Research evaluation

EVALUATION REPORT OF THE UNIT

RIGHT - Regulation of Immunity for therapeutic Innovation in Graft, Tumoral and inflammatory-associated diseases

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université de Franche-Comté - UFC

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

Établissement français du sang - EFS

EVALUATION CAMPAIGN 2022-2023

GROUP C

Report published on September, 19 2023

High Council for evaluation of research and higher education

In the name of the expert committee[1] :

Matteo Iannacone, Chairman of the committee

For the Hcéres[2] :

Thierry Coulhon, President

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

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

MEMBERS OF THE EXPERT COMMITTEE

Chairperson:	Mr Matteo Iannacone, San Raffaele Scientific Institute & University, Italy
Experts:	Mr Raphael Carapito, Université de Strasbourg (representative of CNU) Mr Stefano Casola, The FIRC Institute of Molecular Oncology, Italy Mr Michel Cogné, Inserm, Rennes (representative of CSS EFS) Ms Sophie Conchon, Inserm, Nantes (representative of CSS Inserm) Mr Niclas Setterblad, Sorbonne Paris Cité (supporting personnel)

HCÉRES REPRESENTATIVE

Ms Birke Bartosch

CHARACTERISATION OF THE UNIT

- Name: Regulation of Immunity for therapeutic Innovation in Graft, Tumoral and inflammatory-associated diseases
- Acronym: RIGHT
- Label and number: UMR1098
- Number of teams: 2
- Composition of the executive team: Mr Philippe Saas

SCIENTIFIC PANELS OF THE UNIT

SV4: Immunity, Infection and Immunotherapy

THEMES OF THE UNIT

The unit's scientific subjects are related to inflammation and immunity, in the contexts of transplantation, cancer, hematopoietic stem cell transplantation and red cell transfusion. Focus of team 1 is on immune-mediated inflammatory diseases, transplantation and biotherapies, focus of team 2 on cancer epigenetics, T-cell anti-cancer immunotherapies and cancer biomarkers.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The "host-graft-tumor Interactions – cell and gene engineering" (UMR 1098) was created in 2001 at the Établissement Français du Sang (EFS-BFC) and was labelled UMR 1098 in 2012 by the Inserm, with Inserm, EFS and UFC as supervising institutions. Research activities at the UMR 1098 are located in Besançon for 92% and in Dijon for 8%, the two universities being merged in the consortium COMUE UBFC (COMmunauté d'Universités et Établissements Université Bourgogne Franche-Comté). UMR 1098 is located in at 6 different sites, one in Dijon, the others in Besançon at the Faculty of Sciences and Techniques and the TEMIS Santé campus (EFS BFC building, Health Faculty, University Hospital, and a recent building called BioInnovation).

RESEARCH ENVIRONMENT OF THE UNIT

UMR 1098 was originally focused on allogeneic immune responses and their regulation (Graft Versus Host Disease (GVHD) after stem cell transplantation, or host versus graft reactions in solid organ transplantation), Graft Versus Leukemia effect (GVL) as well as reactions after transfusions. Later, host-tumor interactions became an important topic of the unit that can be perceived in the concept of "mirror image" (unsuitable mechanisms involved in one direction might be exploited in the other one). In parallel, mechanisms of immune mediated inflammatory diseases (IMID) also became a transverse thematic. Importantly, all subjects are related to the clinical practice of the Centre Hospitalier Régional Universitaire CHRU, and most of them are the continuation of previous research. The UMR 1098 unit has evolved from adoptive allogeneic immunotherapy to immune cell-based therapies based on advanced therapy medicinal products (ATMP), including allogeneic NK cells, apoptotic leukocytes, monocyte-derived suppressive cells and skin substitutes (the skin engineering platform). A large biomonitoring platform dedicated to biotherapies and innovative technologies (directly connected to a biological resource center and a clinical investigation center) has been created including up to 28 sample collections and biological follow-up of patients from more than 54 clinical trials. So far, there are more than 15,000 samples collected. The unit obtained the ISO 9001 certificate in 2008 that was renewed in 2015.

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

Permanent personnel in active employment	
Professors and associate professors	26
Lecturer and associate lecturer	19
Senior scientist (Directeur de recherche, DR) and associate	0
Scientist (Chargé de recherche, CR) and associate	1
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	4
Research supporting personnel (PAR)	39

Subtotal permanent personnel in active employment	**89**
Non-permanent teacher-researchers, researchers and associates	5
Non-permanent research supporting personnel (PAR)	24
Post-docs	7
PhD Students	45
Subtotal non-permanent personnel	**81**
Total	**170**

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

Employer	EC	C	PAR
Université Bourgogne - Franche-Comté	39	0	8
EFS	0	4	11
CHRU Besançon	0	0	14
Université de Bourgogne	6	0	0
Inserm	0	1	3
CHU Dijon	0	0	1
Others	0	0	2
Total	**45**	**5**	**39**

UNIT BUDGET

Recurrent budget excluding wage bill allocated by parent institutions (total over 6 years)	2 355
Own resources obtained from regional calls for projects (total over 6 years of sums obtained from AAP idex, i-site, CPER, territorial authorities, etc.)	4 209
Own resources obtained from national calls for projects (total over 6 years of sums obtained on AAP ONR, PIA, ANR, FRM, INCa, etc.)	1 617
Own resources obtained from international call for projects (total over 6 years of sums obtained)	7 678
Own resources issued from the valorisation, transfer and industrial collaboration (total over 6 years of sums obtained through contracts, patents, service activities, services, etc.)	3 185
Total in euros (k€)	19 044

GLOBAL ASSESSMENT

This is an excellent unit, with a strong translational drive particularly in the cancer immunotherapy space.
It is a very large unit with 178 personnel, which is split into two distinct geographical sites. However, there has been a strong effort to make it into one cohesive research group.
The unit has been very successful in attracting the resources to develop an ambitious program, including several biobanks and a promising pipeline of advanced medicinal products.
The unit benefits from a very constructive work atmosphere, an efficient management and implementation of a safe environment.

The unit has an international visibility, mostly due to their leadership in a number of clinical studies, but this could be extended to more fundamental research areas. Four scientists are in the top 2% most cited scientists in the world.
The unit trains a relatively large number of PhD students but could increase its attractiveness towards international postdocs.
The unit is successful in being awarded national and international grants (~138 grants during the evaluation period), both as leader and partner, amounting to ~2M euros/year.
The scientific production is excellent with >1000 papers, with 20% in journals of solid reputation.
One of the unit's major strengths is their impressive clinical pipeline, with strong IPs (8 patents with 3 already licensed), industrial partnerships (24 contracts amounting to >3M euros) and the development of two successful spinoffs (MED'INN'Pharma and Cancell Therapeutics).
Team 1 is excellent due to its particular strength in using its fundamental observations as the basis for the development of original translational studies, clinical trials, or toward innovative development with the creation of start-ups. Areas for improvement include: increasing the number of permanent researchers, strengthening the study of fundamental aspects of the diseases, increasing the attractiveness towards foreign postdocs.
Team 2 is overall outstanding with very satisfactory scientific production, international standing, the launch of several independent clinical trials and the establishment of useful biobanks. While the unit's translational research program is outstanding, the preclinical studies are less well developed and the attractiveness towards international postdocs could be improved.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

R1: "Increase the number of full-time senior researchers and post-docs in order to maintain the quality of the research, to stabilize the teams and to keep focus on the unit's strengths"
Between the period of 2016 to 2021, Team 1 and Team 2 recruited 132 months and 189 months of postdocs, respectively. In total, 10 postdoctoral fellows were recruited in Team #1 and 7 in Team #2 over the contract period. In Team #2, one postdoc has obtained a full-time research position (EFS-BFC) and another has been recruited by the spin off CanCell Therapeutics). A permanent full-time junior researcher was recruited in team #2 in March 2020.

R2: Focus more on mechanistic studies:
The unit has gone some length towards increasing their fundamental research output (for instance through the ROMI network on basic research on blastic plasmacytoid dendritic cell neoplasia).

R3: "We also recommend to gather the teams in the same location to reinforce their interactions; this is planned and should be realized in the near future."
The opening in March 2021 of the Bioinnovation research building within the TEMIS Sante' Campus in Besançon has reached the goal.

B – EVALUATION AREAS

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

Assessment on the unit's resources

The unit's resources are excellent.

Assessment on the scientific objectives of the unit

Along the years the members of the RIGHT unit have managed to develop their research from basic toward translational, clinical and industrial development in an excellent manner.

Assessment on the functioning of the unit

The functioning of the unit is excellent.

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

Strengths and possibilities linked to the context

Regarding the human resources, RIGHT's workforce consists of 178 persons, with 63 in team #1, 77 in team #2 and the remaining 38 people in the common services and platforms. There is a high number (>30) of professors and assistant professors with clinical duties, a clear strength for the unit in terms of translational development of its projects. 36 members of the unit have their HDR, with 13 defenses since 2016. This allowed the supervision of 94 PhD students, and 49 thesis defenses. Members of the unit are involved in the management of 2 Master degrees (Host-Graft Interactions, and Cellular and Molecular Signalisation), and of a graduate school (IN'THERAPI). RIGHT has "diversified" the ways to hire sufficient support staff (technicians, engineers) for its activities: some have permanent positions, others have non-permanent positions paid by the major grants

obtained, and the unit has also been involved in the creation of a "business unit", BioNoveo within the context of FRANCHE-COMTE' INNOV, a partnership foundation created in 2013 by UFC, that allows them to recruit permanent staff.
Regarding the financial resources, the supervisory authorities provide the unit with recurring resources (329 to 509k€/year for a total of 2 355k€). Members of the unit have managed to secure 16 689 k€ over the period from regional, national and European calls as well as products from valorisation and numerous industrial collaboration contracts. The unit's expertise is highly recognized nationally, as shown by its involvement in several national programs: LabEx LipSTIC, Institut Carnot Opale, Bioproduction industrial cluster, national infrastructure ECellFrance for regenerative medicine, FHU INCREASE). In addition to these sources of funding, the associated regular and substantial support from the Conseil Régional BFC is noteworthy (>400k€/year).
Regarding the collective aspect of its research activity, the activity of the technology platforms in the unit clearly benefit the 2 teams. Both teams, and sometimes the PEPITE team which plans to join the unit for the next period are involved in important structuration of the unit, such as the LabEx LipSTIC. The whole unit benefits from important funding such as the ERDF-RIS3 MIMEDIS to develop their different drug candidates. Other funding has been obtained from the Région BFC (Fibrolution team #1, Personalise, RepTil Team#2). A part of the recurring budget of the unit is dedicated to innovative/new projects in the unit and for platform maintenance.
Finally, the unit has benefited of a new building "Bioinnovation" since 2021, with important lab surfaces. Another strength of the unit has been/is its capacity to develop translational research projects and to implement an impressive number of patient cohorts and clinical trials. This is the result of an important involvement of physicians, the effort to develop technical platforms with state of the art equipment, and the capacity to raise funds from competitive national calls, and from collaboration contracts with industrial partners.
A positive development is the addition of the PEPITE and EPILAB teams, which further strengthen the basic preclinical work of the unit.

Weaknesses and risks linked to the context

There is a need to increase the number of full time permanent researchers in the unit. During the period one new researcher appointed by EFS was recruited but this is clearly not sufficient and this lack of permanent researchers could fragilize the unit.

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

Strengths and possibilities linked to the context

The unit RIGHT has two main scientific objectives, the identification of new biomarkers and the development of new biotherapies, shared by the two teams in their specific domains. Over the years the members of the RIGHT unit have managed to develop their research from basic toward translational, clinical and industrial development in a remarkable manner. To fulfil these goals, they participate in, or have set up several national and European collaborative networks.
The unit takes into account the policy of its supervisory institutions, and plays a crucial role as an active partner in the development of biotherapies and bioproduction (UFC, EFS, Besançon Metropole etc…). There is close relationship between RIGHT and EFS (within the industrial cluster for bioproduction, and in the ECellFrance consortium). The capacity of RIGHT to initiate clinical trials based on basic results obtained in the unit, such as for the UCPVax vaccine is definitely in line with the policy of Inserm.
Regarding the governance of the unit, and the involvement of the staff in the definition of the unit policy, there seems to be sufficient opportunities for the information to flow both ways, from the head of the lab toward the staff, and back, with lab councils gathering representatives of all the staff held 3 or 4 times/year. A monthly meeting with senior scientists/PIs and the team and unit directors is an important time for decisions on grant applications, equipment purchase, financial resources etc… A yearly meeting gathers the whole unit for scientific talks as well as social events. There is also an annual management meeting, to comply with the ISO 9001 quality management system, during which the main indicators are analysed and discussed. This is a very positive action to keep track of the progress of the different objectives and to adapt in real time the unit strategy.
Regarding the economic and societal impact, the unit has successfully translated their basic research into applications of relevance for public health, for instance by participating or running clinical trials/studies, and their involvement in the FHU Increased. They also have strong links with patient associations.
RIGHT shows excellence with eight patents filed and three licenced to two start-up companies, spin offs of the unit, created during the period 2016-2021. They benefit, and actively participate in a very fertile economic public/private environment. The unit developed multiple partnerships, and collaborative contracts with private companies (eg ERDF Mimedi, with 6 private companies, or the industrial cluster for bioproduction). This is also facilitated by the geographical proximity within their new building, BioInnovation. Some of the technologies they develop have the potential to be widely applicable elsewhere in France and worldwide, raising the visibility at an international level and promoting further industrial collaborations.

Weaknesses and risks linked to the context

The activities of the unit, from fundamental science to development of biotherapies/biomarkers and to advanced bioproduction rely on many different types of expertise, and a very large panel of equipment. This requires time and has a very high cost. To develop these very different activities in a balanced manner is challenging. The results until now are very impressive, but will require further strong support from local, regional and national authorities

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

Strengths and possibilities linked to the context

A quality management process with an ISO 9001 certification has been implemented and is used for the governance of the unit RIGHT. This allows a follow up on staff training, and occupational health and safety, with indicators that can be monitored in a timely manner.
The staff can benefit from several types of training, either those organized internally in the unit, or locally by EFS, or those proposed nationally by Inserm, etc… The unit's policy is 1 to 3 trainings/year for technicians, and 1 to 5 for engineers. PhD students have the opportunity to attend one international congress during the course of their thesis.
H&S matters are considered in close contact with referent persons from EFS and Inserm who participate to the lab council as well as to the lab manager meetings to address specific issues. Psychosocial risks are also considered, following Inserm policy.
The safety procedures (access to building, and to data) are clearly established in the unit, and detailed in a document signed by all when they join the unit. Safety of data follow a very high standard, provided mostly by EFS. Safety information and risks for the protection of critical data and intellectual propriety are presented to members of the staff during seminars.
The business continuity plan is part of the quality management process, and this was definitely a strength for the unit at the time of the Covid19 pandemic.

Weaknesses and risks linked to the context

Among principal investigators, the M/F ratio is imbalanced, but several actions have been implemented to achieve gender equality. As it is described in the self-assessment, the measures to monitor psycho-social risks might be a bit limited in terms of risk prevention/management. Despite the opening of the new building in 2021, the unit is still scattered over different geographical locations, which can be detrimental to cohesion within each team and between teams. A standardized electronic lab book is missing.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The unit's attractiveness is excellent in terms of funding, translational research strategy, and number of PhD students.

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

Strengths and possibilities linked to the context

Members of RIGHT are regularly invited to present their work in national and international congresses (n=40). Three international meetings were organized by unit members in the 2016-2021 period: (1) First Resolution Days, Besançon, April 4-6th, 2018; (2) Innovative Therapies, Besançon, October 14-15th, 2021; (3) 10th scientific days of autophagy, Besançon, November 18-19th, 2021. Some members have editorial responsibilities in specialized journals (*Vox Sanguins, Transfusion medicine, Frontiers*) and are part of steering bodies (European blood alliance and national reference centers: Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN), federative regional

institute for cancer of Franche-Comté- INCa labeled). Four scientists are in the top 2% most cited scientists in the world (Standford University Ranking 2022).

Weaknesses and risks linked to the context

The external visibility of the unit is driven by only few unit members. International postdocs are under-represented. Despite a good name recognition in different immune/cancer related fields, RIGHT members have yet to organize a major international meeting/symposium/workshop.

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

Strengths and possibilities linked to the context

RIGHT is attractive for students as it currently has 14 and 24 PhD students in teams 1 and 2, respectively. The work of PhD students in promoted in two yearly meetings, of which one is organized by the students. Post-docs are prepared to scientific strategy by their participation to monthly PI meetings.
A further sign of attractiveness is the fact that 11 (assistant)professors have joined the unit in the past period and 6 former PhD students were recruited as assistant professor (5) or professor (1). The unit also recruited a permanent EFS researcher.
The ratio HDR/PhD students is good with 19 HDR for 14 PhD students and 17 HDR for 24 PhD students in teams 1 and 2, respectively. Two master's degrees are managed by UMR1098 RIGHT: "Host-graft Interactions" and "Molecular and Cellular Signalization". RIGHT has welcomed foreign students and professors: four PhD theses in collaboration with Algeria, Thailand (n=2) and Lebanon, three foreign postdoctoral fellows (i.e., Czech, Thai and Indian young researchers) and two invited associate professors/professors.

Weaknesses and risks linked to the context

The recruitment rate of permanent full-time researchers is low.

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

Strengths and possibilities linked to the context

The funding of the unit is consequent and diversified. The unit has been successful in being awarded European grants (2x Horizon 2020 (1 as leader), 2x Interreg (1 as leader), 1x FEDER RIS3, 1x IMI2 call "Engineered T cells, 1x Eurostars). Two Hubert Curien grants with Thailand were also obtained (5 hosted researchers from Thailand). At the national level, the unit leads the LabEx LipSTIC since 2018 (Investment for the future program). The unit has participated to 4 ANR grants, lead 1 young investigator ANR grant and has been awarded 12 clinical/translational grants (PHRC or PRT-K). National grants from Region or State (CPER) have allowed to support the technical platforms. Finally, 50 grants from charities/associations/foundations were obtained.
Overall, more than 75% of the yearly funding (estimated to 2M€/year expect in 2020) comes from external sources, which proves the unit's attractivity in terms of recognition by funding agencies.

Weaknesses and risks linked to the context

No weakness to report.

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

Strengths and possibilities linked to the context

RIGHT has three major plateforms: Biomonitoring platform (together with the CIC), the epigenetics EPIGENxp platform and the team called "Cellule d'interface et maturation en bioproduction" that are all three ISO9001 certified. The list of technological equipment available in the unit is complete and includes recent technologies such as Nanostring ncounter of 10X instruments.

Weaknesses and risks linked to the context

More permanent staff should be dedicated to the platforms.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The scientific productivity of the RIGHT unit is excellent.

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

Strengths and possibilities linked to the context

Members of the two main teams composing the RIGHT unit have significantly contributed to the advancement in the understanding of the pathogenic mechanisms and treatment of several clinically-related topics ranging from chronic inflammation, autoimmunity, transfusion medicine (team 1) to cancer epigenetics, immunity, immunotherapy and biomarker identification (team 2). The strong translational drive of the main studies conducted by RIGHT members is nurtured by basic research findings using pre-clinical models and human tissue specimens collected over the past years by unique biobanks, often coordinated by unit members. Through the UMQVC group, RIGHT has acquired over the past five years a reference position in the development of statistical methodology for risk prediction and stratification in clinical studies, in many of which RIGHT has been actively involved, often as coordinator.
The research production of the unit is by-and-large composed of publications summarizing high-end translational medicine and clinical studies with a total of 1118 publications between 2016-2022 (64% with unit members as first/last authors). Excellent clinical work has secured publication in prestigious specialist journals, reaching in some instances top medical journals including *the New England Journal of Medicine, Blood, and Lancet Oncology*. Original research articles have been regularly published in the best journals of the speciality including *Kidney International, Autophagy, Cancer Research, Cancer Immunology Research, Clinical Cancer Research, Leukemia and Journal of Immunotherapy of Cancer, Frontiers immunology, Cell Reports*. Some articles in prestigious journals have been also co-authored by RIGHT members including relevant ones published in *Journal of Clinical Oncology, Annals of Oncology, Science Immunology* and *Nature Communications*. Overall, RIGHT strives to publish in top, open access journals prioritizing, when possible, quality over quantity. Some collaborations, based on the sharing of some of the technological platforms developed by RIGHT, have occasionally ensured publications in more generalist journals such as *Nature Communications*. Strong national and international visibility of the unit is granted by the leading position that selected RIGHT unit members have in different fields including autoimmune cytopenias, transfusion medicine, cancer vaccines and anti-cancer cellular immunotherapies. Through the ROMI network initiated and coordinated by RIGHT, the unit is at the forefront in basic research and clinical studies focused on blastic plasma cytoid dendritic cell neoplasia.

Weaknesses and risks linked to the context

Development of high-end cellular and molecular biologics, outstanding collection of clinical samples and strong technological platforms is counterbalanced by limited conduction of fundamental research. This setting hampers the unit to exploit its full potential to make fundamental discoveries, as witnessed by the lack of publications in generalist journals with RIGHT members acting as first/corresponding authors.

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

Strengths and possibilities linked to the context

The unit's scientific productivity is well distributed among the teams, with tenured researchers and professors acting in most cases as corresponding authors, and graduate students producing at least one first-author paper before receiving their PhD title.

Weaknesses and risks linked to the context

The research potential of the unit appears under exploited. The strong technological platforms, the advanced expertise in the development of clinical grade biologics and the strong link with the clinical settings (including unique biobanks of human tissue and blood specimens) offer the ideal setting for RIGHT members to become international leaders in specific fields of interest, if only research topics had been more focused and prospective

hirings of talented post-docs and junior investigators directed towards studies on fundamental mechanisms of selected diseases.

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

Strengths and possibilities linked to the context

The compliance of RIGHT research activities with rules and values at the basis of scientific rigorousness and integrity is outstanding. All clinical studies are rigorously evaluated and approved prior to their implementation by hospital ethical committee boards. RIGHT members publish when possible open access articles and openly share published data and codes. The clinical department and methodology group (UMQVC) of RIGHT develops and shares statistical tools to ensure methodological rigor in clinical research without losing contact with the patient's benefit.

Weaknesses and risks linked to the context

No major weaknesses.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

Overall the contribution of both teams of the unit to industrial valorization and therapeutic applications is outstanding, with licensed patents, spin-offs, industrial partnerships and multiple contributions in the various axes connected to the academic and clinical research developed by the unit.

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

Strengths and possibilities linked to the context

The unit has an outstanding activity in terms of non-academic interactions. Both teams of the unit, individually or together, have established partnerships with multiple non-academic and industrial partners (Diaclone, Nanolive, Neurix SA, MED'INN'Pharma, Mallinckrodt Pharmaceuticals, Xenothera, Macopharma, CellProthera, Aurea Technologies, Smaltis, BioExigence …for ATI ; Argen-X, Novigenix SA, Bristol Meyer squibb, Astrazeneca , ALTE, AX, INVECTYS, Roche, Novartis… for TIM-C) in directions highly connected to their academic research. This concerns an impressive number of topics from drug formulations, vectorization with lipoproteins as nano-carriers, cell-based therapies, biomimetic matrix for regenerative medicine, glyco-humanized antibodies, generation of CART-cells against leukemia and solid tumors.
These activities allow national and international interactions or collaborations (notably with the Ludwig institute) and are also locally supported by academic partners (such as the consortium of laboratories LipSTIC LabEx, the CNRS/UFC research), and by initiatives linking academic partners to industrial applications, notably within the Institut Carnot OPALE. With the project to generate "universal" CMH-less macrophages, the unit also participates to the CELESTE Interreg project, which also provides access to various cell sources, including iPSC.
Advanced expertise in production of biologics (SuperMApo, UCPVax and IL-1RAP and CD123 CAR-T cells) has inspired the birth of spin-off companies which witness the attention RIGHT has towards medical exploitation of research findings. The creation of highly successful spin offs (Cancell Tx has already raised sufficient funds to cover Phase I first-in-man clinical trial in AML using IL-1RAP CART- cells) is matched to a "plateau technique ouvert" allowing technology transfer (in the BioInnovation building). The unit thus develops products for the socio-economic world, which are supported by Inserm Transfert, or the Direction de la valorisation of the EFS at the national level. The unit has partnerships with patient associations both in the fields of cancer oncohematology and kidney diseases, and has contributed to recommendations for the general public about ITP. Team 1 has contributed to recommendations from HAS ("Haute Autorité de Santé") about treatment of disorders such as giant cell arteritis, autoimmune hemolytic anemia and autoimmune thrombocytopenia in general. Team 2 also hosts several experts and opinion leaders (lung cancer, hematology) with national and international recognition. It hosts a national medical reference laboratory about plasmacytoid dendritic cell leukaemia.

Weaknesses and risks linked to the context

No major weakness.

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

Strengths and possibilities linked to the context

The unit has outstanding outputs in terms of economic and therapeutic applications. The unit has obtained in total 24 industrial contracts for a total sum of 3 320 k€ (team 1: STEMCIS, CCI productions, Legacy Healthcare, LFB Biotechnologies; team 2: Stemline, Immunogen, Argen-X, Novigenix SA, Bristol Meyer squibb, Astrazeneca , ALTEVAX, INVECTYS, Roche).
Two spin off companies have been set up (team 1: MED'INN'Pharma; team 2: Cancell Therapeutics). The spin-offs are highly successful and Cancell Therapeutics has notably now raised funds to cover Phase I first-in-man clinical trial in AML using IL-1RAP CART- cells.
Team 1 filed 4 patents, of which one about skin engineering and stimulating wound healing, is licensed to MED'INN'Pharma. Team 2 was also successful in filing 4 patents, of which two concerning IL-1RAP are licenced.

Weaknesses and risks linked to the context

No major weaknesses.

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

Strengths and possibilities linked to the context

The unit is regularly involved into scientific dissemination for opportunities like the "Fête de la Science", the "Nuit des chercheurs", a workshop ("Sciences en campagnes") associating scientists, journalists, and artists and workshops to interact with citizens, and the unit has collaborated to public exhibitions. Communication was also with Ligue Contre le Cancer donators' assembly, and patients'committees (as "*Les rendez vous Laurette Fugain*").
A number of papers in the general press were published about the outcomes of the unit and the activities of the spin-offs related to therapy. Communication was also through local radio channels (France Bleu Besançon, TV report on France 3 about CAR-IL1RAP) and through the unit's website.

Weaknesses and risks linked to the context

No major weakness.

C – RECOMMENDATIONS TO THE UNIT

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

The measures to monitor psycho-social risks and in particular risk prevention/management would benefit from the appointment of a person (or two) referent for equality, parity and prevention of sexual and gender-based violence in the unit.
The unit should invest more into investigating basic mechanisms of disease as well as supporting young group leaders. Attention should be brought to the continued formation of the technical staff.

Recommendations regarding the Evaluation Area 2: Attractiveness

Extend the international visibility to more members of the unit and try to increase the rate of permanent full-time researchers other than (assistant)professors, who have teaching obligations.

The unit could increase its attractivity by involving more members, especially from younger generations in editorial activities, congress presentations and organizations, responsibility roles in scientific societies, etc.

A focus to attract international postdocs and young group leaders would be welcome.

Recommendations regarding Evaluation Area 3: Scientific Production

The scientific productivity remains targeted to the best specialist journals. However, RIGHT has the potential to perform fundamental discoveries given the strong technological infrastructure and several unique biobanks of clinical specimens from which fundamental questions can be addressed (i.e. the biobank of BPDCN specimens offers the unique opportunity to perform high-end molecular and genetic studies to investigate the mechanisms of transformation and possible molecular vulnerabilities). A stronger and better integration of the activities conducted by the two teams is expected to further improve the quality of scientific publications of the unit bringing together complementary expertise and technological approaches to address fundamental questions related to immune tolerance/rejection in different pre-clinical and clinical settings.

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

The activity is excellent and the only recommendation can be to maintain such a high-level of innovation despite the energy now necessary for supporting the development of the spin-offs and of the multiple industrial partnerships.
Although there is no signal that this is currently a weakness, it is probably important in the future to remain focused and avoid dispersion into multiple disconnected projects.

TEAM-BY-TEAM ASSESSMENT

Team 1: Transplantation, Autoimmunity, Inflammation: Immune interactions and innovative Therapies (TAI-IT)

Name of the supervisors: Mr Didier Ducloux and Ms Celine Demougeot

THEMES OF THE TEAM

Immune-mediated inflammatory diseases, transplantation and biotherapies.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The former evaluation panel had recommended to "focus the too diversified topics and to recruit more young researchers".
The team reduced the number of research groups from 6 to 3 and focused their research on the three subjects: autoimmunity (located in Dijon), transplantation and transfusion and inflammation.
To date, they were not able to recruit a young researcher. A postdoctoral fellow recruited in September 2021 plans to apply for an Inserm researcher position in 2023.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	15
Lecturer and associate lecturer	8
Senior scientist (Directeur de recherche, DR) and associate	0
Scientist (Chargé de recherche, CR) and associate	1
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	12
Subtotal permanent personnel in active employment	**36**
Non-permanent teacher-researchers, researchers and associates	3
Non-permanent research supporting personnel (PAR)	5
Post-docs	4
PhD Students	18
Subtotal non-permanent personnel	**30**
Total	**66**

EVALUATION

Overall assessment of the team

The overall assessment of the team is excellent.

Strengths and possibilities linked to the context

The team is composed of 63 members (39.05 FTE). One of the strength of the team is to combine their expertise in allo-immunity (transplantation) and in auto-immunity (IMIDs), and to use fundamental findings for biotherapeutic applications.
Another strength is the access to patient cohorts.
Each of the three groups has significantly contributed to knowledge in their field. The scientific production of the team is fair with an average of 10 basic science papers published per year by the team and 6-7 publications in collaboration. More than half of the papers have been published in the best journals of the field (including *Blood, Kidney International, Am J Transplant, J Autoimmun*). The team also published 97 reviews, (some in high profile journals) and many clinical publications. Some members are associate editors of peer-review journals (eg *Front in Medicine, Front in Immunol*).
The team combines many expertises recognized nationally and internationally, with almost 30 invitations to international congresses, and the organization of several conferences including the first and second "resolution days" dedicated to the resolution phase of inflammation.
A strength of the team is its ability to use its fundamental observations as rational for the development of original translational studies, clinical trials (*eg* Trial APO-RA, based on immunomodulatory functions of autologous apoptotic cells; or the SISMIC clinical study based on the results suggesting that dysbiosis plays a role in end-stage renal-disease associated systemic sceptic inflammation), or toward innovative development with the creation of a start-up company, MED'INN'Pharma (MIP) to develop a drug candidate (SuperMApo) which now has 6 employees.
Despite the absence of recruitment of full time researchers on permanent positions, the team is attractive, as demonstrated by the fact that 6 professors or associate professors have joined them. Over the period 10 postdocs were recruited, mostly French, 4 are still ongoing. During the period there were 37 PhD students and 19 defended their thesis. The ratio of PhD students per HDR is correct. There are 14 ongoing theses.
The team received major grants as PI and coordinator, including for example 2x H2020 (EbolaTX and Support-E), 6 PHRC, and one that covers the whole team, from the Région BFC (Fibrolution, for the reprogrammation of macrophages to resolve fibrosis, 412k€). The overall amount of grant leverage is estimated at 450k€/year, over the evaluated period. Additional 270 k€ were raised through industrial collaborations.

Weaknesses and risks linked to the context

There is a critical need of full time permanent researchers in the team. There is only one permanent Inserm researcher with 0.2 FTE. Except students, all other permanent staff have clinical duties.
Most of the publications are in specialized journals of the field (transplantation, transfusion).
There is a limited recruitment of postdocs from abroad or even from elsewhere in France, as several (4) of them had done their PhD in the team before.
Separate locations of the different teams remain a potential weakness, despite the new building, that has become available in 2021.

RECOMMENDATIONS TO THE TEAM

Increase the number of permanent researchers. Strengthen the study of fundamental aspects of the diseases. Increase the attractiveness towards foreign postdocs.

Team 2: Therapeutic innovations in cancer immunology (TiCi)

Name of the supervisors: Mr Olivier Adotevi and Mr Yann Godet

THEMES OF THE TEAM

Cancer epigenetics, T-cell anti-cancer immunotherapies and cancer biomarkers.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

R1: increase international visibility of team 2 by favouring submissions to high profile journals in a more systematic way, and also by participating to European networks.
This has been achieved to some extent through co-supervising a PhD thesis on CAR-T with the University of Tripoli (Lebanon), 5 publications in high profile journals generated by the EPIGENExp Platform, and research programs/networks with international academic or private partners (H2020, ANR with EPFL [Lausanne, Switzerland], Interreg).

R2: The team should try to patent its findings, as this is a source of industrial collaboration and grant money as they have experienced in the past.
Four patents have been registered among which three deal with CAR-T cells. Two patents have been licensed to one of the two spin-offs of the UMR1098 RIGHT Unit, CanCell Therapeutics.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	11
Lecturer and associate lecturer	11
Senior scientist (Directeur de recherche, DR) and associate	0
Scientist (Chargé de recherche, CR) and associate	0
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	4
Research supporting personnel (PAR)	15
Subtotal permanent personnel in active employment	**41**
Non-permanent teacher-researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	8
Post-docs	3
PhD Students	27
Subtotal non-permanent personnel	**40**
Total	**81**

EVALUATION

Overall assessment of the team

The overall assessment of the team is outstanding.

Strengths and possibilities linked to the context

The team includes 77 members (54.5 FTE) and is structured into 4 groups combining studies on autophagy and T cell epigenetics with clinically-oriented investigations centred on development and testing of anti-cancer vaccines, T cell engineering, cancer biomarker identification and development of statistical methods for clinical studies. The team has recently highlighted the role of autophagy and T cell epigenetics in epithelial to mesenchymal transition of malignant cells, and cancer immune evasion. Team members study anti-cancer CD4+ T helper responses in cancer patients, including those receiving vaccination with anti-hTERT peptides. Development of anti-cancer vaccines is matched with advanced immune cell engineering to enhance NK- or CAR-T directed anti-tumor responses. Team clinicians collect and preserve in biobanks, precious human biological specimens from large cancer patient cohorts. They also coordinate the French ROMI consortium which has collected so-far specimens from over 240 BPDCN cases.
Each of the 4 groups significantly contributes to knowledge in their field. The scientific production is satisfactory with an average of 10 basic research papers by the team and 10 collaborative publications per year. More than half have been published in journals of solid reputation (including *Lancet Oncol, J Clin Oncol, Journal ImmunoTher Cancer, Clin Cancer Res, Leukemia, Blood Adv, Cancer Res*). The team also published about 50 reviews, and 300 clinical publications over the contract (one-third from the team, others as collaborations) (some in high-profile journals such as *Lancet Oncol* and *J Cin Oncol*). Some members are associate editors of peer-review journals *(Vox Sanguinis, Transf Med Rev, Front Immunol., Front Med*).
The team has internationally recognized expertise, having received 50 invitations to international congresses.
Translation of basic knowledge on hTERT peptides into the anti-hTERT universal cancer vaccine UCPVax, has inspired 4 independent clinical trials targeting different cancer types. Also, the expertise acquired in T-cell engineering has led to the design of 2 CAR-T cell constructs directed against new targets to treat myeloid leukemia and BPDCN. A tangible product of the team's activities is the birth of CanCell Therapeutics a spin-off company intended to produce GMP-grade anti-IL1RAP CAR-T cells for clinical studies.
Despite the limited recruitment of permanent full time researchers, the team is attractive, as demonstrated by the joining of 5 professors. Over the period, 7 postdocs were recruited, mostly French, 2 are still ongoing. During the period, 30 PhD students defended their thesis. The ratio of PhD student per HDR is adequate. There are 24 ongoing theses. The team received support from European, national and regional funding schemes including from the idex initiative, ANR, INca, PRTK, PHRC, Fondation ARC and PHRC, averaging 420K € per year over the last contract. An additional 2.9 million € were raised through industrial collaborations.

Weaknesses and risks linked to the context

While the unit's translational research program is outstanding, the preclinical studies are less well developed.

RECOMMENDATIONS TO THE TEAM

The mechanistic aspect of the research program could be improved. Increase the attractiveness for international postdocs.

CONDUCT OF THE INTERVIEWS

Date

Start: 23 janvier 2023 à 08h00

End: 23 janvier 2023 à 18h00

Interview conducted: online

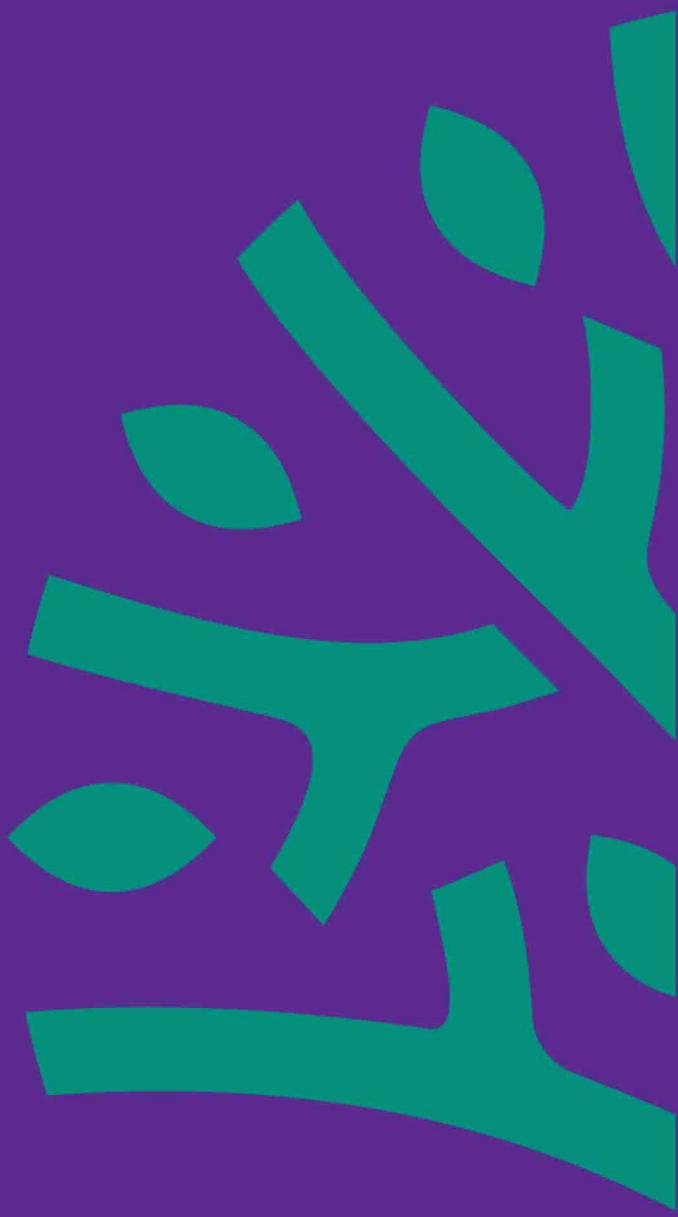
INTERVIEW SCHEDULE

8:55-9:05	Hcéres Rules and procedures by B. Bartosch Public Session (all unit members)
9:05-11:00	Administrative and Scientific presentations of the unit 20' P Saas / O Adotévi, overall presentation of the unit 20' Discussion 20' D Ducloux/C Demougeot, Team "Autoimmunity, Transplantation and Inflammation" 20' Discussion 15' O Adotévi/Y Godet, Team "Immunomolecular Therapies in Cancer" 20' Discussion Public Session (all unit members)
11:00-11:30	Debriefing committee and break (closed door meeting)
11:30-12:00	Meeting with ITAs (in French) In the absence of any managing staff
13:00-13:30	Meeting with researchers In the absence of any managing staff
13:30-14:00	Meeting with post-docs and students In the absence of any managing staff
14:00-14:15	Debriefing (closed door meeting)
14:15-14:45	Meeting with Institution Representatives: UFC, Inserm, EFS (closed door meeting)
14:45-15:15	Meeting with the Management Team of the Unit (closed door meeting)
15:15-18:30	Redaction of the final report (closed door meeting)

GENERAL OBSERVATIONS OF THE SUPERVISORS

In despite of the Hcéres' solicitations, no observations were received within the prescribed timeframe.

The Hcéres' evaluation reports are available online:
www.hceres.fr
Evaluation of Universities and Schools
Evaluation of research units
Evaluation of the academic formations
Evaluation of the national research organisms
Evaluation and International accreditation



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