Research evaluation

EVALUATION REPORT OF THE UNIT

CHIP – Cancer, hétérogénéité, instabilité et plasticité

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Institut Curie

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

EVALUATION CAMPAIGN 2023-2024

GROUP D

Rapport publié le 31/01/2024

High Council for evaluation of research and highter education

In the name of the expert committee[1]:

Patrick Mehlen, chairman of the committee

For the Hcéres[2]:

Stéphane Le Bouler, acting president

In accordance with articles R. 114-15 and R. 114-10 of the Research Code, evaluation reports are signed by the chair of the expert committee and countersigned by the Hcéres chair.

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

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

MEMBERS OF THE EXPERT COMMITTEE

Chairperson:	Chairman Mr Patrick Mehlen, CNRS Lyon
Experts:	Vice Chair woman Ms Julie Pannequin, CNRS Montpellier Mr Robert Ballotti, Inserm Nice Mr Fréderic Chibon, Inserm Toulouse Ms Anabelle Decottignies, Université de Louvain, Belgique Ms Céline Delloye-Bourgeois, CNRS Lyon Mr Stephane Depil, Université de Lyon Ms Nathalie Douet-Guilbert, Université de Bretagne Occidentale - UBO (representative of CNU) Mr Christophe Ginestier, Inserm Marseille Mr Éric Letouzé, Inserm Nantes Mr Eddy Pasquier, CNRS Marseille Mr Niclas Setterblad, Sorbonne Paris Cité (supporting personnel)

HCÉRES REPRESENTATIVE

Mr Kamel Benlagha

REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

Ms Camille Chaudonneret, Inserm
Mr Alain Eychène, ITMO Cancer
Ms Tatiana Malherbe, Institut Curie
Mr Arnaud Tourin, PSL (excusé)

CHARACTERISATION OF THE UNIT

- Name: Cancer, hétérogénéité, instabilité et plasticité
- Acronym: CHIP
- Label and number: U830
- Composition of the executive team: Mr Olivier Delattre (director), Mrs Fatima Mechta-Grigoriou (deputy director)

SCIENTIFIC PANELS OF THE UNIT

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

THEMES OF THE UNIT

The unit Cancer, Heterogeneity, Instability and Plasticity is one of the 13 research units working on the sites of Institut Curie. The main theme of the unit is cancer biology. The six teams constituting the unit are purely working on themes directly related to cancer, pediatric cancers for the teams of O. Delattre and of G. Schleiermacher/F. Bourdeaut, cancer microenvironment for the team of F. Mechta-Grigoriou, the role of DNA repair in cancer for the teams of M.H. Stern and R. Ceccaldi, and finally computational biology applied to cancer for the team of Joshua Waterfall. The unit is obviously holding all the recent technologies and expertises to adequately study the theme of cancer biology.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The U830 unit initially named "Genetic and Biology of Cancer" was initially created in January 2007 with the exceptional lead of O. Delattre. It was renewed in 2013 and then in 2019 with a different name (Cancer, Heterogeneity, Instability and Plasticity) because of the integration of additional expertises and teams. It has historically evolved from a unit centered around the theme developed by O. Delattre to a more multi-thematic unit when other teams/expertises have joined. The U830, currently composed of 6 teams, is located at the main Institut Curie Paris site but spread in different locations in the research center. The unit will, in the new contract, allow the development of two new units based on the two main avenues developed in the current unit. One unit will focus specifically on pediatric cancers and will be headed by O. Ayrault while the other unit will focus on multidisciplinary aspects of cancer biology with specific interests in chemical biology and tumor plasticity/heterogeneity and will be headed by F. Mechta-Grigoriou.

RESEARCH ENVIRONMENT OF THE UNIT

The research environment of the U830 unit is the one of Institut Curie (associate member of the Université PSL) located in an area of Paris with a dense collection of research structures such as École Normale Supérieure-PSL, Collège de France, ESPCI Paris-PSL or Institut Pasteur. The U830 is intrinsically involved in several ambitious structuration projects such as the Curie-SIRIC (from National Cancer Institute-INCA) initially headed by O. Delattre, the PIA RHU Cassiopeia headed by F Mechta-Grigoriou, the PIA RHU ATRACTion and more recently the PIA IHU "cancer des femmes" headed by A Vincent Salomon and the Center of Excellence for Pediatric Oncology Research (PEDIACRIEX23) Paris Kids Cancer headed by O. Delattre.

UNIT WORKFORCE: 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	4
Chargés de recherche et assimilés	5
Personnels d'appui à la recherche	40
Sous-total personnels permanents en activité	**49**
Enseignants-chercheurs et chercheurs non permanents et assimilés	8
Personnels d'appui non permanents	0
Post-doctorants	12
Doctorants	20
Sous-total personnels non permanents en activité	**40**
Total personnels	**89**

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
INST CURIE	0	1	73
Inserm	0	9	10
AUTRES	1	1	2
Total personnels	**1**	**11**	**85**

GLOBAL ASSESSMENT

The U830 unit combines both high-level basic research and highly visible translational/clinical research. The unit is clearly one of the most visible of Institut Curie and one of the most directly focused on cancer research.

Research findings have been published as a large number of scientific and clinical articles, with many contributions in top-tier journals. The presence of key top-level team leaders with international recognition makes the U830 a leading unit in the field of cancer biology. The two thematics of pediatric cancer and tumor microenvironment have acquired clear international recognition.

In terms of attractiveness, the unit is considered as outstanding with successes in very competitive funding schemes such as three ERC, RHU, SIRICs. Team leaders of the unit are very well integrated in the Curie Institute and have been successful in highly visible structuration/funding projects such as the INCA SIRIC, the INCA PEDIACRIEX, the PIA IHU "cancer des femmes", the PIA Equipex ICGex, ERA-NET Transcan Chrysalis, IMI2 ITCC-P4, UM CURE, iPC H2020, Lquidhop, H2020 Vagabond ITN, and Fight Kid Cancer, two teams labelled by la Ligue Nationale du Cancer and more than 10 ANR or INCA funded projects.

The quality of the scientific production in the unit is globally outstanding with repeated publications in *Nature, Cancer Cell, Cancer Discovery, Nature Communication, JNCI, Nature Cancer, Mol Cell.*

The highlights of the unit are the identification of new DNA repair mechanisms in mitosis, the characterization of populations of CAFs with immunosuppressive or metastasis promoting functions, the identification of neoantigens in malignant rhabdoid tumors, uveal melanoma, the identification of plasticity mechanisms in neuroblastoma and Ewing sarcoma, the metabolic heterogeneity of ovarian cancers, the characterization of predisposition and susceptibility genes in uveal melanoma and Ewing sarcoma, the monitoring of genetic abnormalities in a clinical context in pediatric cancers.

The overall condition of work is described as excellent. In terms of training, PhDs and post-doctoral fellows from the different teams have produced well to extremely well.

In terms of valorisation, the unit is also considered as outstanding with 21 patents during the last contract and three start-up founded, as well as impactful public outreach activities.

Overall, the unit is outstanding with five teams assessed as outstanding.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The main recommendation in the previous report was to continue the publication of outstanding research and this has been achieved with publications in *Nature, Cancer Cell, Cancer Discovery, Nature Communication, JNCI, Nature Cancer, Mol Cell*. Other recommendations such as increasing the number of "conseil de laboratoire" and to "stabilize" ITA were put into action.

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 scientific objectives of the unit have been reached. The quality of the research performed in this unit is overall outstanding. Publication in major journals, such as *Nature, Cancer Cell, Cancer Discovery, Nature Communication, Nature Cancer, Mol Cell*., participation in and spearheading of large national and European structuration grants demonstrate the scientific visibility of the leading researchers of this unit.

Assessment on the unit's resources

The unit resources appear outstanding. It has readily access to the different exceptional technological core facilities of Institut Curie. The unit receives only minor core funding from the national bodies (Inserm-Université) but each team has secured impressive competitive fundings (RHU, ERC, IHU, SIRIC, etc.) so it seems that no budget limitation hinders the development of the ambitious scientific program. In terms of technical support, the number of permanent Inserm technical staff is far more important than the average in France.

Assessment on the functioning of the unit

The functioning of the unit appears very good. Technical staff, PhD students, post-doctoral fellows appear to be very satisfied to work in such a stimulating environment. Lack of personal interaction between individual teams has been noted and could be improved by the organization of periodic unit retreat.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The unit has all the necessary resources either in the unit or in the Institut Curie, a leading institution in basic research in France. The relatively small unit is quite attractive for young researchers with 5 CRCN recruited over the last contract.

Weaknesses and risks linked to the context

For a relatively small unit (17 researchers and less than 100 FTE) the variety of lines of research, the diversity of locations of each individual team and pressure on space do not support strong collaborative projects. Future buildings will allow the two emerging units to have more dedicated space.

The unit has resources that are suited to its activity profile and research environment even though it has to be noted the modest recurrent funding from Inserm (250keuros/year).

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

Strengths and possibilities linked to the context

The unit benefits from key French researchers who have international visibility and who have a large scientific vision. Clear objectives have been proposed and have been reached. Modern technologies such as single cell RNAseq, spatial transcriptomics, high-throughput genomics, microfluidic devices are available and used extensively in the unit. They have access to multiple types of human samples including liquid biopsies. The unit has clearly been at the forefront of pediatric cancer research, tumor microenvironment research and more recently DNA repair over the last contract.

Weaknesses and risks linked to the context

None.

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

Strengths and possibilities linked to the context

The unit appears to comply with the regulation on human resources, management and safety. An Ethical committee appears to efficiently tackle the possible issues associated with scientific conduct in the unit.

Weaknesses and risks linked to the context

No specific weaknesses have been noted linked to context.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The unit is globally very attractive. Key researchers of this unit are regularly invited to the most prestigious international conferences on cancer. The unit researchers have also organized several international courses. It is worth noting that only two researchers have editorial board responsibilities. Two members of the unit are elected EMBO members and have received multiple awards. Attractivity is attested by the important number of PhD students and post-doctoral fellows in the units. The unit is very attractive because of three ERC grants (one synergy, 1 starting and 1 proof-of-concept), one grant from DOD, one RHU grant, two SIRIC, one IHU and one Equipex grant. The unit is also very attractive in regards to the exceptional equipment and core facilities.

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

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

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

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

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

The unit has regular publication in major journals, such as *Nature, Cancer Cell, Cancer Discovery, Nature Communication, Nature Cancer, Mol Cell*. Key researchers of this unit are regularly invited to the most prestigious international conferences on cancer (AACR, ESMO, Keystone meetings).

The unit has the ability to recruit new teams during the last contract, to recruit new Inserm researchers during the last contract but also by the overall wellbeing of the various laboratory members.

The unit is outstanding because of the recognition gained through its success in competitive calls for projects such ERC, RHU, PIA Equipex, SIRIC pediacriex.

The unit has major equipment and technological skills as the unit is part of the Institut Curie, a leading institution in basic research in France.

There is an excellent participation in Scientific Advisory Boards even though most of them are French structures or institutions.

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

The main but relative weakness is the relative unbalance between the two most renowned team leaders and the other team leaders who are conducting excellent to outstanding research but who are less visible. It is also interesting to note that few junior teams have been welcomed in the unit during the last period while the excellent leadership of the head of the lab will not continue in the next contract.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The scientific production of the unit is globally outstanding. The unit has published with PIs as last/corresponding authors and PhD students/post-doc as first/Co-first authors in the best journals such as *Nature, Cancer Cell, Cancer Discovery, Nature Cancer, Nature Communication*. They have produced both basic research but also data of pediatric clinical research in journals such as *Cancer Discovery*.

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

Integrity appears to be a central point of vigilance at Institut Curie and thus indirectly in the unit. Institut Curie has appointed a Scientific Integrity Officer and has received the European Human Resources of excellence in research award. Open Science is used as much as possible in the unit.

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

No weaknesses has been noted to the context.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

Teams of the unit have collaborative projects with the economic world as shown by a RHU grant involving academic labs and pharmaceutical companies. They report PhD students under the Cifre status and an exclusive license of patents filed thanks to researchers of the Unit. They filled 21 patents over the last period which is excellent.

Researchers of the unit appear to be highly involved in outreach activity toward the general public.

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

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

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

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

The theme of pediatric cancer is highly exposed to the general public with a large number of communications to the general public by all pediatric cancer team leaders. More generally researchers of the unit were invited to discuss cancer research in various journals/broadcasts such as *Le Monde*, TF1, BFM-TV.

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

There is no specific weakness in this specific general area.

ANALYSIS OF THE UNIT'S TRAJECTORY

The unit has grown over the years as one of the most visible research units in Institut Curie. The national and international leadership of the unit director and his contribution to the genetics of pediatric cancer has put light on this unit over the last decade. The addition, over the years, of teams of excellence exploring other topics of cancer biology such as the contribution of the tumor microenvironment, epigenetics of cancer or DNA repair have increased the strength of the unit but also somehow induced a decrease in the scientific identity of the unit. This has, and the committee fully endorses this proposal, led to the separation of this unit into two separate units that will benefit both from the recruitment of additional teams. The pediatric topic will, in the next contract, become a full unit dedicated to pediatric cancer research and will benefit from the addition of the excellent team of Olivier Ayrault, who will become the next director of the unit. The committee fully endorses the proposed project, which is a very elegant combination of pure basic pediatric research, computational biology and clinical questions. Fatima Mechta-Grigoriou will lead the other unit, which aims at exploring further the power of innovative chemistry into the biological questions of heterogeneity and plasticity of cancer. This new unit named CBC builds on the strengths of the former unit directed by Ludger Johannes, which included chemistry expertise associated with various teams of both the current U830 unit and additional teams joining the Paris Curie site. Altogether the committee is convinced that both units will produce outstanding science.

The profile, resources and organization of the unit appear excellent. The two proposed units appear very attractive.

The CONCERT unit has been very elegantly presented by the future director O. Ayrault. The committee, who is praising the quality of the proposed science and the efforts of synergy between the constitute teams is particularly attentive to three aspects:

(i) O. Ayrault appears to be an excellent choice to head this unit. However, because of the timeline of a new space availability dedicated to this unit, O. Ayrault has proposed to move alone to the Paris site while his lab will stay in Orsay. The committee believes that this will jeopardize the quality of the research of O. Ayrault while the director of the unit needs to be an international scientific leader. The committee urges the national research bodies (Institut Curie, CNRS and Inserm) to help the move of the whole team of O. Ayrault or if members of the teams are not keen to move to the Paris site, the recruitment of new permanent staff members and attribution of dedicated space to allow O. Ayrault to conduct high level research as he has been doing in the past appear mandatory.

(ii) The proposed split of the Bourdeaut/Schleiermacher team in two teams makes sense as there was little scientific interaction between the two PIs in the former team. However, the two proposed teams will rely on team leaders who have clinical duties and no senior scientist to help them conduct high level research. This is more particularly true for the future team of F. Bourdeaut who is proposing a very elegant question-driven translational research that will require full time dedicated researchers. For the team of G. Schleiermacher, while the committee recognizes the excellence in clinical research, they would recommend a transition from technology-driven research to more question-driven research.

(iii) The quality of the research conducted by O. Delattre on Ewing Sarcoma is outstanding but the current proposed composition of the Delattre team is only based on technical staff members and post-doctoral fellows. Losing the Ewing Sarcoma contribution when O. Delattre will retire would be a major loss for French medical research visibility. The committee is thus recommending that during the next contract, O. Delattre identifies a junior researcher/post-doctoral fellow and allows them to grow with him and take over the Ewing Sarcoma project.

The CBC unit has been very convincingly presented by the future director F. Mechta-Grigoriou. The story-telling on the importance of merging chemical biology with outstanding questions of cancer biology is outstanding and the committee has no doubt that the excellent teams composing the CBC unit will produce outstanding science and possibly candidate drugs that may help to fight cancer. The committee was not in a position to evaluate the different teams of the future unit but the quality of the teams and the goodwill of the future director is obvious. The committee is however expressing some concerns:

(i) The committee recommends to take the possible issue of gender balance when looking at a future unit where only one team leader is female. The committee is recommending to welcome or to promote additional female team leaders in the next contract.

(ii) The Ceccaldi team is developing a very promising outstanding line of research, however it is unclear whether the lines of research conducted in his team have any relevance to the main topics of the new unit. This outstanding team should consider either joining another unit in Curie focused on DNA repair or extending his research questions to heterogeneity/plasticity.

(iii) The presence of Raphael Rodriguez in the new proposed unit is mandatory for the link between chemistry and biology that the committee wonders whether adding him as a deputy director could help the good functioning and overall visibility of the unit.

(iv) The quality of the research performed by the chemistry teams should be protected and the committee is somehow concerned that the chemistry would become at the service of the biological teams. The committee wonders whether the unit director should consider setting up a platform where the chemistry expertise is provided to the biological teams while the chemistry teams could continue developing their own research projects.

RECOMMENDATIONS TO THE UNIT

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

None.

Recommendations regarding the Evaluation Area 2: Attractiveness

The attractivity of the unit does not raise any doubt. There is no specific recommendation for this aspect as the unit will close together with the emergence of two units that appear very attractive.

Recommendations regarding Evaluation Area 3: Scientific Production

There is no specific recommendation for this aspect as the unit will close together with the emergence of two units that will produce outstanding science.

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

There is no specific recommendation for this aspect as the unit will close.

TEAM-BY-TEAM ASSESSMENT

Team 1: Diversity and plasticity in pediatric tumors

Name of the supervisor: Mr Olivier Delattre

THEMES OF THE TEAM

The team is involved in the genetic and biological study of Ewing tumours (EwS), malignant rhabdoïd tumours (MRT) and neuroblastoma (NB) for which they could identify major primary genetic abnormalities. Most of these tumours develop from embryonal tissues and constitute accidents of development rather than of tissue renewal or ageing. The team studies their mechanisms of initiation and progression, with three main topics: transcription regulation by methylation, tumor heterogeneity by single cell analysis, and cell plasticity.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

No recommendations from the previous report beside: "maintaining the current excellent activity and publication level". The team clearly fulfill this objective with its outstanding production as attested by major publications in PDC.

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	2
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	14
Sous-total personnels permanents en activité	**17**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	0
Post-doctorants	3
Doctorants	5
Sous-total personnels non permanents en activité	**9**
Total personnels	**26**

EVALUATION

Overall assessment of the team

This is an outstanding team which produces highly relevant work related to genetic alterations involved in oncogenesis of pediatric sarcomas. The team is the world leader in the field with an outstanding level of production. It contributed to 97 publications (25 PDC) during the contract period including *Nat Genet, Cancer Cell, Mol Cell, Nat Comm, JITC*. The team has a strong fundamental activity and obtained numerous results with high clinical potential. Beside the pediatric sarcoma's research projects, the team has developed a strong activity on neuroblastomas. The team is well structured into several subgroups led by senior researchers/clinicians, each of which has an excellent visibility and a remarkable capacity to obtain funding (From European and national sources). The attractivity of the team is outstanding which is concretized by the recruitment of clinicians/researchers which became PI. The team had registered two patents.

Strengths and possibilities linked to the context

The team is the world leader in the field of oncogenesis of pediatric sarcoma. Specially, the team opened new field of fundamental and clinical investigations demonstrating that EWSR1: FLI1 creates thousands of neo-enhancers throughout the genome making EwS a paradigm for oncogene-driven genome-wide reprogramming.

Over the years a senior scientist in the team has become a reference in the field of neuroblastomas. Recently, they contributed to the characterization of the immune microenvironment of neuroblastomas.

Different members of the team have been awarded for prestigious prices (AACR prize, Prix Académie des Sciences), including the team leader who was awarded by the "Inserm Grand Prix 2022". The team members are largely invested and very active as experts for different research evaluation committees (*Ligue Nationale Contre le Cancer*, Inserm CSS2, SFCE, INCa).

The team leader is director of SIREDO (pediatric oncology center which gathers clinicians and scientists in the pediatric oncology field) and is Coordinator of the Paris Kids Cancer PEDIACRIEX application which gathers Gustave Roussy, AP-HP and Institut Curie.

The team repeatedly obtained funding from international (IMI2 (European Consortium, ERC synergy) and national sources (Équipe labélisées Ligue, INCA PLBIO, ANR, ARC-Transcan 2).

Weaknesses and risks linked to the context

Despite the high quality of the research and the potential of attractiveness it creates, the team did not generate recurrent links with non-academic partners. The academic/industrial interface may be further explore.

Analysis of the team's trajectory

The current "Diversity and plasticity in pediatric tumors" team will give rise to 2 distinct teams in the future Childhood Oncology Research Unit: one that will be led by Dr O. Delattre and another one by Dr I. Janoueix-Lerosey.

Dr Watson will join the Rodriguez's team to lead an ambitious research program focussed on DD/WD-LPS.

Staff members are split between the Delattre and Janoueix-Lerosey teams to allow each team to assess their future respective research.

The projects presented demonstrate that they will pursue a high level research on neuroblastoma (Janoueix lab) and Ewing sarcoma (Delattre lab), both focusing on cell plasticity and cancer immunity.

One limitation may reside in the retirement in the coming years of Dr. O. Delattre. The future team led by O. Delattre is only constitued of PAR and PhD/postdoc fellows. There are questions about the continuation of the Ewing projects, which spearheaded the whole unit.

RECOMMENDATIONS TO THE TEAM

The committee recommends to maintain the current outstanding activities and publication level. The identification, within the next mandate, of a PI co-leading the team dedicated to Ewing sarcomas may help to perpetuate this unique activity in the coming years.

Team 2: Stress and Cancer

Name of the supervisor: Ms Fatima Mechta-Grigoriou

THEMES OF THE TEAM

The team has previously established tight relationships between chronic oxidative stress and tumor progression as well as chemosensitivity, in particular in breast and ovarian cancers. The red wire of the projects consists in defining the cellular and molecular bases of both tumor and stromal cell heterogeneities to decipher their impact on cancer progression and response to treatments. The research is structured around 3 axes focused on subtypes of cancer-associated fibroblast (CAF) in breast cancers and their clinical exploitation (Aim1); cellular and metabolic heterogeneity of high-grade serous ovarian cancers (Aim2); and the development of immunocompetent ex vivo devices (tumor-on-chip) to study tumor microenvironmental heterogeneities and to model the effect of therapies (Aim3).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Given its scientific excellence, the team was encouraged to apply for prestigious **European grants**. This item was perfectly addressed as the team leader applied for and obtained two major European grants (two Transcan EURANET grants -360k€ as coordinator, and 300k€ as a collaborator-), and one EURECA project for funding of a PhD student. Of note, the team leader is the coordinator of the recently obtained RHU CASSIOPEIA grant, a major funding promoting both the visibility of the team and the translational axis of its research.

As requested, the team increased the **number of members with an HDR**, with a permanent Inserm researcher that defended her HDR.

A point of attention was to harmoniously manage the **integration of clinical issues** addressed by Pr. Zalcman, PU-PH, who joined the team. Scientific implementation of the lung cancer indication was made in CAFs and Tumor-on-Chip projects. Above all, key publications (*Cancer Discovery 2020*) and the RHU label are concrete illustrations of the strong complementarities in the team, allowing to address major translational issues.

To ensure the **feasibility of novel projects** that rely on the use of breakthrough technologies, as recommended, the team has worked with expert platforms in particular for metabolic profiling and single cell/spatial omics. More precisely, regarding the tumor-on-chip project that is now developed by MC Parrini (IRHC, Inserm), the team collaborates with the physicists of the Curie and Pierre Gilles de Gennes institutes.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	8
Sous-total personnels permanents en activité	**10**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	0
Post-doctorants	3
Doctorants	6
Sous-total personnels non permanents en activité	**11**
Total personnels	**21**

EVALUATION

Overall assessment of the team

Overall, the team had an outstanding research activity during these last 5 years. In particular, the track record is outstanding. The attractivity of the team is also outstanding with impressive grant success and a significant number of students and engineers either in wet lab or bioinformatic. The recent RHU will enable the team to rapidly translate their findings in clinic. Cutting edge technologies are used to address very relevant questions with high translational impact.

The valorisation activities, teaching involvement and inclusion in the society are excellent.

Overall, the committee has no weak point to raise despite the importance to attract new researchers to support the team leader.

Strengths and possibilities linked to the context

The team leader has been successful in recruiting an excellent independent scientist who has already got her HDR which will be beneficial for the PhD supervision. The team attractiveness is excellent which is witnessed by the number of PhD students (6 during the period). The team leader is frequently invited to prestigious congress (AACR, EACR, keystone, etc.) and the lab members have often the opportunity to present their latest research. Over the past mandate (2018-2023), the team has published an amazing number of findings including in very high impact factor journals such as *Cancer Cell, Cancer Discovery, Cell Metabolism and Nature communications*. Additionally, clinicians with amazing number of publications increase even more the track record of the team. These clinicians have a strong involvement in the life of the team (including regular participation to team meetings) who is doing translational research. Moreover, Pr Anne Vincent-Salomon recently joined the team thus strongly increasing the visibility of the team on women's cancer, as she is leading the Women's Cancer Institute (IHU). The publication list enabled the team to obtain numerous grants from many agencies (INCa, foundation ARC, Ligue contre le cancer, ITMO, ANR, etc.) which represents a huge amount of money (almost 5 million euros as a PI and almost 1 million as a collaborator). Researchers and research engineers have also been successful in getting grants during the period of evaluation. Amongst these grants, it is important to highlight the competitive RHU project CASSIOPEIA which will enable the team to rapidly translate their results from bench to bed.

In recent years, the team has brought breakthrough findings in tumor heterogeneity and plasticity in both breast and ovarian cancer. Notably, the team leader has now became a key opinion leader (KOL) in the field of cancer associated fibroblasts (CAF) heterogeneity.

Thanks to experts in the team, they address highly relevant topics such as metabolic plasticity and tumor-on-chip (ToC) models. To address their questions the most cutting-edge technologies are used and the team became a true reference in scRNAseq and spatial transcriptomic including high skills in bioinformatic. The latter is the results of intense efforts to recruit in house bioinformatician and to train students and has led to the development of cutting-edge inovative analytical pipelines. During the period, four patents have been filled.

Multiple interplays with industrial partners have been set up enabling the team to get Cifre fellowships as well as partnerships in grants (Innate Pharma (150k€), Institut Roche (163k€) and Fluigent (150k€)). In particular, the RHU CASSIOPEIA (10 M€) involves partnerships with Roche and Institut Roche.

A remarkable effort has been done to include the team research in the society with radio interviews given by the team leader and team members participate to general audience events.

The team leader is involved in the organization of the Curie Institute, in the teaching, in the scientific committee of the ARC foundation and she is the director of the "Cancéropole Île-de-France". In addition, she has many commitments in European finding bodies.

Weaknesses and risks linked to the context

Even if the team has been very successful these recent years, additional researchers with HDR would be helpful to support the team leader.

Analysis of the team's trajectory

The team is a leader in the field of tumor microenvironment and its relationship with tumor cell heterogeneity with an international recognition. The team proposes to capitalize on its solid bases to continue to decipher the role of cancer-associated fibroblasts (CAFs) in sustaining tumor resistance to treatment. The team proposes to use up-to-date technological approaches (spatial transcriptomic, microfluidic devices, etc.) to evaluate the impact of CAFs on the tumor cell plasticity dynamics and the metabolic rewiring under treatment. The team has already setup a solid workflow to obtain patient samples, to use complex bioinformatic pipelines to analyze OMIC data, and to validate molecular mechanisms using ToC models (Tumor-on-Chip). The research project is innovative and ambitious and should lead to the definition of a thorough portrait of the tumor ecosystems. The scientific community needs to reach this milestone to improve patient care and potentially stimulate the development of stroma-targeting strategies to treat cancer patients. Moreover, the RHU CASSIOPEIA coordinated by the team leader will be a great opportunity to translate their results into clinical trials.

The main challenges of the team in the next years will be the move to a brand-new unit ("Chemical Biology of Cancer" unit). The team leader will become the director of this Unit. Currently, only twos permanent senior scientists (including the team leader) compose the team. The workload related to new management activities of the team leader may destabilize the team's smooth running. The recruitment of an additional senior scientist may help to prevent any related problems.

Moreover, it seems that few collaborations with the other teams composing this new unit have been established. Joining a new unit is an opportunity to aggregate new expertise. The committee strongly suggests to identify transversal research programs to facilitate team integration and to promote the emergence of original research programs.

RECOMMENDATIONS TO THE TEAM

The committee would like to congratulate the team for the outstanding research performed these last 5 years. Taken together the fundings and human resources, the committee has no doubt that this quality of science will last. Following this amazing and unique description of CAF heterogeneity, the committee is looking forward to learning deeper into the molecular mechanisms underlying such heterogeneity and plasticity. The only obvious recommendation to the team would be to potentially attract new researchers to stabilize the team and support the team leader.

Team 3: DNA repair and uveal melanoma

Name of the supervisor: Mr Marc-Henri Stern

THEMES OF THE TEAM

The team's activities are focused on alterations of DNA repair in human genetic diseases and cancer and particularly on homologous recombination deficiency. Research projects are both fundamental and translational and patents were obtained.
More recently, most of the research has focused on uveal melanoma.

Four key facts of research should be highlighted:

1) The identification of new low-penetrance susceptibility genes in uveal melanoma (TERT/CLPTM1L, IRF4, HERC2). The at-risk SNP in TERT/CLPTM1L is associated with long telomeres.
2) The team also discovered that the rare uveal melanoma patients who responded to anti-PD1 had a high mutational load (CpG>TpG) which was due to an inactivating mutation of MBD4.
3) The team continued its studies on SF3B1 mutations (20% in UM) showing that these good prognostic mutations are associated with alternative splicing that creates neo-epitopes (common to all SF3B1mut tumors) that could be the target of a curative vaccine.
4) Finally, thanks to a long-standing collaboration with the Circulating Cancer Biomarkers Team, the group developed efficient methods to detect circulating tumor DNA in UM patients. Patents were obtained.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The main recommendations of the previous Hcéres report were to: i) improve the level of publication; ii) increase the task force and; iii) focus on specific aspects of the project.

Overall, the level of publication has improved (not only in number, but also taking into account the journals in which the papers were published). Importantly, papers with good impact in the area of uveal melanoma were published.

External financial resources and collaborations with industry have also been strengthened.

With regard to the other 2 points, which are obviously linked, the team is determined to remain modest in size, but stresses that it is going to expand thanks to recently obtained funding.

The team is also keen to develop a wide range of projects, because diversity feeds their creativity.

In view of the results obtained in recent years, it is fair to say that, to a certain extent, recommendations have been taken into account by the team.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**6**
Enseignants-chercheurs et chercheurs non permanents et assimilés	3
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	2
Sous-total personnels non permanents en activité	**6**
Total personnels	**12**

EVALUATION

Overall assessment of the team

The team has secured its reputation in the two areas of HDR and UM. With a total of 84 papers published over the 2017-2022 period, the team has shown an excellent to outstanding productivity.

The team's funding capacity is very high. A recent grant from the US Department of Defense to develop therapeutic vaccines against metastatic UM confers an excellent to outstanding attractiveness to the team.

They have transferred many of their discoveries to the clinic and their applications represent major advances in the personalized management of UM and cancers in general. The valorisation is outstanding.

The team is globally outstanding.

Strengths and possibilities linked to the context

The team DRUM, co-led by Mr Marc Henri Stern (DR1 Inserm) and Dr Manuel Rodrigues (oncologist), is relatively small. The organigram mentions 13 members (in addition to the leaders, 1 CRCN Inserm, 2 clinicians, 5 engineers, 2 post-doctoral fellows, 1 PhD).

The team focuses on the study of DNA repair, with 5 publications in the field, including 4 on alterations associated with Ataxia telangiectasia, (last author MH Stern). One of these publications identifies new NBN variants (Nijmegen breakage syndrome, NBS) which affect the localization of ATM encoded by the gene mutated in ataxia-telangiectasia. Two other publications describe genotype/phenotype analyses of ATM mutants, with a fairly detailed description of detection and classification methods, in a methods' article. A work on the identification of tumors with homologous recombination deficiency (HRD), has led to numerous collaborative projects, 2 publications as last-author (T Popova and M Rodrigues) and a patent. The signature identified has been validated in prospective clinical trials and represents a clear advance in HRD diagnosis.

However, the major research area concerns uveal melanoma (UM), which is associated with 22 publications with team members as last author (16 by Mr Stern, 2 by Ms Popova, 2 Ms Alsafadi* and 3 by Mr Rodrigues).

The work on the identification of new UM susceptibility genes (TERT/CLPTM1L, IRF4, HERC2) with low penetrance is particularly noteworthy. The SNP at risk creates in TERT promoter a new binding site for the transcription factor NKX2.4, and is associated with long telomeres (3 publications as last author). It's still a little early to get an idea of the impact of this work on the field, but it's obviously a high-quality piece of work that poses pertinent questions and answers them with effective and appropriate approaches.

The team also discovered that the rare UM patients who responded to anti-PD1 had a high mutational load (CpG>TpG) which was due to an inactivating mutation of MBD4. MBD4 mutations are now sought in the clinic and are indicative of a response to immunotherapies. More recently, they have shown that MBD4 mutations also create a particular susceptibility to cytidine analogues (cytarabine, etc.). This landmark work represents a major advance in understanding the response to immunotherapies in UM and a key clinical advance.

Following the discovery of recurrent mutations in SF3B1, the team showed that these good prognosis mutations, are associated with alternative splicing that creates neo-epitopes. This work is particularly remarkable because the neo-epitopes are common to all SF3B1mut tumors, and thus pave the way for curative vaccines in these neoplasms. Eight publications on SF3B1, five with a team member as last author, and one patent.

Team resources

The team obtained more than 2 M€ of funding for the last 5 years. In addition to the recurrent funding (Inserm, Institut Curie) the Team obtained grant from INCa (as coordinator for PRT-K15, PRT-K19, PHRC-K20, Emergence-17 and INCa SHS-17; as partner for PRT-K16, PLBIO15, PLBIO20), caritative organizations (LNCC équipe labellisée 2018-2023, partner for LNCC epidemiology, ARC partner in a labelised project), and Europe H2020, (as workpackage leader).
The team developed industrial partnerships (Bionano Genomics, Immunocore, Foghorn, Bristol Myers Squibb, Merck, Sharp and Dohme, Johnson & Johnson and Daiichi Sankyo), and obtained patents licensed to Myriad Genetics. The team obtained recently a grant of $ 1.9 M from the US Department of Defense.

Attractiveness & reputation

The team has secured its reputation in the two areas of HDR and UM, as shown by the number of invitations as speaker in national and international conferences. MH Stern is also a member of various scientific organizations, including AACR, EACR, ISOO and is, as well, a writing committee member for UM-related chapters in reference books. Research on UM likely creates a niche for the team.

In addition, both MH Stern and M Rodrigues have teaching duties, which likely facilitates the recruitment of PhD students for the lab and may contribute to the attractiveness of the lab.

Publications
Over the 2017-2022 period, the team managed to publish a total of 84 papers, including 25 as first, last or co-last author, mostly in high ranked specialized journals. In addition, MH Stern signed three book chapters as 1st or last author and 5 patents.

PhD students & post-doctoral fellows
The team currently hosts 2 post-docs and 1 PhD student, a number which is on the low side given the size of the group (total of 13 people). However, under the team trajectory section, the current team composition mentions a total of 16 people including 3 PhD students.

Over the 2017-2022 period however, MH Stern (co-)supervised a total of 7 PhD theses, which is considerable. Importantly, all PhD students and post-docs from the lab appear to finalize their internship with 1st-author publication(s).

Weaknesses and risks linked to the context

No detectable weakness in this team's activity during the last mandate.

The only weaknesses may be those created by the trajectory of the team, *i.e.*, the risk associated with the change of supervisor and the shift in research themes. But future will tell.

Analysis of the team's trajectory

In the near future, the team DNA repair & uveal melanoma will be led by M Rodrigues. The idea is to continue the development of a very translational team with a "bench to bed" philosophy aiming at discovering new therapeutic strategies, prognostic and predictive biomarkers, as well as identifying new mechanisms of tumorigenesis. The focus will still be on HRD gynecological cancers and UM, hence keeping the same trajectory overall. For metastatic UM, based on newly obtained RNA-seq data, one aim is to try to develop therapeutic vaccines and this, thanks to a US Dpt of Defense grant that was obtained recently. Overall, the research projects are diversified enough and offer good chance of success. The team will move to a brand-new unit ("Chemical Biology of Cancer" unit)

RECOMMENDATIONS TO THE TEAM

The committee recommends continuing in the same direction, with the development of research projects of high clinical value, especially in the field of uveal melanoma. The committee encourages the team to develop interaction with the new unit Chemical Biology of Cancer. However, the team should be vigilant regarding the task force and be sure that the manpower will be sufficient to deal with the ambitious research projects, with the development of a new axis on gynecological cancers. Feasibility must be carefully assessed. During the interview, Mr Rodrigues provided elements showing that his clinical workload will leave him sufficient time to successfully assume his new role as team leader.

Nevertheless, MH STERN will become emeritus and will step down as team leader. This is likely to be a handicap for the new team leader M Rodrigues, especially in the absence of a statutory research biologist in the team. The recruitment of an Inserm or CNRS researcher to ensure the sustainability of the uveal melanoma projects in particular, following the departure of MH Stern, must be a priority.

Team 4: Alternativ mecanisms of DNA repair in cancers

Name of the supervisor: Mr Raphaël Ceccaldi

THEMES OF THE TEAM

The Ceccaldi team was created in 2017 thanks to several international and national grants, including an ERC starting and an ATIP-Avenir to Raphaël Ceccaldi, under the name "Atlernative repair mechanisms in cancer". The team studies several aspects of the processes maintaining genome stability in human cells with a focus on compensatory mechanisms for survival that are employed by cancer cells with intrinsic defects in homologous recombination repair (HRD cancers for HR-deficiency).

In collaboration with the lab of Alan D'Andrea (Harvard), they have identified the first-in-class Polθ inhibitor that abolishes ATPase activity and share 2 patents on this inhibitor and the use of NVB for treatment of breast and ovarian cancers. Novobiocon (NVB) induces BRCA-deficient cell death without affecting other cells in preclinical mouse models. They also worked on the role of Polθ inhibitors in mitotic repair and consequently in genomic integrity, showing that they are also interested in more mechanistic questions.

This led them to investigate new vulnerabilities of HRD tumors by studying the role of nuclear NAD+, an essential cofactor for PARP1. They found that the NMNAT1/SIRT6 axis is essential for DNA glycosylase activation, and the absence of this axis induces uracil accumulation leading to DNA gaps and double-strand breaks. They showed that inhibiting the NMNAT1/SIRT6 axis kills HRD tumor cells, including PARP inhibitor-resistant cells, in a synthetic lethal relationship, which is an important finding with nice perspectives for new anti-cancer therapies.

Finally, the team described a new mechanism of nuclear envelope (NE) rupture linked to DNA damage and showed that the ATR kinase mediates NE rupture.

Together, the three main research axes of the lab (mitotic repair, uracil repair and nuclear envelop repair) that aim at developing new therapies for the treatment of HRD tumors are well integrated and bring together mechanistic and translational perspectives. The translational aspect of the research appears to account for the majority of the team's activities.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Not concerned (new team).

The Ceccaldi team has been created in 2017.

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	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**2**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	2
Doctorants	2
Sous-total personnels non permanents en activité	**4**
Total personnels	**6**

EVALUATION

Overall assessment of the team

The scientific production of the team is outstanding with a total of four excellent papers, including one as co-corresponding author in *Nature Cancer* (2021), one *Nature* and one *Molecular Cell* paper as corresponding author (both in 2023) and available in *bioRxiv*.

The team leader, Raphaël Ceccaldi, got an ERC starting grant and an ERC Proof of concept grant. The team also got a total of 7 patents and a start-up company was created in 2023, so that attractiveness and valorisation are also outstanding.

Overall, the team has been evaluated as outstanding.

Strengths and possibilities linked to the context

Despite its rather small size (total of nine persons, including three Master 2 students), the team is actively involved in research.

Scientific output is outstanding, with seven patents regarding the development of new potential therapies for HRD tumors (two on Polθ inhibitors, three on NMNAT1/SIRT6/UNG inhibitors and two about the concept of inhibiting Lamin A/C maturation or the repair of NE ruptures to kill BRCA-mutated cells), four articles: one as co-corresponding author with A. D'Andrea in *Nature Cancer* (2021), two as corresponding author: one in *Nature* and one in *Molecular Cell* (both in 2023) and one available in *bioRxiv*, 11 communications, including three selected oral talk communications (including one Gordon Research Seminar on genomic instability) and three invited speaker presentations (two in France and one in The Netherlands).

The team has a collaborative program with a venture capital firm (ArgoBio Studio) to develop small molecule inhibitors against newly identified drug targets for the treatment of HRD tumors and a start-up was created in 2023.

Significant funding (up to 1698k€) has been obtained, particularly from international sources, including an ERC starting grant and an ERC Proof of concept grant.

They also won scientific awards: Prix Olga Sain, Prix Fondation Tourre; Robert Arceci Innovation Award.

Weaknesses and risks linked to the context

One weakness is the low number of permanent members (2) in the team but this can be explained by the fact that the team is still very young and that the leader wants to keep it small.

Strengthening the team's recognition on a national scale (learned societies, symposia) is one of the minor weaknesses noted.

The paper published in *bioRxiv* in 2021 (Musiani et al, NMNAT1/SIRT6 axis) hasn't come out yet but we understood that the story has changed a lot since its deposit and will be submitted soon.

The search for drugs targeting HRD tumors is very competitive.

The lab prefers not to rely on animal models to study HRD tumor response to drug treatment, which may, at some point, introduce a bias and not reflect the *in vivo* response of tumor cells in the body.

Analysis of the team's trajectory

In the future, the team will likely keep a similar size and will continue to work on the translational perspectives for HRD tumor treatment, which is a very competitive field. Based on the outstanding scientific production of the team over the last few years, we expect the scientific output to keep this high quality.

The startup UNGuard was created in 2023 and the team leader will likely be able to manage both the company and the lab.

The team will likely keep a small size.

This team will integrate the brand-new unit ("Chemical Biology of Cancer" unit) which focuses on tumor heterogeneity and plasticity with, however, little obvious thematic overlap with the current research activities of the team which is mostly using *in vitro* approaches.

RECOMMENDATIONS TO THE TEAM

The committee recommends continuing excellent research in this area and consolidating the team with more permanent members.

Scientific and thematic links in understanding tumor heterogeneity and plasticity must be strengthened within the new unit or alternatively the team may consider to investigate joining another research unit in the Institut Curie focused on the more fundamental aspects of DNA repair.

Team 5: Translational research in pediatric oncology:from ontogenesis to new treatments

Name of the supervisor: Ms Schleiermacher Gudrun

THEMES OF THE TEAM

The RTOP team performs translational research on two childhood cancers: neuroblastoma (Schleiermacher group) and rhabdoid tumors (Bourdeaut group).

The group led by Dr Schleiermacher focuses on the genetic and epigenetic heterogeneity of neuroblastoma tumors as well as their clonal evolution, notably using liquid biopsies from patients enrolled in clinical trials. They also explore drug screening in order to develop novel therapeutic strategies for neuroblastoma patients.

The group led by Dr Bourdeaut develops innovative models of rhabdoid tumors in order to explore the immune response in these tumors and ultimately design more effective immunotherapies. It also investigates the epigenetic vulnerabilities of these tumors and how they could be therapeutically exploited.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The main recommendation from the previous evaluation were: 1) to increase human resources of the team since both Dr Bourdeaut and Schleiermacher have important clinical duties; 2) to ensure sufficient bioinformatics power to perform all the necessary omics analyses and their integration; 3) to support highly ambitious research projects with adequate support in terms of funding, infrastructures and expertise.

The first point appears to have been partially addressed through: 1) the recruitment of top-class PhD students thanks to the participation of the team in competitive doctoral programs such as Vagabond ITN from Horizon 2020, EureCa PhD Program from Curie Institute and 2) the establishment of three permanent research engineer positions, which are funded by the team's grants.

For the second point (bioinformatics), the team chose to rely mostly on collaborations (with U830 Waterfall team and U900 core bioinformatic & Cavalli team). Inserm is also supposed to open a contest in 2023 for a permanent research engineer position in the Bourdeaut team which will strengthen this aspect.

The third point was addressed by securing competitive funding from Europe, INCa and charities, establishing tight collaborations with other Curie teams both inside and outside of the U830 unit, thus allowing access to all the required infrastructures and workflows for effective translational research.

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	0
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	13
Sous-total personnels permanents en activité	**13**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	4
Sous-total personnels non permanents en activité	**7**
Total personnels	**20**

EVALUATION

Overall assessment of the team

The overall assessment of the team is excellent. The scientific production is outstanding with a total of 106 publications over the evaluation period. The attractiveness is excellent with invitations to present at national and international conferences but low recruitment of senior scientists (post-doc or permanent researcher, teacher/researcher). The valorisation is outstanding. Both PIs of the team are established international leaders in their respective fields, who lead large-scale innovative multi-center clinical trials and occupy key positions in the steering committees of international medical societies. Attention however must be paid to the team workforce in order to train the future generation of cancer researchers while ensuring constant scientific guidance despite the heavy clinical and/or institutional commitments of the team leaders.

Strengths and possibilities linked to the context

Both PIs are clear international leaders in their respective fields. Their scientific production is outstanding, with more than 100 publications including ~25 as PDC during the evaluation period. A significant proportion of their articles have been published in top-tier journals such as *JCO*, *Cancer Cell*, *Cancer Discovery*, *Acta Neuropathol*, *Cell Rep*, *Clin Cancer Res*, *JNCI* or *Int J Cancer*. Both team leaders are regularly invited to give conferences in prestigious national and international meetings, and exert important responsibilities in scientific societies (Gudrun Schleiermacher is president of ANRA, chair of SIOPEN, INRG and member of scientific committees of international pediatric cancer consortiums; Franck Bourdeaut is member of SFCE's scientific committee, chair of the SIOP Europe ATRT working group 2019-2023, and member of the steering committee of the SIOP Europe Host Genome Working group). The team has been very successful in obtaining competitive fundings through national calls (INCA PLBio, PRTK, Ligue Contre le Cancer) as well as through industrial partnerships and European collaborations. The team has trained four PhD students, five Master 2 and 1 post-doc and demonstrated international attractiveness (12 different nationalities).

Schleiermacher group
The team has developed a unique know-how in pediatric cancer genomics, especially the genetic heterogeneity of neuroblastoma, and in the analysis of circulating tumor DNA. They coordinate several large-scale national (France Médecine Génomique, MICCHADO) and international (MAPPYACTS) sequencing projects, giving access to tremendous clinical and genomic cohorts. There is a good balance between the molecular characterization of patient samples, and the establishment of a PDX cohort for high-throughput drug screening. Given these assets and the clinical leadership of the PI, the team is in an ideal position to pursue high-level translational research.

Bourdeaut group
A major asset of the team is the development of unique mouse models mimicking the natural development of rhabdoid tumors, and their molecular diversity, allowing realistic preclinical studies. They have generated very promising pre-clinical results on epigenetic vulnerabilities and immunotherapies. The team skillfully integrates basic, pre-clinical (innovative mouse models) and clinical research (e.g, the PI leads an EZH2 inhibitor clinical trial). Again, these assets and the clinical leadership of the PI puts this team in an ideal position to pursue high-level fundamental and translational projects, with rapid implementation of the results in clinical practice.

Weaknesses and risks linked to the context

No particular weakness was identified in the evaluation. Some points of improvement however can be highlighted with regards to scientific interactions within the team, bioinformatic analytical power and the lack of permanent researcher.

1) Lack of scientific interaction within the team
Despite having published over 100 articles during the evaluation period, only 6 have been co-authored by the two team leaders together. The interaction between the two groups is not obvious from the publication record and the description of the aims. This lack of interaction was also visible during the presentation to the committee - each team co-leader presented the work of their respective group independently, with no transversality. Both groups would have probably benefited from more cross-over projects and co-supervision of students and staff members.

2) Need for bioinformatics power

The group led by Dr Schleiermacher has generated tremendous datasets through national and international cancer genomics projects, which require important bioinformatic power in order to be fully valorised. This is a critical point that is currently addressed by relying on collaborations with leaders in this field (Team Waterfall in U830 and core bioinformatic platform & Cavalli team in U900). However, this aspect could be strengthened by the recruitment of a dedicated post-doctoral or permanent bioinformatician within the team.

3) Team structure
Finally, the ratio of research support staff / researcher is extremely high (12 ITA, 1 post-doc, 0 CR, 0 MCU, 0 DR). Efforts should be made to attract and recruit permanent researchers within the team – this is particularly important for research teams that are led by physician-scientists who have high clinical duties and institutional responsabilities.

Analysis of the team's trajectory

As part of the new Children's Oncology Research Unit, the RTOP team will be separated in two distinct teams led by F. Bourdeaut and G. Schleiermacher, in accordance with the respective specificities and expertise of both leaders.

F Bourdeaut team is an expert in ATRTs and recognized internationally in this field. The team proposes to focus on SMARCB1-deficient cancers and to implement and capitalise on the elegant genetic and patient-derived models that they set up. The research project is innovative and perfectly coherent with the positioning of the team at the crossroads of fundamental and translational research. The research axes are built on solid background and know-how on SMARCB1-deficient cancer models and single cell-based bioinformatic approaches to drive advances in the fields of epigenetic modifiers and immune-based therapies.

The team leader has obtained a professor position in 2023 and will also become the deputy director of the Concert unit. Although a permanent position for a bioinformatician is expected in the team, the workload for the team leader related to his clinical, team leader and deputy unit director positions may be intense. Recruiting additional senior scientists may help stabilizing the team and offer more opportunities to host PhD students and postdocs.

G Schleiermacher team has recognized expertise in clinical and translational research on pediatric solid tumors, more specifically neuroblastoma, both at the national and international levels. The team proposes to exploit the huge amount of omics data generated in the last years to depict the bases of neuroblastoma intratumor and interpatient heterogeneity, with the underlying objective to decipher mechanisms of resistance to treatments. The team is integrated in a range of national and international initiatives, with direct inputs to the clinics, and proposes to implement omics data to build precision medicine approaches for neuroblastoma care. The proposed project is very ambitious and in line with the intense efforts that the team made to collect and generate pediatric patient-derived data. The composition of the future team has been clarified during the visit. The team leader may need some additional permanent researcher staff to handle the tremendous amount and types of large scale datasets that the team plans to explore.

RECOMMENDATIONS TO THE TEAM

Both future teams would benefit from additional staff scientists to achieve their ambitious research objectives and maintain their outstanding scientific production, especially since the team leaders devote substantial time to their clinical and institutional activities. The committee therefore strongly encourages the team leaders to recruit post-doctoral researchers willing to apply for permanent research positions in the team (or permanent researchers to join their team). Particular attention should be paid to the workforce of the future team led by Dr Bourdeaut, given his future responsibilities as Deputy Director of the upcoming Childhood Oncology Research Unit.

Team 6: Integrative functional genomics in cancer

Name of the supervisor: Mr Joshua Waterfall

THEMES OF THE TEAM

The team studies how transcriptional regulation and dysregulation shape solid tumor immunology.

The first axis focuses on the mechanisms of aberrant transcription regulation leading to the generation of tumor specific transcripts and neoepitopes. The team has developed technological and computational tools to: (1) identify tumor specific neotranscripts; (2) determine which neotranscripts are translated into neo-peptides presented by the HLA; and (3) identify and characterize the T cell clones that recognize these epitopes (in collaboration).

The second axis focuses on the gene regulatory networks underlying anti-tumor T cell responses. It involves: (1) mapping the heterogeneity of T cells in different tissues; (2) inferrring the gene regulatory networks orchestrating T cell identities through chromatin accessibility analysis; and (3) determining the spatial distribution of these T cells and their interactions with other cell types.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Not applicable (new team).

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	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**1**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	2
Doctorants	1
Sous-total personnels non permanents en activité	**3**
Total personnels	**4**

EVALUATION

Overall assessment of the team

The overall assessment of the team is outstanding. The scientific production is outstanding with 21 publications since 2017 including *Cancer Cell, Mol Cell, Sci Immunol* or *Nat Medicine* as first or last authors. The attractivity of the team is excellent. It has a high international visibility, developed an excellent network of collaborators, locally and externally, and demonstrated a remarkable capacity to obtain funding and attract international young scientists. The valorisation of the research is outstanding, with the deposition of 5 patents, including several licenced in 2 clinical stage biotechnology startups in which the team leader is involved as consultant.

Strengths and possibilities linked to the context

The team has been very successful in developing an original and fruitful research topic, adressing the complementary contributions of transcription regulation to both the generation of tumor specific antigens and the differentiation and response of T cells.

The team is an entirely computational lab and is internationally well-recognized for their technological skills in terms of computational algorithms, 'big data' analysis and single-cell sequencing. Leveraging a network of local and external collaborators, they could apply these developments and obtain very significant results in diverse cancer types including breast, lung or pediatric cancers.

The team has been highly productive since its establishment in January 2017, with 21 scientific papers, including 9 with lab members first or senior authors in eminent journals like *Cancer Cell, Molecular Cell, Science Immunology* and *Nature Medicine*. Of note, they published a series of high impact publications revealing different mechanisms leading to the generation of neo-transcripts and neoepitopes in several tumor types. These include the expression of endogenous retroviruses in rhabdoid tumors (*Cancer Cell* 2019), oncogenic chimeric transcription factors driving tumor-specific expression in Ewing sarcoma (*Mol Cell* 2022), or non-canonical splicing junctions between exons and transposable elements in lung cancer (*Sci Immunol* 2023).

The team has established a high international visibility. The team leader is routinely invited to speak at major scientific conferences and institutional seminar series (including EMBL-EBI, NCI, NIH) and has organized 3 international courses on immunology and cancer immunotherapy. He also serves on the scientific advisory boards of the Bioinformatics and Single Cell Technology Development platforms of Institut Curie, is co-director of the Adult Sarcoma and Desmoid Medico Scientific Program of Institut Curie, and organizes a single cell analysis group (CELL) involving several Parisian research centers.

The interaction of the team with the private sector is excellent. They have deposited 5 patents derived from their scientific discoveries, several of which have been licensed to 2 clinical stage biotech startups spun out from Institut Curie (Egle Therapeutics and Mnemo Therapeutics), for which the team leader is an active consultant. Their determination to foster the clinical application of their discoveries is also evidenced by the national program with France Médecine Génomique, leveraging their RNA-seq classifier to help the diagnosis of cancers of unknown primary location.

The team obtained competitive fundings, including from foundations (BMS Foundation, MSD-Avenir, Sarcoma Foundation of America, La Ligue Contre le Cancer) and the government (France 2030, INCa, Inserm, ANR). They were able to attract young scientists and trained 3 engineers, 3 masters students, 5 post-docs and 7 PhD students. The lab members, from 10 different nationalities and 5 continents, have diverse scientific backgrounds (clinicians, computer scientists, mathematicians, bioinformaticians), ensuring that all the skills and expertise required for the projects are represented.

Finally, the team is very active in communicating their findings to the general public. They have participated in discussions with high school students in france. The team leader was invited at a public-facing conference during Berlin Science Week, and their translational project with France Médecine Génomique was reported in mass media (*Le Monde* and *Le Parisien*).

Weaknesses and risks linked to the context

Although significant fundings were obtained, the anticipated technological developments are expensive and the team could benefit from more substantial fundings, e.g. through European calls.

It is recommended to establish a long-term collaboration for immunopeptidomic validation of the neoepitopes identified in silico with the development of highly sensitive approaches.

Analysis of the team's trajectory

The team, created in 2017, has been very successful in developing an original research topic, leveraging innovative computational developments. The team leader has attracted students and engineers of different backgrounds necessary to conduct trans-disciplinary research. He has constructed a dynamic network of local and external collaborators. The team is now internationally recognized in the field. The trajectory of the team is highly promising as it will build on previous work to push forward its 3 research axes, incorporating new technological developments. The team is in an ideal position to continue their high-level research, with important implications for patient care. The team will join the future Pediatric Cancer Unit. This is a coherent positioning, since it is planned to focus more on pediatric tumors, where there is a need to identify alternative tumor-specific antigens and better characterize T cell responses.

RECOMMENDATIONS TO THE TEAM

The committee recommends to the team to continue their excellent research activity and projects. The team leader may consider applying for European or International grants (e.g. ERC) to consolidate the excellent scientific record on the team and secure comfortable funding for future projects.

CONDUCT OF THE INTERVIEWS

Dates

Start: October 16th of 2023 at 8.30 am

End: October 17th of 2023 at 6.30 pm

Interview conducted online

INTERVIEW SCHEDULE

Monday Oct 16th

08h00-08h30	Connexion du comité
08h30-08h45	Présentation du comité à l'unité
08h45-09h30	*Présentation du directeur :* O Delattre : (Faits saillants, Bilan, Portfolio) : (20 min). Questions/ Discussions (15 min)
09h30	*Team leader presentations*
09h30-10h00	Team 1
10h00-10h30	Team 2
10h30-11h00	Team 3
11h00-*11h30*	*Team 4*
11h30-12h30	*Debrief of the committee (closed doors)*
12h30-13h30	Break// Lunch
13h45-14h15	Team 5
14h15-14h45	Team 6
14h45-15h30	Debrief of the committee (closed doors) Meetings with the staff: closed doors
15h30-16h00	Meeting with technical/administrative staff
16h00-16h30	Meeting with students/
16h30-17h00	Meeting with researchers/post-docs W/0 team leaders
17h00-18h00	Réunion à huis clos du comité

Tuesday Oct 17th

08h30-09h00	Connexion du comité
09h00-11h00	Présentation de la trajectoire de l'Unité: Unité « Chemical Biology of Cancer » : équipes M Rodrigues, Ceccaldi, Mechta-Grigoriou, Johannes, Rodriguez, Lamaze, Seano, Gauthier, Kevrann Directrice : F Mechta-Grigoriou (10min) M Rodrigues, G Seano, A Gauthier, C Kevrann Discussion : 20min Unité « Children's Oncology Research Unit » : équipes Ayrault, Bourdeaut, Delattre, Janoueix-Lerosey, Schleiermacher, Waterfall Directeur : Olivier Ayrault (10min) I Janoueix-Lerosey (10min) Discussion 15min
11h00-11h30	Réunion avec les tutelles : Inserm / Université / Curie (huis clos) Inserm : DR Camille Chaudonneret ITMO Cancer Alain Eychène Université PSL. : Arnaud Tourin (excusé) Institut Curie : Tatiana Malherbe
11h30-12h30	Réunion du comité avec la direction : le directeur actuel/futurs et adjoints
12h30-13h30	Lunch
13h30-17h30	Travail du comité à huis clos

PARTICULAR POINT TO BE MENTIONED

No particular point. The interview was conducted by visioconference as expected.

GENERAL OBSERVATIONS OF THE SUPERVISORS

CENTRE DE RECHERCHE

Institut Curie

Direction
26 rue d'Ulm
75248 - Paris Cedex 05

Alain PUISIEUX, Directeur
Tél. : +33 (0)1 56 24 66 22
Email : alain.puisieux@curie.fr

Unité U830 INSERM
Olivier DELATTRE, Directeur
Tél. : +33 (0)1 56 24 66 79
Email : olivier.delattre@curie.fr
Secrétariat : Carole Drique
Email : carole.drique@curie.fr

Objet

Comments to HCERES Evaluation report of the Unit CHIP - Cancer, Hétérogénéité, Instabilité et Plasticité
DER-PUR250024542
Evaluation campaign 2023-2024 / Group D

HCERES
For the attention of HCERES President,
Mr Stéphane Le Bouler
and the HCERES Expert Committee

Paris, 14th December 2023

Dear All,

We would like to send our warmest thanks to the members of the HCERES Expert Committee for their works, their questions and very constructive discussions during the evaluation process.

We are also grateful for the very clear and detailed report reviewing our activities and trajectory.

We do not have any special comments excepted for some factual modifications in the report content (please see enclosed list).
Finally, we have also taken due note of your very relevant recommendations.

Yours sincerely,

Pr Alain PUISIEUX
Directeur du Centre de Recherche de l'Institut Curie

Dr Olivier DELATTRE
Directeur de l'Unité U830

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

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

Évaluation • Recherche • Enseignement supérieur
Hcéres

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

hceres.fr @Hceres_ Hcéres