Research evaluation

EVALUATION REPORT OF THE UNIT

Oncostem - Modèles de cellules souches malignes et thérapeutiques : applications thérapeutiques

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Paris - Saclay,
Institut national de la santé et de la recherche médicale - Inserm

EVALUATION CAMPAIGN 2024-2025
GROUP E

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High Council for evaluation of research and highter education

In the name of the expert committee :

Yulia Skokova, chairwoman of the committee

For the Hcéres :

Coralie Chevalier, president

In accordance with articles R. 114-15 and R. 114-10 of the Research Code, the evaluation reports drawn up by the expert committees are signed by the chairmen of these committees and countersigned by the president of Hcéres.

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

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

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Experts:	Ms Aurélie Bedel, université de Bordeaux (representative of the CSS Inserm) Ms Florence Sabatier, Aix Marseille Université (representative of the CNU)

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CHARACTERISATION OF THE UNIT

- Name: Modèles de cellules souches malignes et thérapeutiques : applications thérapeutiques
- Acronym: Oncostem
- Label and number: U1310
- Composition of the executive team: Mr. Turhan Ali, director of the unit.

SCIENTIFIC PANELS OF THE UNIT

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

THEMES OF THE UNIT

UMRS 1310 Oncostem (Models of malignant and therapeutic stem cells) is a single team unit dedicated to the development of innovative experimental cellular therapies from induced pluripotent stem cells (iPSCs), new game changers in the field of biotherapies. The unit's program focuses on the modelling of cancer stem cells and therapy-resistant tumour cells using iPSC- derived 3D-cancer organoids, with the goal of discovering novel targets that can be used to improve immune cell therapy in leukaemia and solid tumours. Oncostem is structured around two axes linked to Cithera (Centre for iPS Therapies), a French cell therapy centre created with the mission of generating iPSC-derived cells for clinical use. These axes, which bridge the gap between scientific discovery and its translation into new medicines are axe 1) discovery of novel therapeutic targets in Chronic Myeloid Leukaemia (CML) and solid tumours using iPSC models, and axe 2) development of innovative translational cancer treatment strategies using iPSC and iPSC-derivatives.
Each axe is composed of several sub-axes. For axe 1 these are: development of leukaemia progression models from BCR-ABL-expressing iPSCs; 3D-cancer organoids for drug screening; and the iPSC haplobank project. For axe (2): development of novel CAR-cell strategies from universal iPSC, and active immunotherapy models (cancer vaccines), as well as innate immune cell therapy.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

Oncostem UMRS1310 was created in 2022, following the restructuring of the previous UMRS 935/UA09, as a single monothematic Unit, with the main goal of generating iPSC-derived models and immunotherapy strategies in the field of oncology and haematology. The director of UMRS1310 is also the scientific co-director of UMS45 Cithera (Centre for IPS cell therapy), the platform that coordinates the medical and industrial exploitation sector of IPSC stem cells within the Ingestem infrastructure, with the goal of improving translation of experimental projects at Cithera for clinical applications. **Oncostem and Cithera are thus inextricably linked.** Oncostem is located within the "Andre Lwoff Institute" Campus CNRS of Villejuif, while Cithera is located in Genopole Evry (funded by CPER Region Ile de France and University Paris Saclay).

RESEARCH ENVIRONMENT OF THE UNIT

Oncostem has strong links with local, national and international structures and projects.
Within the Villejuif campus Oncostem benefits from the proximity of both Universitary hospital structures (Molecular Cytogenetics Department at Paul Brousse Hospital University, the School of Medicine of the University Paris Saclay, Gustave Roussy and the Paris Saclay Campus Cancer) and two other Inserm Units (U1193 and U1197) organised through the UMS44 (Paul Brousse/Kremlin Bicêtre). This allows privileged access to shared technological platforms (confocal and time-lapse video-microscopy, animal facilities (conventional and NSG Mice), in vivo imaging (3D-IVIS), flow cytometry, Cell sorter, and a proteomics platform, but also to clinical cohorts, data and samples to support research in oncohematology. Relation with healthcare structures are favoured by the medical positions of the unit directors, and contribute to facilitated transfer of knowledge to medical innovations. There are also connections with reference NGS plateform (Sequoia Bioinformatic platform of Ile-de-France). Members of the unit participate in integrative structures of the University Paris Sud (Labex Lermit, Synchrotron Saclay) for pluridisciplinary programs in the field of cancer and stem cell biotherapy. Since 2020, the unit is part of the 'Health and Therapeutic Innovation' (Healthi program) at the University of Paris-Saclay. The Oncostem Unit is affiliated with regional clusters including the Paris-Saclay Cancer Cluster (PSCC) Biocluster-an ecosystem to accelerate therapeutic innovations in partnership with industrial actors- and the DIM BioconvS of the Ile-de-France region. In addition Oncostem benefits from a strong link with Cithera (centre for IPS cell therapy) within the Genopole biocluster, providing a supportive environment for biotechnological innovations. During the mandate, Oncostem is or was involved as leader in structures created by the Future Investments Programme PIA, such as the Idex IRS "BioTheralliance" for collaborative programs in gene and cell therapy between the Universities of Paris Saclay, Evry and Versailles and the national Research Infrastructure Ingestem supported by the PIA3 and the PIA4 from 2012 to 2019. At the European level, the Unit participates in programmes on large-scale development of cell- and stem cell-based

therapies: Consortium « RESTORE » from the FET-Flagship program; Cost-Action European program 'Haplo-IPSC'; international consortium GAIT Global Alliance for IPSC Therapies (GAiT); IPCEI program 'The Drug Cell" (approved 2024) selected by the DGE (Direction general des entreprises), gathering public stakeholders (Inserm and CEA) and private organisations from start-ups to large companies that develop new cell therapies and advanced therapy medicinal products (ATMPs) across the European Union.

UNIT WORKFORCE: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maîtres de conférences et assimilés	3
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	10
Sous-total personnels permanents en activité	**17**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	10
Post-doctorants	4
Doctorants	3
Sous-total personnels non permanents en activité	**19**
Total personnels	**36**

DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: in physical persons at 31/12/2023. Non-tutorship employers are grouped under the heading "others".

Nom de l'employeur	EC	C	PAR
AUTRE	1	0	5
U PARIS SACLAY	5	0	1
Inserm	0	1	4
Total personnels	**6**	**1**	**10**

GLOBAL ASSESSMENT

Oncostem is a single team unit located within the Paul-Brousse Hospital. **For all of its activities, the unit is intrinsically linked to Cithera (Centre for iPSC Therapy),** a platform of clinical production of advanced therapy medicinal products (ATMPs) in Evry, and PIs of Oncostem are also involved in the management of Cithera. Both possesses a unique position in France in human induced pluripotent stem cells (iPSC) research, particularly through the establishment of a biobank of iPSC lines and their GMP-grade production. Using iPSCs, the unit develops innovative experimental cancer models, and innovative cancer treatment approaches. The unit also develops 3D-cancer organoids for its studies. The main cancers studied are chronic myeloid leukaemia (CML) and human hereditary solid cancers. For solid tumours, immunotherapies are developed using CAR-NK cells and CAR-macrophages derived from iPSCs. The unit also develops anti-tumour vaccines using iPSCs as a source of tumour antigens.
Oncostem/Cithera attractiveness is excellent. At the European level, Oncostem was partner of the European grant Restore project (2018-2020, 79 000 € for Oncostem/Cithera) and Cost-Action Haplo-iPSC (travel funds). Members were the PI of the European innovation council (EIC) Pathfinder Challenges (MUTAVAC, 1.8M€, 2022-2026, to Oncostem/IPSIRIUS). At the national level, Unit members were partners in i) two ANR-supported projects (2017 and 2020, ii) one Idex-funded project (PIA PEPR Biotheralliance).
Oncostem/Cithera members are heavily involved in the scientific organisation and management of the University of Paris-Saclay and in several European networking activities, such as the International Stem Cell Banking Initiative (ISCBI), National Institute for Biological Standards and Controls (NIBSC), International Society for Cell and Gene Therapy (ISCT), etc.

The team's scientific output is very good. 111 articles were published during 2018-2023 period; 53% of these cover the main research topics of Oncostem, and most of them (53) are signed in leading position, mostly in low-impact journals (e.g. Cells, Cancers, Genes, Oncotarget...). Oncostem members were also collaborators in high-level publications unrelated to the main area of research of the unit (Cell 2020, Nat Comm 2021, Nat Cancer, in 2020). The interactions with industry and the economic impact are excellent, as evidenced by numerous accepted patents (4, one of which with 3 international licenses) and several collaborations with industry, for example with Catapult, London. The European Innovation Council (EIC) Pathfinder Award for Oncostem team in 2022 led to the creation of a spin-off company, IPSirius. Members of the unit have numerous consulting activities (Novartis, Bristol Myers Squibb, Incytes Biosciences, Abbvie) and participate as experts in national agencies (Medicen Pôle de compétitivité: 'Biomaterials and Stem Cell Engineering', Genopole,, etc.). Clinical studies for iPSC-vaccines were initiated and a clinical trial in the context of EIC Pathfinder Award 2022 is on the way. Overall, the unit, together with Cithera members, possesses unique expertise in the development of experimental cancer models and anti-cancer immune therapeutics based on the iPSCs. It has excellent national reputation and is highly recognised internationally. Major weakness of the unit is the quality of scientific publications, although the number of publications is high. The future trajectory of the unit with the focus on iPSC-based modelling of solid tumours and development of anti-tumour immune therapies is timely and may have a high impact for both, basic research and clinical translation. It would be important for the success of the unit to identify main projects with potential for successful development, and intensify the cooperation with academic (to reduce geographical isolation) and industrial partners to promote their clinical translation.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The previous report advised the unit:
1) to focus on the research activities on the iPSCs and their therapeutic applications in cancer.
During the contract period, Oncostem has generated, presented and published (including scientific publications, poster and oral presentations at international conferences) a solid amount of data for all of the proposed objectives of the unit. Many of them are based on iPSC models of leukaemia and several cancer types.

2) to "pay attention to the quality of publications rather than their numbers. This will be possible only if the research performed in the unit is much more focused. "

The important recommendation to focus on the quality of publications rather than their quantity was only partially addressed. The unit continues to produce multiple publications of moderate quality instead of paying attention to reorganising group constellations and project management to increase the quality of publications.

3) "Team 3 leader will be 65 years old at the beginning of the new contract. He is the leader of numerous future projects and PI for numerous funding, but he will not be able to continue as an active member of the unit. What will be the unit organisation at his departure?"

The previous team 3 leader continues to actively manage Oncostem projects despite his age. Another team leader is taking over the leadership of Oncostem in the next mandate. In addition, a new team leader has been recruited and will start in the unit in 2025. Unfortunately, the new leader was not available for the interviews and we cannot assess his leadership quality.

4) "The interplay between Ingestem and this research unit is very important for the unit's life and should be clarified"

This was not clarified

5) "scientific strategy should not be based solely on technology but on shared specific biological and/or medical questions."

During the contract, the unit not only worked on technological developments, but also used their innovative models to decipher biological questions. Some of their technological know-how is derived from biological questions, for example vaccination based on iPSC-derived peptides. In their field, technology is also very important for clinical translation and a rare high expertise.

B - EVALUATION AREAS

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

Assessment on the scientific objectives of the unit

Since 2022, the unit has refocused its research objectives on the development of cancer models and immunotherapy innovative strategies derived from iPSC cells. These scientific objectives are very pertinent and in total adequation with the international visibility and leadership of the team in the field, and the technological expertise and higly supportive environment of the Cithera platform, ensuring a high level of innovation. The unit addresses major challenges for future cell-derived immunotherapies to meet current medical needs, and are aligned with the major national strategic orientations that emphasise the economic development of biotherapies.

Assessment on the unit's resources

Oncostem/Cythera resources are excellent and adapted to the ambition of the scientific objectives. The budget has seen an increase over the past four years (from 447 k€ to 1441 k €), highlighting the significant share of self-generated resources (about 90%) associated to the recurrent budget from the university and Inserm. The unit has an active grant seeking policy at the national and European level that provides not only financial resources but also fixed-term contracts for engineers and postdoctoral fellows.
Human resources of the unit encompass nineteen permanent positions, including seven University/medical researchers, two CR1 Inserm Researchers, seven engineers and two permanent technicians.

Assessment on the functioning of the unit

The unit's functioning complies with expected principles and standards in terms of non-discriminatory policy, recognition of everyone's work in terms of publication authorship, encouragement of training, promotion of doctorate and post doctorate careers. Group projects/leaders are not clearly identified. The unit organises time for exchanges and collective discussions dedicated to scientific life to favour synergism between basic research and platforms activities. Procedures are in place for data security. Environmental risk prevention and sustainable development are considered.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The Oncostem unit works on cancer resistance and innovative treatments to improve patient care. Over the years Oncostem has developed expertise in the iPSC field with a focus in onco-haematology. They proposed two research axes: the first one, translational, is to use iPSC for regenerative medicine in cancer treatment (to derive immune cell production, in particular NK cells or vaccines), the second one, more fundamental, is to use cancer-derived iPSC for cancer stem cells resistance modelling and to discover new druggable targets. These two aims are very relevant, with very original approaches, unique in France. The unit is located in Paul-Brousse Hospital and includes eight permanent medical researchers, providing access to patient cohorts. The team has an important international visibility in the CML and iPSC fields. They coordinate the national network Ingestem (2012-2026), they participated to the creation of FFSCR (French Society for Stem Cell Research), obtained an Integrateur label for the Cithera platform, and coordinate a PEPR program. They are implicated in cancer biocluster with IGR, in the Healthi program, Labex Lermit in Paris. They benefit from the Cithera platform for GMP production and clinical translation, participate in many European (Restore Network, Fletflag, Costaction -Haplo-iPS- program) and international (GAIT consortium (Global Alliance IPSC Therapeutics, ISCBI for iPSC biobanking…) networks and collaborate with industrials (IPCEI program 'The Drug Cell", Paris-Saclay Cancer Cluster (PSCC) Biocluster).

Weaknesses and risks linked to the context

The field of cancer immunotherapy is highly competitive. Innovation and creativity are required to be competitive and to propose the future of regenerative medicine for oncology. In this highly competitive context, necessary interactions with other teams working on immunotherapy is lacking within the closed environment of the unit.

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

Oncostem is a singled-team unit comprised of 36 individuals in total, including 6 professors or assistant professors, one full-time researcher, ten permanent technicians and administrative persons, and nineteen non-permanent within three PhD students and four postdoctoral fellows. The unit has strong link with Paul Brousse Hospital (department of haematology and oncology), with access to patient cohorts.

The unit shares technical platforms with two other units in Andre Lwoff Institute, in Villejuif, near Paul Brousse Hospital. The link with Cithera, to allow clinical grade production of iPSC-derived immune cells, are strong. They benefit from update equipment and the possibility of translation. Over the assessment period, the unit recruited two research engineers. Financial resources of Oncostem are obtained in the context of Cithera; they rapidly grew from 340k€/year (2018) to 1400k€/year (2023). Of these, 40k€/year (2%) are from the University Paris Saclay and 150k€/year (10%) from Inserm. In addition, the obtained grants from charities (Vaincre le cancer);1 ANR as coordinator in 2020, Idex and PEPR.

Weaknesses and risks linked to the context

The separation between the Cithera platform and Oncostem is not clear

The leaders of Oncostem obtain funding and valorise their research, thanks to Cithera. For example, staff numbers and grants obtained in the report include those from Cithera.
Cithera moved from Villejuif to Evry genopole in 2020 and there is no other research unit working on immunotherapy at Paul Brousse Hospital, where Oncostem is located. This weak synergy with other cancer institute disperses the workforce of the unit, mainly composed of researchers with medical and teaching activities (only one full-time researcher). The two permanent technical support staff are retiring at the end of 2024.
Group projects/leaders from Oncostem and Cithera are not clearly identified.

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 sex ratio is balanced between PhD students and researchers. Students sign articles and present their work in the national and international congress. A journal club and research meeting are held once a week. A unit council was created as recommended in the previous report.
Non-permanent engineer expertise is well recognised, and they are often recruited by start-ups once their contract expires.
The unit encourages staff to attend training workshops and congresses, fostering the development and implementation of new technologiàes.
Health and safety obligations are standardised following UPC and Inserm rules. Tasks including newcomer training are shared by the technical staff.
Intellectual property is secured through the use of electronic books, allowing validated protocols to be shared.
The Unit implemented a policy for lowering CO2 emissions: it encourages the attendance of online meetings and congresses, and promotes travel by train/carpooling.

Weaknesses and risks linked to the context

The technical staff has a high turnover, with the risk of losing important expertise. Except for engineers, promotion of career advancement was not detailed. Although there are seven HDRs in the unit, out of eight theses, seven are supervised or co-supervised by two Oncostem members.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The unit's attractiveness is excellent as evidenced by the active participation and leadership of unit members and Cithera in recognised national and international consortia and societies (IPCEI project "The Drug Cell", as co-leader, GAIT (Global Alliance IPSC Therapeutics) networking, etc. The unit has an excellent national and international reputation in the generation of patient-specific iPSCs, iPSC-based tumour modelling and the generation of immune cells from iPSCs for tumour immunotherapy. Its reputation is also excellent in the field of CML, but less visible in the field of solid tumous. Financial resources of Oncostem rapidly grew from 340k€/year (2018) to 1400k€ (2023), thanks to Cithera partnership. They obtained grants from charities (Vaincre le cancer), one project supported by the ANR in 2020, prior to the creation of U1310, one Idex-funded project as partner PIA PEPR Biotherapie Bioproduction, coordinated by Cithera. The unit contributes to disseminating knowledge and results in congress and specific workshops (AACR, ASH, EHA, SFH, and FFSCR). Two associate professors were recruited, and 5 international postdocs hosted. Nine PhD students were formed during the evaluation period.

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

Unit members belong to national, European and international networks for iPSC use in regenerative medicine: FSCRC (French Stem Cell Research Society), members of ECELLFrance, A French research infrastructure for regenerative medicine, with links to ISCCR (International Society for Stem Cell Research), member of IPCEI project "The Drug Cell", GAIT (Global Alliance IPSC Therapeutics) networking, International Stem Cell Banking Initiative (ISCBI), Alliance for Regenerative Medicine (ARM), HESI Cell Therapy - Tracking, Circulation, and Safety Committee (CT- TRACS), the Foundation for Cell Therapy Accreditation (FACT). The unit secured European contract Fetflag-Ship in collaboration (80K€ for the unit), BioTheralliance PIA Idex Paris Saclay (270K€ for the unit), PIA PEPR Biotherapie Bioproduction (592€ for the unit) and Vaincre le Cancer (3X) as coordinator (57, 74 and 51K€). Up-to-date equipment is accessible to the unit, such as microfluidic culture system Callisto, single cell C1-system from Fluidigm, Genomics10X for single cell genomic studies, and Seahorse for metabolic studies. Thanks to Cithera, the unit has made major investments in state-off-the-art equipment for iPSC with CellSelector (Aviso), LEAP (Cyntellect) for adherent cell analysis and sorting, Molecular analyses and bioinformatics platform (Miseq (Illumina) for NGS, the Metafer (MetaSystem) for karyotype/FISH, and software for bioinformatics. The PIA3 fund was dedicated to automation equipment with closed culture system (Clinimacs Prodigy) in three clean rooms for clinical grade iPSC derivation and the production of gene edited cells. New equipment for upscale process of clinical grade iPSC and derivatives and preclinical studies has been obtained in 2022/23 by the program France 2030 Grand Défi. During the past contract, Oncostem trained five international postdoc students. Five PhD students defended their thesis with publications as first author. Unit members presented at international (American Society Haematology (ASH), International Society for Stem Cell Research (ISSCR), International Society for Cell & Gene Therapy (ISCGT) and national (Société Française d' Hématologie) meetings. They annually organised a research meeting with members of the Terry Fox laboratory, BC Cancer Agency, Canada and Stem Cell Technologies.

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

Invitations to international meetings are rare and organisation of national or international meetings is absent. Many publications from the unit with high impact are in collaboration, not in Oncostem research fields (Covid thematic for example, bioinformatic contribution).

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The scientific production of the unit is very good. 120 original articles and four reviews were published in good quality journals specialised in stem cells cell-based therapy, leukaemia, oncology and onco-immunology (ex: Leukaemia, lymphoma, Hematologica, Stem Cells, Sci Rep). About 50% of these are signed in leading position.

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

Oncostem has made significant progress in the achieving all of its primary objectives. Particularly, with the identification of a set of embryonic genes involved in CML progression and TKI resistance (Exp Hematol 2020),

the group was the first to analyse the existence of transient 'stem cell states' at the single cell level. This suggests that eradicating CML stem cells requires targeting this primitive fraction using the targets identified. They have also generated iPSCs and haematopoietic cells from CML patients (Stem Journal 2022) and demonstrated that the CML iPSC-derived haematopoietic cells are highly genomically unstable, mimicking one of the key features of CML (Cancers 2023). The unit was the first to generate an *in vitro* "blast crisis in dish" model of CML (Cells 2023). They also used the data from the transcriptome analyses of these cells to design an NK-CAR strategy to specifically target CML blasts by identifying CD25 as a highly expressed gene. Oncostem scientists have established reproducible protocols for the generation of iNK and iMacrophages from iPSCs, which are planned to be translated into clinically relevant products at Cithera. They have designed a CAR-CD25 construct based on the structure of the anti-CD25 antibody basiliximab and generated NK92 cells expressing CAR-CD25, which successfully targeted K562 leukaemic cells in vitro and in vivo (Cells 2023). The generation of iMacrophages (M1 type) against solid tumours from iPSCs is also under development.
Oncostem scientists have developed iPSC models of hereditary human cancers with germline mutations in RET, C-MET, BRCA1 and MSH2 (Cells 2023), and produced lung progenitor and terminally differentiated alveolar cells that recapitulate the transcriptome of non-small cell lung cancer from primary patient samples. They also used the c-MET-mutated iPSCs to generate lung 3D organoids and c-MET-mutated iPSCs for a human glioblastoma (GBM) model (BBA 2020).
The unit also developed and experimentally tested IPSC-derived anti-tumour vaccines, used in combination with a histone deacetylase inhibitor (HDACi) or immune checkpoint inhibitors (ICIs) (Front Med, 2021). Oncostem scientists were the first to demonstrate the clinical relevance of an off-the-shelf allogeneic iPSC-based vaccine combined with an ICI antibody as a novel cancer immunotherapy for aggressive TNBC and NSCLC (publication in progress).

Altogether, members of the unit published 111 original articles, 4 reviews and 2 book chapters, about 50% of them as leading authors. The level of production is proportional to the size of the team, and the different research axis of the unit are represented among the scientific production. Work of the team is regularly and mainly published in specialised journals on stem cells and oncology (Stem Cells, Leukaemia, Lymphoma, Haematologica, Ann Int Med...). Some of the articles (5%) on topics unrelated to the research of the unit (including SARS-Cov-2 related during the Covid period) were published as multi-institute collaborative work in prestigious general interest journals (Nature Communications, JCI, Nat Cancer, Dev Biol, Science Advances).

Oncostem adheres to the principles of research integrity and ethics. The research has been carried out using validated and reproducible procedures that are controlled by supervisors, and monitored by accountable technical staff. Papers published by Oncostem were preferably published in open access journals. All experiments involving patient samples were initiated after ethics board approval and after obtaining informed and signed consent. In the case of animal experiments, all procedures were initiated in accordance with the 3Rs and the ARRIVE guidelines.

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

Most publications on the main research topic of the unit, i.e. iPSCs for translational research/clinical applications are in low-impact journals. Top-level publications are collaborative and not on the main topic of the unit (covering virology, gastroenterology, transplantation).

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The inclusion in society is excellent, mainly due to strong connexion with Cithera. Four patents were filed, and one was licensed at the European level leading to the creation of a spin-off (Ipsirius). The unit has fruitful partnerships with industrial actors (Flash therapeutics, Planktovie, Catapult).
Oncostem participates in dissemination of research in the society through involvement in cancer charity association, and by teaching and training activities for students in pharmacy, medicine and science

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 Oncostem unit, through its strong connection with Cithera, ensures a continuum between basic, translational and clinical research, and provides a potent environment for value creation. The unit relies on Inserm Transfer to ensure the proper compliance of its industrial relationships and innovation transfer activities to the economic sector.

The unit develops a dynamic and successful valorisation policy. This is attested by its capacity to fill a significant number of patents (4 obtained during the last contract). They also established a spin-off company (iPSirius) from three licensed patents related to an agnostic cancer vaccine strategy against metastasis (iLAB award), and granted at the European level (EIC Pathfinder C&GT challenges). They are also very active in the development of research tools in the field of bioinformatics for e.g. the analysis of OMICS data, prediction of HLA presented immunogenic tumour antigens.

Together with Cithera, the unit deploys numerous collaborations with the industrial sector thanks to a unique and internationally visible expertise responding to the current challenges of large-scale IPSC technologies and medical applications in the field of oncology. Among representative witnesses of this strong orientation towards the economic environment are the Etincell project that uses RNA based technologies in immunotherapy, in collaboration with Flash Therapeutics (Atige program), and the SOFT cell project that is developing a bioreactor for the expansion of iPS, with the the Planktovie company.

UMR1310 have been selected are also actively involved in the IPCEI (PIIEC) project called “The Drug Cell”, that develops an ecosystem with pharmaceutical companies that promote biomedicine with an acceptable cost to society.

By their implication in "Vaincre le cancer" association, Oncostem participates actively in researching dissemination activities (patient brochure, videos, newsletters, conferences for the public).
Many of the unit members are teachers very involved in Biotherapies education (European Workshops, Ingestem workshop, 2 international master 2, Medicine Faculty, AgroParis-tech, Polytechnique...).

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

No major weakness or risks were identified regarding the social and economic impact of the unit.

ANALYSIS OF THE UNIT'S TRAJECTORY

The reorientation of the unit has been successful and has had a positive impact on its progress, leading to a better focus on iPSC-based development of experimental leukaemia/cancer models and novel immunological cancer therapies. The Oncostem/Cithera laboratory is now well recognised on a national, European and international level in the field of iPSC-based development of tumour models, in particular CML and 3D organoids of solid tumours, and new anti-cancer therapies with a focus on immunotherapy. The recruitment of a CR with glioblastoma expertise in 2025 will be important to consolidate the new solid tumours axis. In the future framework, the proposed objective of expanding the applications of iPSCs models in cancer research and immune anti-cancer therapies will be an important step to further underpin national and international recognition.

RECOMMENDATIONS TO THE UNIT

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

1. It is important to develop a clear demarcation between the Oncostem unit and Cithera in order not to lose the "uniqueness" of Oncostem. Funding and personnel attribution should be clearly separated from Cithera. Oncostem's role is to provide innovation to the unique GMP facility of Cithera. Innovative projects emanating from Oncostem will ensure the competitiveness of the unit in proposing innovative biotherapy for clinical translation, including for Cithera.
The unit should consider focusing on fewer projects with most innovation and potential for clinical translation. It should clearly define priorities within individual projects for clinical translation, taking into account high costs for the development of clinical trials. Close collaboration with Biotech companies will ensure clinical translation.

2. For the long-term sustainable success of the unit, it is important to identify the future leaders (e.g. by recruiting young researchers with a high profile or by promoting the visibility of promising researchers of the unit). The committee also recommends building research groups for synergic work on each selected project, in order to increase the scientific quality of the data that will lead to high-level publications and thus increase the attractiveness of the unit.

3. Ideally, Oncostem should be located closer to Cithera and other cancer research institutes, in order to develop bidirectional collaborations and promote education.

4. The two permanent technical support staff will both retire at the end of 2024. It is recommended to find suitable personnel in time to avoid a serious gap in the achievement of the unit's objectives and to avoid losing essential expertise in the field of iPSCs research, which is not trivial and requires many years to gain sufficient experience.

5. A strategy should be developed to prevent or mitigate the frequent turnover of technical staff.

6. A detailed plan for promotion of Oncostem scientists at different levels of their scientific careers is recommended (promote project leaders, career development, HDR, increase visibility). Researchers need to be officially implicated in PhD supervision

recommendations regarding the Evaluation Area 2: Attractiveness.

As mentioned above, it will be important to identify the future leaders of the unit. More HDRs are required for young scientists to successfully develop their projects and to achieve independence and higher visibility.
To be competitive, the unit needs to be focused and prioritise projects with transferability to clinic.
Oncostem could benefit from interacting with other groups working on immunotherapy, ideally by being physically closer to them.
An Oncostem WEB page should be developed to improve visibility.

In order to increase its attractiveness, the committee encourages association with high-profile cancer institutes.

Recommendations regarding Evaluation Area 3: Scientific Production

By increasing the number and quality of publications focused on the topic of the Oncostem unit, and by publishing more frequently in research journals other than the MDPI or Frontiers journal families, the attractiveness of the unit will be increased.

The number of PhD students and postdoctoral researchers should be increased, for example through Marie Curie fellowships and by new HDRs in the Unit.

Application for EU grants by Oncostem scientists, such as ERC, is recommended to reach "excellence" and to be attractive for young postdocs.

It is important to stay focused on a few innovative projects and encourage synergy. Identifying group projects with specific group leaders and priorities will positively impact scientific production.

An external SAB could help to prioritise projects.

The committee emphasised the need to prepare for the future of the team, as the unit will be moving from the historic CML field to solid cancers. Recent and future recruitment will be assets for this transition.

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

Clinical trials should be emphasised, and transferability to biotech considered early in the development process.

Oncostem is encouraged to focus on innovative research transferable to clinic (via Cithera)
The unit should focus on the clinical translation of its results, which is rather weak at this stage.

CONDUCT OF THE INTERVIEWS

Date

Start: 04 December 2024 at 9 AM

End: 04 December 2024 à 4:30 PM

Interview conducted: online

INTERVIEW SCHEDULE

9h00-9h30	closed door meeting of committee
9h30-9h35	presentation of the committee
9h35-10h15	Presentation by the director, open to all the Unit (20 minutes presentation: bilan (15 min), trajectoire (5 min), 20 minutes questions Ali Turhan (present director), Franck Griscelli (future director)
10h20-10h50	Discussion with PhDs and postdocs
10h50-11h20	Discussion with research scientists other than unit directors
11h20-11h40	Discussion with support staff (technical and administrative personnel)
11h40-12h10	committee debrief
13h00-13h30	Meeting with the managing bodies Thierry Doré : VP Recherche Université Paris Saclay Eric Deutch : vice-Doyen Recherche Faculté de Médecine Paris Saclay Bruno Quesnel, IT Cancer Philippe Arhets : Inserm délégation régionale
13h30-14h00	Closed door meeting of committee (in presence of the Hcéres scientific advisor)
14h00-14h30	Discussion with the directors (past and future)
14h30-16h30	Final debriefing, finalise report

PARTICULAR POINT TO BE MENTIONED

NA

GENERAL OBSERVATIONS OF THE SUPERVISORS

The institution responsible for submitting the application, which is also responsible for coordinating the response on behalf of all the research unit's supervisors, did not submit any general observations.

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

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