 start-ups and 1 team spin-off; support to therapeutic precision medicine decision). The discoveries emanating from the lab's research are implemented in routine clinical care by physicians of the team in the different departments of the APHP center in the framework of their clinical duties.

Strengths and possibilities linked to the context

The team is composed of 50 members among them 34 permanent researchers (14 PUPH, 3 MCUPH, 9 PH, 1 MCF, 4 DR, 1 CR, 2 IR) and sixteen short-term contracts (7 post-doctorates, 8IE and 1 IR):

It is strongly translational and is organised accordingly with a large proportion of clinicians (26 out of 50 permanent researchers).

Five hundred and twenty-six papers are in the oncology field, reflecting the strong predominance of clinicians in the team. Research is focused on the analysis of tumour heterogeneity to improve treatment and cancer patient care through the characterisation of the tumour ecosystem, using well-established technical tools as well as innovative technologies. A strength is the access to 9 large cohort of tumours and their molecular analysis at the cellular and tissue levels. Since 2000 the team has carried out pioneer work in the field of ctDNA in cancer. More recently it has developed advanced assays to validate ctDNA universal markers using large multicentric cohorts, as well as new strategies based on: (i) high multiplexing including NGS-based strategies; (ii) molecular programming; and (iii) new multimodal analyses to improve the sensitivity and specificity of marker detection (Eur. J. Cancer 2021).

The team has obtained recurrent funding grants to support its research activities (800 k€/year from Inca PRTk, Itmo Cancer, ANR, Carpem, ANRS, SATT and several private funding). The PI and several team members contribute to European programs. Mercuric (140k), NIRBTEST (126k), IMMUCAN (120k), Inca PRTK (444k), ITMO Cancer (300k), ARC.

The team successfully recruited several permanent staff: two former postdocs as MCF and PHU, two former PhD students as PHU. It also actively supports the promotion of its younger scientists (2 HDR in the last period, and 4 promotions from MCU-PH to PU-PH), or PIs (1 DR1 CNRS in 2019). The team has 24 PhD students, including 9 theses still in progress and fifteen defended.
The team has a strong visibility: the PI is head of the SIRIC CARPEM and the Cancérôpole Ile de France and participate to the French genomic plan (Médecine France Génomique 2025) as members of the Executive Board of one of the two sequencing platforms).
The team has nonacademic interactions at several levels: collaboration with 4 private companies (Owkin, Veracyte, Combined Therapeutics, Natera), two CIFRE theses (Integragen, Biomnis). Some senior PIs of the team have filed patents and are co-founders of three start-ups: METHYS Dx, EMULSEO, Minos.

Members of the team have advisory activities for AstraZeneca, Eli Lilly, Takeda, Biocartis, Roche, Servier, Pierre Fabre Ipsen, Novartis, MSD, Merck, GSK, Amgen. Some also contribute to the definition of international and national clinical practice guidelines in different cancer types, belong to national networks, are experts for regulatory agencies (ANSES, ANSM, Agence de Biomédecine), and participate to the French genomic plan (Médecine France Génomique 2025, as members of the Executive Board of one of the two sequencing platforms). The discoveries emanating from the lab's research are implemented in routine clinical care by physicians of the team in the different departments of the APHP in the framework of their clinical duties.

Weaknesses and risks linked to the context

Team mostly composed of clinicians with less time dedicated to research.

Analysis of the team's trajectory

For the next mandate, spatial transcriptomics will be added to the omics analysis of tumours to improve their stratification and related precision medicine approaches. The team will also include a group focused on mitochondrial studies. A project focused on metabolic precision medicine will also be developed. Technical innovation for the circulating DNA analysis (microfluidics) is also a great progress in the field that was pioneered by the team. The collaboration with the to-be-created MUST team (bioinformatics) will help to develop new methods for patient stratification and PhD thesis in co-direction will be proposed. The CRC management team, together with team 11 and team 5 PIs, will have to be vigilant to ensure that team 5 can develop its own identity while continuing to provide bioinformatics expertise to team 11 and other CRC teams.

RECOMMENDATIONS TO THE TEAM

The team could take advantage of the large collection of data available to them to study the metabolic shift in tumours.
The departure of a senior bioinformatician who will start as an independent PI within CRC (team 5) will require changes in how bioinformatic needs are addressed within team 11. This has been anticipated through individual training of team 11 members, and the creation of a CRC core bioinformatics group.

Team 12: Drug Resistance in Hematological Malignancies: DRIHM

Name of the supervisor: SUSIN Santos

THEMES OF THE TEAM

The team is focused on drug resistance and the physiopathology of hematological malignancies, including Chronic Lymphocytic Leukemia (CLL), Waldenström's Macroglobulinemia (WM), B-cell Prolymphocytic Leukemia (B-PLL), intraocular and cerebral lymphomas, and Systemic Mastocytosis (SM).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Previous recommendations on scientific production and activities:
'The translational interactions would benefit from the recruitment of young post-doc and permanent scientific investigators'. Three post-docs were recruited following this recommendation.
'Furthermore, increasing the level of expert technical staff for genome editing, and animal work is recommended': the team no longer works with animals and clinicians with genome-editing expertise were recuited.
'Partnerships with industry to obtain funding for PhD students (Cifre) … through the SIRIC and national and international inter-groups / selected industrial partners'. This issue was addressed: participation in SIRIC CURAMUS and collaborations with industry allowed recruitment of two PhD students.

Previous recommendations on the team's organisation and life:
'Actively recruit young post-doc fellows and permanent scientists, in order to fully leverage the excellent clinical resources for doctoral training and further high impact papers in the coming five-year contract'. Two clinicians (MCU-PH), and one associate professor (MCU) were recruited, but no permanent scientists.

Previous recommendations on scientific strategy and projects
'Bioinformatics support'. This issue was not addressed specifically by the team. Instead, the center is proposing the creation of a Bioinformatics core facility for the unit as a whole.

'Reinforce scientific interactions across its three research axes, particularly in regard to the systemic mastocytosis axis'. This research axis has been phased out.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maîtres de conférences et assimilés	4
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	6
Sous-total personnels permanents en activité	**14**
Enseignants-chercheurs et chercheurs non permanents et assimilés	3
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	6
Sous-total personnels non permanents en activité	**10**
Total personnels	**24**

EVALUATION

Overall assessment of the team

The scientific production of the team is excellent with original publications as first, last or corresponding authors in top tier journals in the field of onco-hematology (Am J Hematol, 2021; Blood, 2020; Cancer Discovery, 2019; Blood, 2019; Blood Advances, 2019).
The attractiveness is excellent. Team members are active in two international and two national research consortia in the field of lymphoid malignancies. The team is part of the SIRIC Curamus. Three researchers were recruited (2 MCU-PH and 1 MCF) and three post-docs (2 foreign) were hosted. As leader, the team obtained an international contract (74 K€), 4 SIRIC CURAMUS grants, two contracts with industrial companies (Roche, Beigene) and 23 contracts with charitable foundations. The societal impact is excellent. Through large-scale biomarker validation efforts, including immunogenetics, in the setting of clinical trials (particularly in CLL/WM), the team is contributing to improved precision medicine practices for patients with lymphoid malignancies.
The team produced two patents, one of which is licensed.

Strengths and possibilities linked to the context

The team is composed of 22 people working on the physiopathology, treatment resistance and precision medicine practices in B-cell malignancies with special focus on chronic lymphocytic leukemia, B-cell prolymphocytic leukemia and Waldenström disease. The team has a strong and successful collaboration with Institut Gustave Roussy for in depth mechanistic analysis as demonstrated by high impact papers (Blood. 2019;) and Cancer Discovery (Cancer Discov. 2019 – co last senior author).
Of a total of over 220 publications, published by the team, fourteen were original articles that were published as first, last or corresponding author position. Of these, a number were in top tier journals in the onco-haematology field (Blood 2020, Blood Adv, 2019, Cancer Discovery 2019, and Leukemia 2017).
Team members are active in two international and two national research consortia in the field of lymphoid malignancies [ERIC – European Research Initiative in CLL, euro-clonality, ECWM (European Consortium for Waldeström macroglobulinemia, and in France, GFCH (cytogenomics) and French Innovative Leukemia Organisation (FILO). The team recruited three young investigators but no full researcher, as yet (INSERM, CNRS).

The team receives a high amount of funding (375–400 k€ per year) from multiple sources (public and industry) mostly at the national level. As leader, the team obtained an international contract (74 k€s), 4 SIRIC CURAMUS grants, two contracts with industrial companies (Roche, Beigene) and 23 contracts with charitable foundations (Fondation ARC, GEFLUC, Ligue contre le cancer, Association Laurette Fugain, Fondation Capucine, Force Hemato, etc.)

The team benefits from strong connections with national clinical networks through the Pitié-Salpêtrière hospital and the FILO clinical network for mature B-cell malignancies (prolymphocytic, lymphocytic and lympho-plasmacytic) and with the Ceremast clinical network for mast cell malignancies. The team coordinates the GFCH national network on onco-cytogenomics in blood cancers.

The team's work is visible through international networks in the disease entities of interest, in which team members and leaders are highly active (ERIC, Euro-Clonality, ECWM, and the FILO nationally).
Team members received 43 seminar invitations during the period of evaluation at the national and international level.

The team is contributing to improved precision medicine practices for patients with lymphoid malignancies through large-scale biomarker validation efforts, including immunogenetics, in the setting of national and international clinical trials (particularly in CLL/WM). The team produced two patents, one of which is licensed.
Team members are heavily invested in training at the national level in onco-hematology.

Weaknesses and risks linked to the context

The main publications of the team arise from the translational and clinical work.
The team could capitalise more on its strong clinical networks (FILO CLL, Waldenström) to develop its own more fundamental research program and compete with strong groups in the field in the USA and Spain.

Analysis of the team's trajectory

The scientific project of the team is centred on mature B-cell malignancies organised through three axes:

1) Mechanisms of drug resistance in CLL and development of potential therapies;
2) Physiopathology of Waldenström's macroglobulinemia;
3) Characterisation of intraocular and cerebral lymphomas.

The first axis is subdivided in four complementary research programs: genetic abnormalities found in Chronic Lymphocytic Leukemias (CLL; gain 2p, del 8p and 8q abnormalities); BCR signalling (essentially through

European collaborations); metabolic reprogramming in CLL; and the study of the tumour microenvironment through extravesicular vesicles.
The second axis is focused on Waldenström's macroglobulinemia, a rare disease for which strong clinical expertise is to be found in the Pitié-Salpêtrière Hospital. This axis is subdivided in three programs, one focused on the WM molecular and micro-environmental landscape, and distinct from the research program developed in CLL, a second one investigating the protein expression specific of this malignancy by flow analyses, and a third one focused on the BCR structure found in WM (immunogenetics). The added value of the second research program focused on flow in WM, and regarding epigenetic subtypes (methylation, recently published by the team – US collaboration) and the study of disease heterogeneity including in pre-malignancy, and the microenvironment is clear and original. The use of flow as a differential diagnostic tool in MW from other small B cell disorders is less clear. Differential diagnosis of WM from marginal zone lymphoma, for example, is helped by the specific genetic features of WM (MYD88 and CXCR4 mutations).
The last axis is emerging and will characterise the very rare intraocular and cerebral lymphomas using unique samples from the French national network dedicated to this disorder.
The mastocytosis axis is absent from the proposed trajectory, although the expertise will be redeployed to the MW program. The trajectory of the team is almost exclusively descriptive with few fundamental research projects. The valorisation of the excellent clinical results could be further increased in impact by undertaking deeper functional validation approaches.

RECOMMENDATIONS TO THE TEAM

The upcoming project, while addressing excellent clinic-pathological questions – appears mainly descriptive, albeit by state of the art 'omics' approaches (single cell sequencing, spatial 'omics).
It will be important for the team to build up functional validation approaches of their findings through wet bench experiments, as proposed in the CLL genetic program.
The team is well positioned to identify specific and original research topics of high clinical potential and to extend their discoveries to more fundamental knowledge.
This could be prioritised for the upcoming mandate and would further increase the impact of the team's overall production.
The team could leverage its national and international connections to attract in a basic science investigator in B cell biology to develop these aspects.

Team 13: Génomique fonctionnelle des tumeurs solides : FUNGEST

Name of the supervisor: ZUCMAN-ROSSI Jessica

THEMES OF THE TEAM

The main research activity of the team is focused on the molecular characterisation of liver tumours, mesothelioma, and HPV-related cancers, mainly in adults but also in children with benign and malignant tumours. Through a 'bench to bedside' strategy, the team aims to identify new cancer driver genes and therapeutic targets to improve therapeutic management, new genetic markers associated with cancer development to improve cancer prevention, and specific features of tumour heterogeneity and evolution to identify mechanisms of therapeutic resistance. The team combines multidisciplinary approaches, ranging from genomics, genetics, cell biology and bioinformatics with large clinically annotated tumour collections.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team addressed all recommendations from the previous evaluation. Notably, the organisation between clinicians and researchers has been adapted to support the translational aspect of the projects. The mesothelioma research activity and production have been improved during the mandate.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	8
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**14**
Enseignants-chercheurs et chercheurs non permanents et assimilés	4
Personnels d'appui non permanents	3
Post-doctorants	3
Doctorants	11
Sous-total personnels non permanents en activité	**21**
Total personnels	**35**

EVALUATION

Overall assessment of the team

The scientific production of the team is outstanding, with top-level publications as lead author (Cancer Discovery 2021, Lancet Oncology 2022, Nature 2021, Nat Commun 2019) and remarkable contribution in liver cancer and mesothelioma. The attractiveness and international visibility are outstanding, as attested by the team's capacity to raise competitive national (3 INCa, 4 ITMO Cancer, 1 ANR, 2 Ligue labeling) and European grants (HORIZON MISS-2021-CANCER-02-03). The interaction with the society is also excellent, as attested by their participation in the guidelines for the management of the patients of liver tumours or HPV tumour risk.

Strengths and possibilities linked to the context

The team's organisation is fully coherent with their research activity and scientific objectives, both at the quantitative and qualitative levels, with eight professor-clinicians and three Inserm researchers, 6 staff technicians/engineers, and thirteen postdocs/PhD students. The team has maintained a very good balance between senior staff scientists and young researchers.

The team has an impressive record of competitive funding as coordinator (e.g. 3 INCa 4 ITMO Cancer, 1 ANR and 2 Ligue labelling team competitive grants) with a total amount of 2.2 M€/year. Remarkably, they obtained an important European project as part of the HORIZON MISS-2021-CANCER-02-03 (Understanding Gene

ENvironment Interaction in ALcohol-related hepatocellular carcinoma). Notably, they coordinate two WPs of the grant (5.2 M€ in total) with the participation of team 11 for bioinformatics analyses.

The scientific production of the team during the mandate is impressive both at the qualitative and quantitative level with 365 original research publications, among which 28.2% were signed in first or senior positions. Some of their findings were published in the highest journal reputation of their speciality (Gastroenterol, J Hepatol, Can Discovery, Lancet Oncology) or generalist journals (Nature and Nat Commun). As examples, they uncovered alterations in cancer driver genes in pediatric liver tumours, frequent pre-neoplastic somatic mosaicism in young children with hepatoblastoma, and new mechanisms of resistance to cisplatin with the involvement of cell plasticity (Cancer Discovery 2021). These results pave the field of transferring genomic data in clinical practice. In Lancet Oncology (2022), they reported new genetic polymorphisms associated with the risk of hepatocellular carcinoma in European patients with high alcohol intake and enlightened the role of the WNT/ß-catenin in the early step of hepatocarcinogenesis. Clinical use to predict the risk of HCC in cirrhotic patients was next validated by the team in 2023. Finally, they dissected heterogeneity in malignant pleural mesothelioma through histo-molecular gradients for clinical applications (Nat Commun 2019).

The international visibility is outstanding in the domain, as attested by the contribution of their research work in gastrointestinal cancer. Several members of the team received important national and international prizes and awards. As an example, the team leader was nominated Highly Cited Researcher by Clarivate (2021 and 2022), awarded by the French Academy of Medicine with the Albert 1er de Monaco prize (2021) and was nominated Chevalier de la Légion d'honneur (2018). The team was very successful in attracting young scientists over the period (25 PhD students including 9 medical doctors and 10 postdocs), including thirteen foreigners (8 students and 5 postdocs). All PhD students published at least a manuscript in a peer-review international journal as first or co-first author, and from the last decade, all the students and postdocs have obtained permanent positions in a hospital, university, or in private companies.

The activity of the team in national and international scientific policies is remarkable, as attested by their participation in editorial journals of their speciality. Notably, the team leader was senior editor of JHEP, the highest reputation journal in the domain, and since 2018 she is editor in chief of JHEP Reports. The team is also very active at national and international professional associations (presidency of the International Liver Cancer Association in 2020–2023, chair and vice chair of the SIG Hepatobiliary Neoplasia at the American Association for liver disease, 2019–2022), national and international charities (e.g. FNRS physiopathology scientific Committee in Belgium) and evaluation in funding institutions and projects (e.g. scientific committee of Institut Curie, CRUK of the Early Detection Program in UK since 2019, SAB for CRCL and CLB of Lyon, 2018–2020).

Team 13 activities have a strong impact on society. As an example, team members have participated in the definition of the guidelines for the management of the patients at the national, European and international levels, in particular for the management of liver tumours or HPV tumours risk surveillance. Team members also share their knowledge with the public. For instance, several PIs were interviewed in the press, by TV or video (e.g., le Monde, Médecine Science).

The team interacts with private companies, as attested by several research funding from pharmaceutical companies (e.g. Bayer, Roche, Sanofi, BMS), two deposited patents and 4 software deposited on GitHub.

Weaknesses and risks linked to the context

Sample and data management are not optimal to exchange and collaborate with hospitals and clinical centers.
The interaction with the private sector is moderate in regards to their exceptional translational potential in cancer therapy.

Analysis of the team's trajectory

The team project for the next contract is very ambitious but clearly defined and it lies in the continuation of the team's research activity and strategy. Importantly, it capitalises on GENIAL, their European project part of the HORIZON MISS-2021-CANCER-02-03. With three major, non-exhaustive orientations integrated in the CRC 4 transversal axes for the future contract, they plan to: (i) further identify the interactions between exposure to various risk factors and genetic predisposition in HCC, notably those related to alcohol and viral exposure; (ii) identify new therapeutic targets and profiles of response to treatments in pediatric and adult liver cancers and mesothelioma; (iii) and refine the analysis of tumour heterogeneity to identify new biomarkers useful for diagnosis and prognosis in those cancers.

RECOMMENDATIONS TO THE TEAM

The committee congratulates the team for their exceptional scientific output and recommends the team to continue their outstanding research activity and projects. The team is encouraged to foster their interaction with the private sector whenever possible.

Team 14: Structures bactériennes impliquées dans la modulation de la résistance aux antibiotiques : MICROB. RESIST

Name of the supervisor: ARTHUR Michel

THEMES OF THE TEAM

The team focuses on the biosynthesis of peptidoglycan, the main component of the bacterial cell wall, and the inhibition of this pathway by different drugs. The goal of their work is to provide insights into the mode of action of drugs blocking the assembly of peptidoglycan, to decipher the mechanisms of antibiotic resistance and to design new strategies to combat multi-resistance.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team addressed the recommendations from the previous evaluation. Notably, the team now focuses its efforts on two challenging projects concerning antibacterial strategies. The team will be moving to another unit (LBM/Pasteur unit) in which research interests and expertise may be more directly relevant to the team.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	effectifs
Professeurs et Assimilés	4
Maîtres de conférences et assimilés	
Directeurs de Recherche et Assimilés	1
Chargés de recherche et assimilés	
Personnels d'appui à la recherche	
Sous-total personnels permanents en activité	**5**
Enseignants-chercheurs et chercheurs non permanents et assimilés	
Personnels d'appui non permanents	
Post-doctorants	
Doctorants	5
Sous-total personnels non-permanents en activité	**5**
Total personnels	**10**

EVALUATION

Overall assessment of the team

The team's scientific production is outstanding in the field with 28 peer-reviewed articles, some of them in top-ranked journals (Nat Commun, Elife, EMBO J, AAC, PNAS, Nucleic Acids Res) and remarkable methodological innovations (such as mass spectrometry analyses (Elife, 2022).
Attractiveness is also outstanding: the team obtained, as coordinator, three ANR contracts, one European grant (JPI-AMR NAPCLI, 273K€ for the team) and one PIA and three ANR and one NIH grant as partners.
Eleven PhD students and three postdocs were trained. The team also contributes significantly to education (2 steering committees and coordinator of 2 Master programs).
The societal impact is low.

Strengths and possibilities linked to the context

The team is currently composed of ten members, including five permanent researchers (1 DR, 4 PU) and five PhD students.
The team has published 28 articles since 2017, including first and last author publications in top journals (EMBO J, Nat Commun, eLife and Nucleic Acids Research).
This team has a high visibility in the fundamental research on the bacterial cell wall and antibiotic resistance. In particular it has demonstrated the mechanism of inhibition of L, D-transpeptidases, the regulation of peptidoglycan synthesis by the alarmone (p – ppGpp in E. coli, and the optimisation of treatments based on the repurposing of existing drugs. (Nat Commun 2019, 2022, Elife 2022, EMBO J 2021, AAC 2018, PNAS 2018, Nucleic Acids Res, 2021, Chemistry 2018). The team has excellent funding with a total of 1.75M€ grant in the period (7/10 as leader): three ANR as coordinator (Peptidoadapt, Mycwall, Regopeps, 741K€), three ANR as partner

(TranspepNMR, SyntRNA, Chembiotic, 507K€), one PIA AMI-Antibioresistance as coordinator (300K€ for the team), one European grant (JPI-AMR NAPCLI, 273K€ for the team), one RO1 NIH grant (350K€) as partner.

The team is very attractive and visible, as evidenced by the number of PhD/MD-PhD (14) and Postdoc (3) recruited.

The PI was invited to five international meetings on the bacterial cell wall and antibiotic resistance and is a member of the editorial board of Antimicrobial Agents and Chemotherapy since 2017. The team is also involved in several steering committees (Vaincre la mucoviscidose, BioAster,…). The team is also involved in student training (coordinator of 2 Master programs).

Team members are involved in societal outreach: Interviews (France culture), You Tube 'Innovation et antibiotiques'.

Weaknesses and risks linked to the context

The team is small (5 permanent members) with no permanent technical staff and no CNRS/INSERM researchers.
The PI has secured most of the funding. However, he will retire in 2025.
Translational research efforts and outreach to industrial partners are modest.
The team's presence in social media is low.

Analysis of the team's trajectory

The objectives are in line with the expertise and previous research of the team. These goals include i) development of narrow-spectrum drugs and new therapies using innovative strategies (optimisation of treatment with a triple combination of drugs and design of prodrugs activated by ß-lactames), ii) characterisation of the inhibition mechanism of known targets as the penicillin-binding proteins (PBPs) and L, D-transpeptidases (LDTs), and iii) understanding the mechanisms of peptidoglycan polymerization, in particular in response to environmental conditions and during biofilm formation. Based on a method developed in the team, they will also investigate the mode of action of drugs on peptidoglycan assembly in M. tuberculosis and E. faecium. This project is well designed and ambitious. The team, even if small, has all the expertise required for the feasibility of the project.

RECOMMENDATIONS TO THE TEAM

The team has valuable and rare expertise in the biochemistry, genetics, and chemistry of the bacterial cell wall. The committee congratulates the team for their scientific results and recommends the team to continue their outstanding research activity. The committee, however, encourages the team to improve its participation in international conferences and presence in social media. It also recommends the team to develop efforts to attract young scientists with high profiles for applications for a permanent position at the CNRS/INSERM and to secure the technical personnel required to develop their future projects.
The team will leave the CRC. The team should take advantage of this move to establish new collaborations in the new host unit, which has strong expertise in chemistry and biophysics applied to biology. The committee recommends that the transition between the CRC and the new unit occur as smoothly as possible under conditions that allow the team to continue developing their projects.

Team 15: MOLECULAR ORAL PATHOPHYSIOLOGY

Name of the supervisor: BERDAL Ariane

THEMES OF THE TEAM

The team works on oral physiopathology with a focus on environmental genetics and dental-oral diseases. The research is centred on three axes: 1 – understanding the environmental impact on tooth biology, 2 – implementing dental genomics from bench to bedside and 3 – exploring new cell therapies in oral surgery. The scientific approaches rely on the use of cell lines, animal models and Biobank/cohort exploration to cover a wide array of objectives ranging from basic science to a translational and preclinical work that can be translated to patients.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has actively contributed in developing translational research through the creation of a start-up (StarCell Therapeutic). The team has increased the visibility of CRC based on a large number of international communications in international meeting and in Media (recommendation 3).

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	5
Maîtres de conférences et assimilés	4
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**12**
Enseignants-chercheurs et chercheurs non permanents et assimilés	4
Personnels d'appui non permanents	4
Post-doctorants	0
Doctorants	6
Sous-total personnels non permanents en activité	**14**
Total personnels	**26**

EVALUATION

Overall assessment of the team

The scientific production of the team is excellent with 140 articles, of which 43 as first, last or corresponding author in specialised journals (J Dent Res, and Environ Health Perspect).
The attractiveness is excellent to outstanding: the team secured €2 million (H2020, ANSES, IDEX and foundations, PhD-CIFRE). The team attracted 6 Postdocs, 7 PhD students, and visiting scientists (University British Columbia (x2); Max Planck Institute). It also obtained eight associates and three full professor positions. The team is integrated in oral and craniofacial rare disease European networks (ERN-Cranio, O-Rare disease Network). Team members presented 60 communications in national and international meetings (Europerio, Denmark, Congrès de la SDS (Society for Dental Science) and the work of the PIs was acknowledged by two prizes (Prix André LICHTWITZ de l'Académie de Médecine, Prix Naturalia et Biologie).

The impact on society is excellent: the team made major contributions to promote oral/dental science in France, Europe and worldwide. They have three patents and are running one clinical trial (MAXIBONE). They also developed a start-up (Starcell). The team also communicates to patients' organisations.

Strengths and possibilities linked to the context

The team is structured with two CNRS/INSERM researchers (1 CR and 1 DR), eight clinicians-Professors and eight clinicians (teachers). The team also included ten to fifteen PhD students, postdoc and master students.

The team has a unique expertise in the field of oral physiophathology. They combine basic research on cell and animal models to a patient-oriented translational research. Projects are organised in three themes: 1/gene environment, 2/mechanism of rare diseases and 3/cell biotherapies, each led by an independent researcher.

Team has secured 1.7 million euros of funding to cover experimental, clinical and salary costs. European funding included H2020 (400k€ from the Maxibone project), the Odontologie UPR (244k€) and the AHPH/INSERM (200k€ for FHU). The team also secured 24 small grants (10 to 50 k€) from private associations (Gueules Cassées, Foundation Avenir).

The team published 131 original research publications, 43 signed in first or senior position. Articles were published in excellent journals in the field (J Dental Research), and publications evenly distributed among the three axes. Some of the team contributions stand out in the field, such as their demonstration that teeth is a health readout for exposure to pollutants (Environ Health Perspect. 2022), and their contribution to dental development through cell tracing studies in mice (J Dental Res 2022).

Seven PhDs were defended and 6 postdoctoral contracts were obtained. The team also attracted French and foreign researchers for short visits (1–6 months). They obtained eight associates and three full professor positions.

The team is involved in a large number of national activities: Inserm (CSS3) committee, university and dental faculty scientific committees. They also contribute to national networks (ex: rare disease Networks/ERN Cranio) and have developed international networking with Canada, Australia, Latin America and Asian countries.

The team was involved in a number of start-ups and industrial projects (StarCell therapeutics, H2020 MAXIBONE The team actively promotes opensource knowledge on oral health through debates, webinars, and expertise shared within university and health agencies.

Weaknesses and risks linked to the context

The team has no permanent technical support and is mainly composed of clinicians. The two permanent researchers from CNRS (CR) and Inserm (DR) are senior and no permanent young scientists have been recruited in the team over the last contract.

The publications are excellent in the field but the team lacks major publication in more generalist journal to widen their visibility out of the oral pathology field.

Analysis of the team's trajectory

The team is one of the CRC founders and is currently based at CRC. The team trajectory was well anticipated for the next quinquennial contract. One DR and the deputy director left CRC in 2023 to join the Odontologie Santé Université Paris Cité. The rest of the team will follow once space becomes available.

RECOMMENDATIONS TO THE TEAM

The Committee congratulates the team for the excellent work achieved during their stay at CRC and their major contribution to the field of oral physiopathology. The committee recommends that the team continue promoting its excellent oral physiopathology research at their new location (UR 2496 Pathologies, Imagerie et Biothérapie Orofaciales, Montrouge Paris Université Paris). The strong valorisation by the team should also be maintained and further extended to promote the research field in France and worldwide. The committee recommends the recruitment of permanent full-time researchers and technical staff members to support the ambitious research plan, and consider applying to ERC funding based on their innovative research in the field of facial/bone reconstruction.

Team 16: Maladies métaboliques, diabète et comorbidités : METAB.DIAB

Name of the supervisor: FOUFELLE Fabienne

THEMES OF THE TEAM

The team METAB.DIAB consists of two research axes: the first one studies the complex relationship between NAFLD and type 2 diabetes, and the mechanisms of lipid-induced insulin resistance which is a key feature of type 2 diabetes; the second one is focused on understanding the signalling and pathophysiological roles of the hormone aldosterone and its receptor (the mineralocorticoid receptor (MR), with the objective of translating preclinical data to clinical studies including the development of interventional clinical trials when possible.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Team members were encouraged to maintain their international recognition and partnerships, and pursue effective collaborations with physicians to reinforce the translation research, more specifically in the NAFLD field:

An emblematic paper of the collaboration with physicians was published in Cell Reports Medicine. It associates basic researchers with diabetologists and hepatologists. The team published twelve papers that associate a basic researcher and physicians. They also obtained two ANR grants associating a basic researcher of the group and diabetologists.

The team should pursue its efforts in training students and in recruiting post-docs or junior researchers:

The team recruited several postdocs and PhD students, including foreigners from EU (Spain, Italy, Poland, Greece) or other countries (China, Romania, Japan, Mexico, Brazil) as well as several trainees that have all been associated with publications. They also hosted several MDs as postdocs (including two from Japan) and PhD students (from France).

The team should pursue its efforts in reinforcing the emergent transversal projects between the two groups, which are extremely promising:

The team developed a transversal projected centred about NGAL/MR and NAFLD and benefited from interactions between the groups to implement novel phenotypic expertise, particularly concerning adipose tissue and liver metabolism. Two papers were published jointly.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maîtres de conférences et assimilés	2
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**11**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	4
Doctorants	3
Sous-total personnels non permanents en activité	**7**
Total personnels	**18**

EVALUATION

Overall assessment of the team

The number and quality of publications are excellent: 86 papers as first or last authors; Thirty percent in the top ten journals including Diabetes, J Hepatology, Cell Rep. Medicine.
The capacity of the team to fund research is excellent (920K€/year). The team obtained two European contracts (Marie Curie CoFUND; FP7 EU and UK-Diabetes) and 7 ANR grants as PI.
The team hosted 9 PhD students (2 from abroad: China and Romania) and fifteen post-doctoral researchers (6 from abroad: China, Spain, Mexico, Greece, Japan).
Translation of the research to the clinics is outstanding with two randomised multicenter clinical trials and one phase one trial; One patent licensed to industry. Technology transfer capacity is also excellent with three patents and a total of 830K€ from private companies for research funding.

Note: this team will quit the CRC and move to ICAN (Paris): the Foundation for Innovation in Cardiometabolism and Nutrition. The ICAN is a center of excellence in the field of cardiometabolic diseases: diabetes, obesity, hepatic diseases (steatosis), diseases of the heart and blood vessels.

Strengths and possibilities linked to the context

The team includes a total of 7 women and 7 men (excluding PhD students and trainees). Three DR, two CR, 3PUPH, two MCUPH, 4 post-doc. The team is structured in two groups, each of them combining basic research, translational and clinical programs. The first group studies the complex relationship between NAFLD and type 2 diabetes and the mechanisms of lipid-induced insulin resistance, a key feature of type 2 diabetes. The second group studies the signalling pathways and pathophysiological roles of the hormone aldosterone and its receptor, the mineralocorticoid receptor (MR), with the objective of translating preclinical data to clinical studies including the development of interventional clinical trials when possible.
The total budget of the team was of 920k€ per year. An average of 93% of this budget corresponds to external grants obtained by team members from international (FP7, EU, Fibrotarget, Marie Curie-cofound as partner) and national grants (7 ANRs as PI: IMHOTEP, MITOSTAR, SONIC, NADRANK and DETOXING, grants from RHU and IHUs…), or from four private contracts.
Members of the team published 86 papers as the first or last author and 220 total publications. Thirty percent of these papers are in the top 10% of the journals (Cell Rep Med. 2020, Kidney Int. 2018).
The visibility of the team is excellent as attested by the organisation of numerous congresses: – co-organiser of the 4x Endoplasmic Reticulum International meetings (2017/2019/2021), Chair of the European Section of the Aldosterone Council annual meeting (Paris/2017, Roma/2019), Chair or co-chair of the international Aldosterone Conference (2019, 2020). The team hosted 9 PhD students (2 from abroad: China, Romania) and fifteen post-doctoral researchers (6 from abroad: China, Spain, Mexico, Greece, Japan). Members of the team participate to research steering and scientific expertise bodies at international, European and national level (members of FFRD (Federation Francophone de recherche sur le diabète), Institut Danone, member of the INSERM Specialised Scientific Committee Pathophysiology CSS3, (since 2022) and of the scientific council of the IHU iCAN). One member is also president of the ECOS-Sud Committee, expert for the Ministry of Education and Research (since 2017) and president of the INSERM Specialised Scientific Committee Pathophysiology CSS3 (since 2022).
The team established several partnerships with industrial partners (Bayer SAS, Astrazeneca, Poxel, Enterome) in various scientific areas, leading to about 830 K€ of external resources for the period. Three patents have been filed during the 2017–2022 period and have an international extension. One patent led to recognition in 2020 as APInnov 2020 – Trophée brevet prometteur – APHP. Several randomised clinical trials were initiated: 1) a randomised multicenter clinical trial testing the potential benefit of MR blockade in kidney transplantation with graft from donors with extended criteria (EPURE-Transplant); 2) a safety clinical trial testing preconditioning of brain-dead donors with MRA for organ preservation (CANREO-PMO); 3) a randomised trial testing the impact of MRA eplerenone on arterial stiffness in kidney transplant patients (EVATRAN).

Weaknesses and risks linked to the context

The team has no technical staff, but many grants to hire CDDs.
Team 16 must consider renewing its staff with talented young researchers/clinicians for future recruitment (INSERM, CNRS and/or clinicians….).

Analysis of the team's trajectory

This part was not assessed as the team is moving to another center for the next mandate.

RECOMMENDATIONS TO THE TEAM

The team is encouraged to develop of 3D models to study metabolism. There is an urgent need to recruit a new engineer to perform animal studies.

Team 17: Éthique, recherche, translation : ETRE

Name of the supervisor: MAMZER Marie-France

THEMES OF THE TEAM

Team 17 is deeply engaged in applied ethics, focusing on the investigation of changes in healthcare and research practices. The role of patients as partners, especially in cases of cancer, is one main topic.
The research aims to delve into the realm of applied ethics, specifically examining the impact of expert committees as well as patient committees on patient engagement and decision-making within the realm of cancer care. The transfer of knowledge from experts to patients has been shown to be the key in addressing complexity. Additionally, the team has undertaken pioneering work related to artificial intelligence in healthcare.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

In 2017, HCERES recommendations highlighted the creation of a research team focused on translational ethics as a valuable opportunity. One team member was involved in the review during the previous evaluation of CRC. The unit's role and position were yet to be fully established at that time, enabling 'societal' modifications within the CRC. Discussions revolved around developing research ethics within the CRC, strengthening integrity policies, and enhancing communication with the public through scientific mediation. The development of ethics remained an open topic for elaboration, spanning research ethics and original contributions to the field of ethics. This consideration was addressed with the creation of the team.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**7**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	1
Post-doctorants	0
Doctorants	8
Sous-total personnels non permanents en activité	**11**
Total personnels	**18**

EVALUATION

Overall assessment of the team

The scientific production of the team is very good in light of limited resources (148 articles as PI, 8 book chapters) in good (Therapie) to very good (J. Transl med, BMC Med Ethics) journals. The attractiveness of the team is good: involvement in SIRIC CARPEM and emphasis on teaching and education. The team secured no funding, except for staff recruitment.
The team trained PhD candidates (2–3/year) and Master's students (8–10/year). The team involvement in public engagement and contribution to the society is excellent through partnering with patients in research and organising conferences for the general public.

Strengths and possibilities linked to the context

The team is composed of fifteen researchers (6 PUPH, 6 PH, 3 other status). Research themes included: conflict between patients and medical teams, detail analysis of conflict of interest and their resolution, violation of scientific integrity (case reports and detailed analysis) place of IA in decision-making, ethics related to the costs of the new therapeutic approaches citing a few examples.

The team operates with an average annual budget of 111 K€. Out of 248 articles, 148 are original articles, 26 are reviews and 74 are articles in non-English-speaking journals. Thirty-six original articles are published as first, last or corresponding authors in high-quality journals (J. Transl Medicine), and 112 in collaboration.
The team currently hosts six PhD students (5 defended their theses and one dropped out). The team is 75% supervised by a single HDR. It also hosts 8–10 Masters students per year.

The team is involved in public engagement through partnering with patients in research and organising conferences for the general public.

Weaknesses and risks linked to the context

The team is made up of twelve researchers, but 9 are employed at 0:33 full-time equivalent. The unit's small size hinders scientific productivity and the impact of its research and interventions on CRC members' practices with only CRC 100 staff having taken the proposed ethics training course. Three PhD students have defended their thesis without publication. Apart from publications, the team's activities are low (21 papers presented at meetings, no congresses organised, 1 researcher with a PEDR and 1 secretary general of the SFFML).

Analysis of the team's trajectory

The team will be integrated team 11.

RECOMMENDATIONS TO THE TEAM

An essential point to consider is related to the nuanced nature of ethics, which varies across countries due to differing legal frameworks, religious beliefs, and cultural contexts. Engaging in research and education related to ethics within the CRC is a unique and commendable undertaking. This initiative deserves recognition and appreciation but a significant concern is the possible perception of ethics as a superficial facade (alibi). The team's role should be strengthened in the direction of a platform for teaching, education, and evaluation. More than creation of IRP4 dedicated to ethics, staff sensitisation and continuing education should be mandatory, with at least the equivalent of a full day dedicated to ethics and scientific integrity. Furthermore, integration within a research-focused group is recommended for the team's research endeavours. To ensure visibility, this research topic should contribute to the drafting of a charter of good practice in ethics and research integrity, which could be amended and implemented to enable the transfer of the group's research on the evolution of our society's perception of ethical issues in biomedical research and scientific integrity, into daily CRC practices. A concern is a potential decrease in team visibility upon integration into a larger team. The team should extend its influence across various groups, through the development of transversal activities.

Team 18: VENTECLEF/IMMEDIAB.LAB

Name of the supervisor: Nicolas VENTECLEF

THEMES OF THE TEAM

The team integrates scientists and clinicians with a research interest in the mechanisms that govern diabetes and a focused interest tissue macrophage regulation. The team members study specific transcriptomic and epigenomic program that governs tissue inflammation in diabetes and explores the immune regulation of pancreatic islet function and insulin secretion and the existence and function of metabolic tissue macrophage population in diabetes and obesity conditions. Clinical work of the group aims at improving the prognostic and care of diabetic patients to prevent associated comorbidities (cardiovascular risk, limb amputation, …) and provide new therapeutic options.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

According to previous HCERES recommendations: Team 18 has actively contributed to increase the international visibility of the CRC (recommendation 3). Team18 has organised three International Febs Summer School in Greece (2017, 2019 and 2023) and contributed to 'la fête de la science' as well and diffused science in media (equilibre-Magazine de la Fédération française du Diabète) as listed in portfolio 3. Team 18 has not taken advantage/benefit from the improved in-house intellectual property management (following recommendation 2), as none of the work done by the team resulted in patents or start-up creation. Regarding the recommendation made to improve the equilibrium between the three departments to limit the risk of weakening physiology driven discipline (recommendation 7). Team 18 is one of the five teams who decided to join other research units in Paris closer to their respective scientific fields, suggesting that taken action were not sufficient to address this recommendation.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maîtres de conférences et assimilés	2
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	4
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**12**
Enseignants-chercheurs et chercheurs non permanents et assimilés	3
Personnels d'appui non permanents	6
Post-doctorants	6
Doctorants	6
Sous-total personnels non permanents en activité	**21**
Total personnels	**33**

EVALUATION

Overall assessment of the team

The scientific production of the team is outstanding with 106 of these articles are signed as main authors and 18% published in top journals (Nature Commun, Diabetes Care, Nature Cancer, Circulation, Immunity…).
The attractiveness is outstanding: the team obtained €4.3 million through numerous national and international sources as PI (13 ANR, 3 European Foundation for the Study of Diabetes (EFSD), …). The team leader received a Senior ERC and team members have been supported by young researcher programs (ANR JCJC, ATIP avenir INSERM, Emergence). The team has also recruited three permanent young researchers.
The impact on society is outstanding: major collaborations with AstraZeneca, Lilly, Servier, CIFRE PhD contracts, creation of a start-up (IRIADE). The team is also actively involved in clinical recommendations for diabetes care and glucose monitoring in France and Europe. The team shows a solid implication in sharing its knowledge with the general public through a number of social events (fetes de la science, public seminars,…) and media communications and exchanges with patient-centred associations.

Strengths and possibilities linked to the context

The team applies pluri-disciplinary approaches to explore the pathological context of Diabetes ranging from fundamental/translational researches to epidemiological/clinical studies and technological innovation. While Team fundamental researches focuses on the mechanisms that govern tissue inflammation in diabetes with a major interested in monocytes and tissue macrophage regulation, their clinical/epidemiologic studies aim at improving the prognostic and care of diabetic patients.

The team has shown capacity to raise national (13 ANR as PI) and international as (European Foundation for the Study of Diabetes (EFSD) funding, with more than 3/4 of all its obtained contracts led as PI. It is worth mentioning that half of team contracts are of international origin, among which should be listed a top-notch European Research Council (ERC 2017–2023) grants and a HORIZON (1.2 M€) grants which have been obtained by the team Leader. The excellent capacity of fundraising is not limited to the team leader as junior team scientists are also very competitive through major National and EU funding program (ANR & EFSD, ATIP-Avenir).

The team has 329 published articles and more than 20,000 citations in the last five years (2017–2022). One hundred and six of these articles are signed as main authors and 18% published in top journals (Nature communication, Diabetes Care, Nature Cancer, Circulation, Immunity…). Those publications cover areas including clinical innovation, fundamental research and epidemiological reports. They imply contribution of the tenure researchers and clinicians and can be exemplified with two excellent articles published in 2022 in Nature Com and Diabetes Care.

Attractiveness: the team have managed to secure the recruitment of three permanent researchers (INSERM and CNRS) with an excellent background and strong scientific potential. The latest point should support the growing of the team and the extension of the current scope of research to Diabetes-associated topics (obesity, NASH, cardiovascular complications, etc.). Doctoral students and postdoctoral fellows have shown a major contribution to the scientific production of the Team which should support a solid attractiveness partly as suggested by 7 PhD dissertation and three running theses between 2017 and 2022.

The team is involved in clinical recommendation in France and Europe for diabetes care and glucose monitoring. The team show a solid implication in sharing its knowledge with the general public through a number of social events (fetes de la science, public seminars) and media communications and exchanges with patient-centred associations.
The team's relations with the industrial and socio-economic world: a number of major collaborations with three contracts with pharmaceutical companies (AstraZeneca, Lilly, Servier), one CIFRE PhD contracts, and the creation of a start-up (IRIADE), and contribution to clinical guidelines.

Weaknesses and risks linked to the context

While the overall evaluation of the team is excellent, a number of weaknesses or risks should be pointed.
The lack of permanent technical staff should be considered as a major risk regarding the maintenance of the current technical knowledge and expertise of the team. A clear strategic plan structuring defines subgroups with specific research focus and recruitment strategy may facilitate the overall long-term organisation/evolution of the team. Physical location of the basic and clinical research is unclear, a unique site strategy should be favoured to facilitate collaborative daily work, scientific exchanges and sample manipulations. The teams move to INEM may have addressed these issues.
Maintenance of top-notch level of funding should be anticipated while the major ERC and Horizon-contract ends, as it may impact and reduced the overall financial research capacity of the team will have acquired during the duration of those major contracts.

The attractiveness of the team is solid and supported by the recruitment of three young scientists, but it appears unclear whether some of them may emerge as independent team leaders and leave the group. This point is further highlighted by one ATIP-Avenir funded Researcher, and the unclear situation of a researcher (Camille Bleriot) recruited in 2022 but not listed as a team member. The recruitment strategy of new medical and scientific students (Master and PhD) is also unclear. It should be clarified how student recruitment is envisioned to maintain the balanced multidisciplinary expertise within the team.
The team has contributed to creating a Diabetes dataset from Lariboisière and Bichat hospitals, but its positioning in National and international effort to structure a clinical database or its integration in a French/international reference centre on diabetes and metabolic diseases remains unclear.
While the Scientific production is second to none, the economical valorisation through patents and start-up creation lag behind, to that extent how much the collaborative contracts with pharmaceutical companies are limiting the internal valorisation processes and should be overcome? Does a valorisation strategy exist with Inserm-Transfert or an equivalent structure? As the team is addressing major health issues in the Diabetes field through the use of human material and data, the question of ethics and patient agreement need to be properly addressed through appropriate legal documents. This point remains unclear in the overall strategy of the group and may limit the publication of innovative research and its subsequent valorisation.

Analysis of the team's trajectory

Team18 did not provide trajectory details. The team has moved to the Institut Necker Enfants Malades (INEM) in January 2022 to further develop its research.

RECOMMENDATIONS TO THE TEAM

Team18 moved to INEM at Necker Hospital in January 2022. No major recommendations will be proposed regarding the future evolution of the team. These aspects will be addressed and evaluated within the INEM HCERES Document.

Team 19: Recherche en santé numérique pour un système de santé apprenant : HeKA

Name of the supervisor: ZOHAR Sarah/BURGUN Anita

THEMES OF THE TEAM

The HeKa team pursues research in the field of medical informatics. More specifically, their main theme is the extraction of relevant data from medical records, in conjunction with the development of machine learning models to represent medical knowledge, leading to patient stratification and predictions of optimal therapy. In addition to implementing more classical methods of machine learning, the team has put a great emphasis on the integration and adaptation of artificial intelligence (AI) methods in their topics.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Previous recommendations were to streamline knowledge extraction from medical records, introduce AI, and to propose methods of optimising patient regimens. The scientific output as well as the actions of the team towards society were addressed fully. The team managed to propose competitive solutions or to act as important actors or partners. Treatment optimisation, one of the most formidable challenged in health-related research, was addressed through involvement in integrated projects and access to competitive funding.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maîtres de conférences et assimilés	2
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	6
Sous-total personnels permanents en activité	**17**
Enseignants-chercheurs et chercheurs non permanents et assimilés	3
Personnels d'appui non permanents	0
Post-doctorants	2
Doctorants	34
Sous-total personnels non permanents en activité	**39**
Total personnels	**56**

EVALUATION

Overall assessment of the team

The scientific production was excellent with 435 papers (: Artificial Intelligence in Medicine, 2022; Biometrics, 2022). The team now has broad expertise in medicine, medical informatics, and mathematical modelling/AI. The attractiveness iso outstanding (2017–2023:>10M€ funding, recruitment of 2 CR and 1 DR). The societal impact is excellent to outstanding through participation to medical informatics advisory or executive boards (HEGP, French National Rare Disease Registry, Imagine Institute), spin-offs, and software packages development.

Strengths and possibilities linked to the context

Research highlights of the team reflect the necessary tools and steps to achieve its main objectives. Extraction of information from medical records entails the adaptation of natural language processing (NLP) techniques to the medical field (in French!). The team has released a widely used software library for this purpose (Neuraz, 2020) as well as metrics to identify comparable patients (Chen, 2022). To represent patients in the health system often implies representing their trajectories (and comorbidities) in this system. This is a classical topic where metrics to compare patients are key. HeKA team has also tackled this type of question at a population scale to provide alert systems for pandemics, including space and time, which is a timely and innovative topic (Priulh, 2022). Towards the challenging goal of personalized medicine inferences, deployment of AI methods led to two

important contributions, one technical paper offering the community a very useful library (Chadebec, 2022), and Cottin, 2022 that discloses a deep-learning system to improve prognosis in patients.

The HeKA team has an excellent score at attracting extramural funding with an average rate of roughly 1M€/yr. They were also very effective in getting PhD students (59), including 6 with an industrial fellowship. The number of postdocs is on average (6). Several clinicians were attracted by the team, including one from Lausanne (CH). Beyond highlights, the number of publications is very high (435 papers including conference communications). The visibility of journals remains modest (see weaknesses below), which is inherent to the specific field of research. A number of software packages have been made available too.

Team visibility and attractiveness are high as exemplified by the participation of several senior team members in important medical informatics-related commissions, but also the number of PhD students trained and the number of clinicians associated with the team. Team members are also involved in various spin-offs such as Implicity (monitoring of implants), CODOC, and Sonio (prenatal ultrasound monitoring). Four patents were granted, notably in partnership with Dassault Systems, AP-HP, etc. Lastly, information or animation for the general public is not forgotten targeting patient associations (EURODIS, FAIR), keynote lectures at Pharma HealthTech, but also interviews for Le Monde, France Culture, or TF1.
The relationship with the private sector is quite active as already reported above regarding PhD fellowships, patenting, or the creation of spin-offs.
The current main strength of HeKA is its technical expertise and integration in many research networks and the health system. This remarkable position, gained by excellent work over many years, should lead to major contributions. From that perspective, the interest of HeKA for so-called new generation clinical trials, integrating advanced medical informatics, and their design sounds very timely.

Weaknesses and risks linked to the context

Medical informatics has remained for quite some time a minor topic compared to bioinformatics or classical biostatistics. Since a few years, it has emerged as a main priority and perhaps other actors in health and research started to better understand its specificities. The successful development of HeKA – also in terms of funding – almost perfectly reflects this. Such a high level of expectations implies the need to deliver actual impact on health beyond convenience informatics. If this is not achieved to a sufficient extent, there is a risk of disregard by funding bodies.

Although the team has obtained publications in well-respected specialized journals in its field, the absence of papers in medical, biological, or generic journals might limit HeKa's development.

Lack of clear interface with bioinformatics might be a limitation for certain future projects, especially in the direction of clinical trials since many include omics data. In a more minor mode, the same comment may apply to ethics. Applications of medical informatics might raise new ethical questions.

Analysis of the team's trajectory

The team's trajectory is very coherent, following the previous evaluation's recommendations and integrating mathematics and computer science additional strengths, capitalising on the very good integration in the clinics. Interestingly, in 2020, the team has revised its objective following the arrival of INRIA personnel. Before this date, the objectives were driven by necessity (ability to extract knowledge from patient records, introduce AI and develop methods of inferences to improve therapy). They report technical successes in these endeavours, but lack of manpower for hardcore cs/math stuff. Starting in 2021, an emphasis is put on knowledge extraction and representation. The interest for the design of future clinical trials involving advanced medical informatics is mentioned here. Lastly, the move to a new place is obviously a loss for the Cordeliers, but an excellent opportunity for the team.

RECOMMENDATIONS TO THE TEAM

The chosen strategy and the opportunity to exploit a strong, recent interest in electronic health and related AI by the French government will certainly foster HeKa development. It is recommended that purely academic objectives should be kept as an important goal, and the point raised regarding publication in biological, medical or more generalist journals is an important element. Such journals are certainly ready to welcome excellent publications in medical informatics with convincing application showcases, and HeKa is very well positioned to do this.

While it is clear that in a topic such as medical informatics, achievements and focus are easier to define in technical terms, or as specific applications (in a specific clinical study, etc.), it would be interesting to know what is special about HeKA that is not 'just' excellence. From the auto-evaluation, one reads rather standard material. Specific classes of algorithms or models could be put forward, or the application of developed tools to specific diseases or medical areas.

CONDUCT OF THE INTERVIEWS

Dates

Start: 15 novembre 2023 à 9 h

End: 17 novembre 2023 à 18 h

Interview conducted: on-site

INTERVIEW SCHEDULE

HCERES Agenda
Unit: CRC
November 15,16,17 2023

November 14th: arrival of committee members

Day one: November 15th

9:15 a.m.-9:30 a.m. CRC welcome (coffee) *salle Club*
9:30 a.m.-10 a.m. Closed door meeting of committee *salle Club*

Farabeuf seminar room
10 a.m.-10:20 a.m. Presentation of the committee to the Unit 10:20 a.m.-11 a.m.
Presentation by the director, open to all the Unit
(20 minutes presentation, 20 minutes questions)
11 a.m.-11:15 a.m. Coffee break
11:15 a.m.-11:50 a.m. team 9 KROEMER Guido *(15 min presentation, 15 min questions; 5 min PI alone with committee)*
11:50 a.m.-12:25 p.m. team 1 BEHAR-COHEN Francine
12:25 p.m.-1 p.m. team 2 COLNOT Sabine

1 p.m.-2 p.m. lunch (boxed lunch), *salle club*
2 p.m.-2:30 p.m. committee debrief of morning session, *salle Club*

Farabeuf seminar room
2:30 p.m.-3:05 p.m. team 3 CRAMBERT Gilles
3:05 p.m.-3:40 p.m. team 4 CREMER Isabelle
3:40 p.m.-4:15 p.m. team 5 de REYNIES Aurélien
4:15 p.m.-4:45 p.m. committee debrief
4:45 p.m.-5:20 p.m. team 6 DESDOUETS Chantal
5:20 p.m.-5:55 p.m. team 7 FAVIER Judith
5:55 p.m.-6:30 p.m. committee debrief

7 p.m. Dinner close to CRC

Day 2: Thursday November 16th
9 a.m.-9:15 a.m. Arrival of committee/coffee, *salle Club*

Gustave Roussy seminar room
9:15 a.m.-9:50 a.m. team 8 GALON Jérôme
9:50 a.m.-10:25 a.m. team 10 LACROIX-DESMAZES Sébastien
10:25 a.m.-11 a.m. team 11 LAURENT-PUIG Pierre

11 a.m.-11:30 a.m. committee debrief, *salle Club*

11:30 a.m.-12:05 p.m. team 12 NGUYEN-KHAC Florence
12:05 p.m.-12:40 p.m. team 13 ZUCMAN-ROSSI Jessica

12:40 p.m.-1:30 p.m. Boxed lunch *salle Club*
1:30 p.m.-2 p.m. committee debrief, *salle Club*

2 p.m.-2:35 p.m. team 14 HUGONNET Jean-Emmanuel
2:35 p.m.-3:10 p.m. team 15 BERDAL Ariane
3:10 p.m.-3:45 p.m. team 16 FOUFELLE Fabienne

3:45 p.m.-4:30 p.m. *Coffee break; committee debrief, salle Danton*

4:30 p.m.-5:05 p.m. team 17 MAMZER Marie-France
5:05 p.m.-5:40 p.m. team 19 ZOHAR Sarah/BURGUN Anita

5:40 p.m.-6:30 p.m. *committee debrief, salle Danton*

Day 3: Friday November 17th

9 a.m.-9:30 a.m. Arrival of committee/coffee, *salle Club*

9:30 a.m.-10 a.m. Committee splits in three groups for discussion with:
1/students (*salle Ancel)*; rep. Isaïas Hernandez
(Robert-Alain T., Christophe G, Virginie L., Claire R., Jean-Daniel T.)
2/post-docs rep. Amine Madji
(Philippe B., Mary C., Jacques C., Ruggero DM)
3/permanent researchers (other than team leader) (*salle du Conseil)*
rep. Catherine Monnot
(Philippe J, Alice C., Elfride D., Eric D., Serge R.)
4/administrative personnel, supporting staff (IE, IR..)(*salle Gustave Roussy)* rep. Isabelle Gali-Fauroux
(Stéphanie V., Christophe D., Philippe R., Rodrigue R.)

salle Club

10:15 a.m.-10:45 a.m. committee debrief

10:45 a.m.-11:45 a.m. Meeting with managing bodies

11:45 a.m.-12:15 p.m. Closed door meeting of committee

12:15 p.m.-1 p.m. Meeting with the director and deputy directors

1 p.m.-18 H Final debriefing of the committee with box lunch

End of the session: 6 p.m., departure of the committee

PARTICULAR POINT TO BE MENTIONED

The visit was interrupted by a terrorist alert. The DU and PIs are to be commended for rapidly finding an alternative solution for the presentations.

GENERAL OBSERVATIONS OF THE SUPERVISORS

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

à

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

Paris, le 9 février 2024

Objet : Rapport d'évaluation CRC - Centre de recherche des cordeliers

Cher Collègue,

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

Sorbonne Université n'a aucune observation de portée générale à formuler sur le rapport d'évaluation transmis.

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

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

Université Paris Cité

Le Président

Paris, le 5 février 2024

HCERES
2 rue Albert Einstein
75013 Paris

Objet : Rapport d'évaluation de l'unité **DER-PUR250024379 – CRC - Centre de recherche des cordeliers.**

Madame, Monsieur

L'Université Paris Cité (UPCité) a pris connaissance du rapport d'évaluation de l'Unité de Recherche **CRC - Centre de recherche des cordeliers.**

Ce rapport a été lu avec attention par le vice-doyen recherche et le doyen de la Faculté de Santé d'UPCité, par la vice-présidente recherche d'UPCité et par moi-même. Nous signalons une description incomplète de la représentation de notre université page 3 du rapport (cela est également indiqué dans les erreurs factuelles rapportées par la directrice de l'unité, madame Jessica Zucmann, à la tutelle déposante, Sorbonne Université). Je vous remercie de bien vouloir corriger ces omissions dans la version définitive publique du rapport.

Avec le doyen de la Faculté de Santé, nous souhaitons souligner que le CRC est l'une des unités majeures d'UPCité. Elle est colabellisée par Sorbonne Université, l'INSERM et le CNRS. Sa restructuration, avec des équipes partantes et l'arrivée de nouvelles équipes a été accompagnée par les tutelles. Basée sur l'avis d'un scientific advisory board international, elle est dédiée à recentrer et à renforcer la thématique du CRC sur l'origine et la physiopathologie des maladies, le cancer se situant au centre de cette thématique.

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
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