Research evaluation

EVALUATION REPORT OF THE UNIT

I-STEM - Institut des cellules souches pour le traitement et l'étude des maladies monogéniques

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Évry-Val-d'Essonne - UEVE,
Institut national de la santé et de la recherche médicale - Inserm

EVALUATION CAMPAIGN 2024-2025
GROUP E

Rapport publié le 27/03/2025

Haut Conseil de l'évaluation de la recherche et de l'enseignement supérieur

In the name of the expert committee:

Juliette Azimzadeh, 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 exact certified data extracted from the deposited files by the supervising body on behalf of the unit.

MEMBERS OF THE EXPERT COMMITTEE

Chairperson:	Ms Juliette Azimzadeh, Centre national de la recherche scientifique – CNRS, Paris
Experts:	Ms Frédérique Magdinier, Aix-Marseille Université - AMU Mr Valéry Matarazzo, Aix-Marseille Université- AMU (representative of the CNU) Ms Annarita Miccio, Institut national de la santé et de la recherche médicale – Inserm, Paris (representative of the CSS Inserm)

HCÉRES REPRESENTATIVE

Ms Marie José Stasia

REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

Mr Franck Lethimonnier, Inserm
Ms Marie-Josèphe Leroy Zamia, Inserm
Ms Laurence Parmentier, Inserm
Mr Vincent Bouhier, Université Evry Val d'Essonne

CHARACTERISATION OF THE UNIT

- Name: Institut des cellules souches pour le traitement et l'étude des maladies monogéniques
- Acronym: I-STEM
- Label and number: UMR 861
- Composition of the executive team: Director: Cécile Martinat (DR2 Inserm), Deputy director: Christelle Monville (PR, UEVE)

SCIENTIFIC PANELS OF THE UNIT

SVE 3

THEMES OF THE UNIT

UMR861/I-STEM is dedicated to research on new therapeutic approaches exploiting human pluripotent stem cells, notably cell therapy and drug discovery, for the treatment of monogenic diseases. The unit comprises two teams, the "Innovative Therapies for Ectodermal Monogenic Diseases" team directed by the deputy director and the "Neuromuscular Diseases" team led by the director of the unit.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

I-STEM was created in 2005 through a partnership between AFM-Téléthon and Inserm. The unit is located in Corbeil-Essonnes, 40 km south of Paris, on the Génopole campus. I-STEM is composed of UMR 861, a joint research unit between Inserm and Université Evry-Val-d'Essonne (UEVE, associated with Université Paris-Saclay) evaluated by the present committee, and a second administrative entity, the Centre d'Etudes des Cellules Souches (CECS), affiliated to AFM-Téléthon. Members of both entities work in close collaboration within I-STEM.

RESEARCH ENVIRONMENT OF THE UNIT

The unit is located in the Genopole biocluster, which hosts laboratories and companies dedicated to biotechnology and genomics and genetics research, and is situated close to the UEVE campus. The Genopole also hosts Généthon, also affiliated with AFM-Téléthon, and the Institut des Biothérapies (BIRD), which oversees all AFM-Téléthon's research centres. I-STEM is housed in a 1,600 m^2 facility at the Centre de Recherche Clinique et Translationnelle (CRCT), managed through a partnership between AFM-Téléthon, Genopole, the Centre Hospitalier Sud-Francilien and UEVE.
In addition, the unit participates in the InnovAND university hospital institute (IHU) coordinated by the AP-HP and dedicated to neurodevelopment, the Labex Revive for stem cell research, the DIM BioconvS for synthetic biology, biotherapy and bioproduction, and the PEPR Biotherapies and Bioproduction.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	3
Directeurs de recherche et assimilés	4
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	29
Sous-total personnels permanents en activité	**41**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	1
Post-doctorants	2
Doctorants	7
Sous-total personnels non permanents en activité	**11**
Total personnels	**52**

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
AUTRES	0	5	24
INSERM	0	2	5
UEVE	5	0	0
Total personnels	**5**	**7**	**29**

GLOBAL ASSESSMENT

I-STEM is a leading institute in France for stem cells and rare diseases. The unit's scientific objectives, which aim to identify therapeutic solutions for monogenic diseases using innovative cell biology and tissue engineering approaches, are excellent. Initially focusing on the use of embryonic stem cells, the approaches deployed have been broadened to include for instance induced pluripotent stem cells and organoids. Recent technological innovations have also made it easier to generate cellular models for specific pathologies, enabling to progressively refocus the research, notably on neuromuscular diseases.
I-STEM has outstanding resources, with substantial funding (€37m over the whole period), half of which comes from AFM-Téléthon, and the rest from external funding (mainly national and regional). AFM-Téléthon provides I-STEM with a major advantage by funding the majority of salaries, i.e. 27 of the 40 permanent positions at the current time, in addition to running costs and equipment. This has enabled I-STEM engineers to develop and maintain exceptional expertise, particularly on the CECS platforms. The unit derives considerable benefit from these platforms (i.e. cell biology, high-throughput sequencing, bioproduction, imaging, high-throughput screening and genome editing), and in return participates in the development of their expertise through a high level of synergy between the two components of I-STEM.
Overall, the functioning of the unit is excellent and the unit's members express great satisfaction with their working environment and the unit's leadership.
I-STEM's attractiveness is excellent, with a remarkable ability to mobilise external funding (15 ANR and FRM grants, Fondation Maladies Rares, PIA programmes, Horizon-Europe, i.e. a total of around €14 million). The presence of CECS's cutting-edge platforms also contributes greatly to I-STEM's attractiveness. Members of the unit are regularly invited to national and international conferences, and participate in various scientific committees and societies. However, efforts to improve the unit's international visibility need to be pursued. There are also persistent difficulties in attracting young researchers, due to the unit's off-center geographical location and its lack of connection with a university hospital.
The unit's scientific output is very good to excellent, with a total of 117 publications in 2018–2023 (59 in first/last/corresponding author position), with articles in Stem Cell Research, Nature communications, JCI insight, iScience, Scientific reports, Biomaterials, J Invest Dermatol, Stem Cell Reports, American Journal of Human Genetics. However, the number of high-impact publications in which I-STEM teams are leaders could be further increased by achieving the right balance between translational and more fundamental research.
I-STEM's contribution to society is outstanding, with three clinical trials initiated during the evaluation period and seventeen patents filed, five of which are under license. The members of I-STEM are also highly involved in interactions with the general public (high school students, patients and their families), particularly in the context of the Telethon.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Recommendations on scientific production and activities (criterion 1)

- Changes in the way equipment platforms are operated and maintained are excellent. A robust forward strategy to ensure suitable upgrades and repairs should be generated. It is timely to evaluate the current I-STEM drug library now that several screening campaigns have been completed.

The unit has updated its strategic plan in 2020, listing equipment that needs to be replaced. New equipment has already been acquired, including two Clinimacs Prodigy instruments for automated cell processing, and a new high-throughput screening. With respect to upgrading the chemical library, I-STEM has initiated collaborations with the Lead Discovery Center in Germany, which has expertise in medicinal chemistry and is integrated within the European Lead Factory, and with the national infrastructure ChemBioFrance.

- There needs to be evidence of early engagement with Pharma to show that if suitable drugs are discovered, then there is a translational route forwards for patient benefit.

I-STEM takes advantage of AFM-Telethon's business development department to identify industrial partners. The unit has been successful, with three clinical trials initiated during 2018–2023. However, funding the transition to phase 3 of clinical trials remains challenging.

- Directors are encouraged to invite more frequently local and foreign seminar speakers, notably those working in related areas but using different stem cell models.

Weekly seminars are organised by a committee of four young scientists. Priority is given to themes complementary to those developed within the unit.

- Visibility of I-STEM may have slightly decreased over the past few years and should be improved. The committee noted excellent engagement (e.g. the Director of I-STEM now leads the French Society for Stem Cell Research), which bridges to international audiences. There was also evidence of French-UK bridging alliances. In line with the previous point above, improved international communication should also be exploited to recruit postdoctoral fellows.

Group leaders have taken part in international conferences (around 10/year) and are involved in European and international networks and scientific organisations (vice-chairmanship of the "Physiology and pathophysiology" panel of the Marie Sklodowska-Curie Actions postdoctoral fellowship, International, EU networks Dreams and Recognition).

Recommendations on the unit's organisation and life (criterion 2)

- Long-term succession planning for the post of cell therapy Directorship should be initiated.

Following an evaluation in 2022 by a scientific committee mandated by AFM-Telethon, an international advisory board (IAB) comprising clinicians, industry professionals and academics have been set up in 2023 to assist in the selection process for the new director.

- Clarity is required on how strategic decisions are made: how to balance resources between strong and weaker projects.

Strategic decisions are taken by a steering committee composed of all group leaders, which meets on a weekly basis. The unit also drew on the recommendations made by the evaluation committee appointed by AFM-Telethon in 2022 to identify priority projects.

- Extra opportunities for career development for junior staff and postdocs should be considered (e.g. limited teaching responsibilities), which may enhance the attractiveness of I-STEM.

Teaching opportunities exist for postdocs and young researchers at UEVE, Université Paris Saclay and other Paris universities. However, reaching most teaching locations requires the use of a motor vehicle and can be time-consuming, which is an issue for some young researchers in the unit.

- The leadership should discuss with the researchers the numbers and frequency of meetings to create an appropriate balance with benchwork.
The frequency of meetings is decided by the steering committee and the institute committee. Some events, such as journal clubs, have been dropped to reduce the amount of time spent in meetings.

- The leadership should consider engaging with the researcher (postdocs and students) to encourage them to invite external speakers in topics they deem of interest.

The weekly external seminars are now organised by a committee of four young researchers and postdocs, who select the speakers they wish to invite.

Recommendations on scientific strategy and projects (criterion 3)

- Careful consideration is needed to balance the complexity of models with throughput, as well as the challenge of combinatorial drug screening. In this regard and with the cumulative experience I-STEM now has on its 20,000-compound library, it would be timely to understand whether this library should be evolved or added to with additional chemistry.

See above.

- The unique facilities at I-STEM mean there is potential to turn international competition into collaboration and could be developed further.

The I-Stem teams established new collaborations during the course of the mandate, mainly at the national level.
- In line with the previous point, I-STEM is encouraged to develop a more global perception of tissue regeneration – possibly via collaborations – and take into account not only diseased or missing cell replacement but also inflammation, vascularisation, local stem cell recruitment… in order to improve their very promising tissue repair strategies.

I-STEM has invested in tissue design in collaboration with CECS platforms. This has led to the development of 3D layers of RPE cells for retinal transplants (Stream program). Work has also been initiated on assessing the potential of cell-free cell therapies.

- The impact of the location of I-STEM should be evaluated and how these might be overcome (for example, might a private bus service be an option?).

There have been no improvements in this respect, but the Grand Paris project to develop transport could ease this problem in the years to come.

B - EVALUATION AREAS

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

Assessment on the scientific objectives of the unit

I-STEM's scientific objectives, aimed at identifying therapeutic solutions for monogenic diseases, are excellent. The unit has initiated a transition towards broader cell biology and translational biology approaches, as well as a gradual refocusing of its research topics, notably on neuromuscular diseases. Translational research has been fruitful, thanks in particular to the CECS's cutting-edge platforms, and has led to three clinical trials.

Assessment on the unit's resources

The unit's financial resources are outstanding (37 M€ over the whole period), half coming from AFM-Téléthon, and the rest from external funding, mainly national (21%) and regional (17%). Human resources are stable, with a majority of CECS staff. The unit benefits greatly from the CECS's platforms, whose activities are developed in synergy with those of the teams.

Assessment on the functioning of the unit

The unit's functioning is excellent, and the personnel express a high degree of satisfaction with the operation of the unit and its leadership. Members of the unit are encouraged to take responsibilities and feel that their work is well recognised. Scientific animation is very dynamic, with in addition to the usual meetings, topical meetings that contribute to the training and cohesion of the unit. Students and postdocs are satisfied with their supervision. One comment is that participation to an international conference is not systematic for PhD students ands postdocs. Also, the advancement procedures for CECS staff are not sufficiently transparent.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

I-STEM's scientific objectives, which aim to identify therapeutic solutions for monogenic diseases, are consistent with the goals defined by AFM-Telethon and the supervisory bodies. Originally focused on the use of embryonic stem cells, the unit has initiated a transition towards broader cell biology and translational biology approaches for monogenic diseases. Taking advantage of the major technological advances of recent years (iPSC, Crispr, organoids), I-STEM has initiated a gradual refocusing of its research themes, in particular by reinforcing its effort on neuromuscular diseases.
The unit takes full advantage of the CECS platforms to develop ambitious technological approaches (tissue culture, biocompounds, cell-free cell therapy, non-invasive quality control, etc.). Translational research has been fruitful, leading to several clinical trials. This includes cell therapy products, with one clinical trial starting in 2019 (Stream program for retinal repairs) and a program in preclinical phase (the Pace program for skin healing). In addition, pharmacological research involving drug repositioning led to two clinical trials during the evaluation period (Lisphem and Audiowolf).
The unit's two teams are each made up of independent sub-groups with their own scientific objectives, but with common experimental approaches, which contributes to maintaining the unit's coherence. The unit's scientific objectives are discussed by the steering committee. The IAB set up in 2023 will also help define scientific objectives in the future.

Weaknesses and risks linked to the context

Strong emphasis of the unit on translational approaches limits its ability to carry out more fundamental work and can impact the profile of scientific publications. The diversity of research themes must also be managed to prevent dispersion of resources and a loss of coherence beyond common experimental approaches.

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 has substantial financial resources (37 M€ for the whole period), about half of which come from AFM-Telethon, and the rest from project calls, mainly national (21%) and regional (17%), as well as from industrial partnerships (8%), European contracts (4%) and supervisory bodies (1%). However, it should be noted that the CECS funding includes the salaries of all CECS staff.

Human resources have remained stable over the past few years. The unit comprises a majority of CECS personnel (5 research directors/researchers and 23 engineers), and personnel from Inserm (3 research directors/researchers and 5 engineers), UEVE (5 professors/assistant professors) and AP-HP (1 clinician). Only around 1/5 of the engineers are non-permanent. The possibility of recruiting not only engineers, but also researchers via AFM-CECS is a major asset for I-STEM.

The unit benefits from CECS's state-of-the-art platforms, whose technological development is in synergy with the teams' research projects.

Weaknesses and risks linked to the context

The unit receives comparatively little support from its supervisory bodies in terms of human resources, particularly for technical staff positions. Most of them depend on AFM-Téléthon funding, which can fluctuate.

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

Governance is via a steering committee formed by the director team and group leaders, which meets every week. An institute council with an advisory role meets every three months. Scientific animation is very active (weekly lab meeting, invited seminars and journal club, monthly meetings for PhD students and postdocs) and includes specific events organised on subjects relevant to the unit's work: in-house training sessions ('I-STEM school') and discussion groups ('taskforce meetings'). In addition, a three-day retreat for all unit members is organised each year to discuss research projects.
Training is provided internally ('I-STEM school') or via training courses offered by Inserm.
Overall, I-STEM members are very satisfied with the way the unit operates and how it is managed by the director team. Researchers are encouraged to assume responsibilities and to seek their own funding. They sign their publications as the last author if they are project leaders, which facilitates obtaining the HDR. Technical staff are also involved in publications and have the opportunity to present their work at internal seminars and at the annual retreat. They have opportunities to take on responsibilities and are systematically involved in meetings of collaborative networks in which they participate. PhD students and postdocs have first author publications and receive internal support through dedicated seminars at which they present and discuss their work in the presence of group leaders and other PhD students/postdocs.

Weaknesses and risks linked to the context

The advancement process for CECS staff is not sufficiently transparent and there is little feedback on the arbitration of applications. There is very little opportunity for technical staff to change teams.
PhD students and postdocs do not systematically attend an international conference. The unit's students and postdocs are relatively isolated, as they have no contact with young scientists from neighbouring institutes.
There are no student/postdoc and technical staff representatives on the unit council, nor a psychosocial risk referent. CECS staff often have difficulty registering for Inserm training courses because they are not considered a priority, even though they belong to an Inserm unit.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The attractiveness of I-STEM is excellent due to its ability to mobilise important external funding (15 ANR grants and FRM funding, Fondation Maladies Rares, PIA programs, Horizon-Europe, i.e. a total of around €14 million), the presence of the CECS cutting-edge platforms, and more generally from the Genopole environment, allowing developing innovative therapeutic approaches. I-STEM members are regularly invited to national and international conferences (42), and participate in various scientific committees and societies (Inserm CSS7 Committee, UEVE Board of Directors and Research Vice-Presidency, ANR, Marie Sklodowska-Curie Actions, etc.). Efforts to improve the unit's international visibility need to be pursued.

Strengths and possibilities linked to the context

I-STEM enjoys a very good to excellent scientific reputation, with numerous invited communications (42) at national and international conferences. I-STEM members are also members of various scientific committees and societies (Inserm CSS7 Committee, UEVE Board of Directors and Research Vice-Presidency, Fondation Maladies Rares Scientific Council, AFM-Téléthon Scientific Council, ANR Regenerative Medicine Committee, Marie Sklodowska-Curie Actions Vice-Presidency for postdoctoral fellowships, International Society on Stem Cell Research, Society of Myology, French Society on Stem Cells). Three members of the unit also received awards or distinctions during this period, including "La Recherche Prize", "the Alfred Kastler Biology Prize", and "Chevalier de l'Ordre du Mérite").
The unit has secured the recruitment of a UEVE assistant professor and an Inserm researcher. The research themes of two Inserm CRCNs have been supported by Genopole funding (Atige). Recruitment of students is also satisfying, with fourteen PhD theses initiated during the evaluation period (11 defended), and around ten Master's students hosted each year. Training is encouraged for students/postdocs and non-permanent staff via both Inserm and in-house courses. PhD students and postdocs are also supported if they wish to teach.

The unit has demonstrated an excellent ability to mobilise financial resources (15 ANR grants and funding from FRM, Fondation Maladies Rares, PIA programs, Horizon-Europe), for a total amount of around €14 M over the evaluation period.
Finally, the unit greatly benefits from the CECS platforms, which are free of charge for the unit members. The unit's needs vis-à-vis the platforms are defined by the steering committee and discussed with the platform managers, which enables innovative approaches to be developed for both research projects and translational applications.

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

International visibility has increased but can still be improved. Difficulties in recruiting international postdocs due to location and transport difficulties persist. The fact that the unit is not physically associated with a university hospital also limits the possibilities of recruiting medical or pharmaceutical students.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The unit's scientific output is very good to excellent, with a total of 117 publications in 2018–2023 (59 in first/last/corresponding author position), with articles in Stem Cell Research, Nature communications, JCI insight, iScience, Scientific reports, Biomaterials, J Invest Dermatol, Stem Cell Reports, American Journal of Human Genetics. The number of high-impact publications in which I-STEM teams are leaders needs to further increase.

Strengths and possibilities linked to the context

Scientific production of the unit is very good to excellent, with a total of 117 publications in 2018–2023 (59 in FLC position). These include papers in Stem Cell Research, Nature Comm, JCI insight, iScience, Scientific reports, Biomaterials, J Invest Dermatol, Stem Cell Reports, Scientific Reports, and the American Journal of Human Genetics. The work is on the whole published in reliable peer-reviewed journals. Published work includes the development of protocols for the efficient conversion of human pluripotent stem cells into specific cell types, such as spinal motor neurons (Development, 2021 and patent PCT/IB2020/000972), the development of stem cell-based products for cell therapy applications in retinal and skin diseases (Biomaterials, 2020 and patent PCT/FR19/050529), the automation of pluripotent stem cell differentiation production for large-scale production (Scientific reports, 2019 and patent PCT/FR19/05029), the development of new cell models for rare diseases (Biomedicines, 2022; Journal of Investigative Dermatology, 2022; 2x Stem Cell Research, 2023), the development of imaging (American Journal of Human Genetics, 2021) or drug screening technologies (Scientific Reports, 2019) and the results of a clinical trial for myotonic dystrophy type 1 (Brain, 2018).

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

The trend over the last period is very positive but there is still room for improvement in the quality of publications. The majority of high-impact publications are still collaborations in which the unit's teams are not leaders.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

I-STEM's contribution to society is outstanding, particularly in terms of clinical applications (3 clinical trials initiated during the evaluation period) and valorisation (17 patents filed, including 5 under license). I-STEM members are also highly involved in interactions with the general public (high school and college students, patients and their families).

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

I-STEM's contribution to society is outstanding. Seventeen patents have been filed including five licensed (efficient specification of spinal neuronal motor neuron subtypes from human pluripotent stem cells, a process

for obtaining endothelial cells from pluripotent stem cells, process for differentiating pluripotent stem cells into fibroblasts of connective tissue underlying an epithelium, process for obtaining pre-vascularised dermo-epidermal tissue, AAV transduction vectors for introducing foreign DNA into mammalian cells).
In addition, three clinical trials were launched during the evaluation period: two drug trials (Lisphem for Phelan McDermid syndrome and Audiowolf for Wolfram syndrome) and a cell therapy trial for genetic retinitis pigmentosa (Stream). The results of a phase 1/2 trial carried out during the previous term (Myomet) for the treatment of myotonic dystrophy type 1 were also published, and led to two phase 3 trials in France and Italy.
I-STEM members are also very involved in interactions with the general public, on the one hand, through actions aimed at high school and college students, in particular via the "1000 researchers in schools" operation initiated by the last director of the unit, and, on the other hand, through interactions with patients and their families, via the Telethon among other initiatives.

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

So far, no share of licensed patents has been returned to the unit.

ANALYSIS OF THE UNIT'S TRAJECTORY

The proposed trajectory is in line with the previous mandate and is consistent with the expertise of I-STEM members and the resources available. A five-year strategic plan has already been positively evaluated in 2022 by a scientific committee mandated by AFM-Telethon, and in 2023 by the IAB.

The scientific objectives of the next mandate will firstly be to continue developing new therapies based on the use of tissue-engineered products for the treatment of retinal and skin pathologies. These approaches will aim to develop more complex products and products invisible to the immune system, to develop cryopreservation of composite products, to increase production, and to develop medical devices enabling clinicians to access these products. Another objective will be to develop non-destructive, less expensive quality controls, and exploiting artificial intelligence. Finally, work on "cell-free cell therapies" based on the use of extracellular vesicles will be pursued, in particular for treating muscle pathologies.
With regard to disease modelling, current projects will be continued, with a reinforcement of programs focusing on neuromuscular diseases. A first objective will be to develop more complex models based on co-culture (e.g. neuromuscular junctions), possibly using micro-fluidic approaches, and organoids. Another objective will be to develop therapeutic approaches based on the identification of compensatory mechanisms, enabling certain cell types to remain unaffected by deleterious mutations.
Finally, pharmacological approaches will be pursued, on the one hand, with drug repositioning in the case of ultra-rare diseases, and on the other with research into new chemical entities for diseases such as myotonic dystrophy type 1. Access to broader chemical libraries will be provided via partnerships (Lead Discovery Centre, ChemBioFrance). One objective will be to develop complex models - cocultures or organoids - compatible with screening with the repositionable drug library.

The unit plans to continue developing partnerships with industry, drawing on the services provided by Inserm, UEVE and AFM-Téléthon. On the other hand, discussions with institutes with converging strategic interests will be initiated in order to stimulate collaborations and scientific exchanges.

In terms of organisation, the trajectory foresees a strengthening of the steering committee's role in decision-making, as well as the involvement of the IAB. The replacement of the last director (who created the unit) at the head of the CECS will also be one of the key decisions at the start of the next mandate. Other planned developments include a strengthening of scientific leadership, the switch to electronic laboratory notebooks, and initiatives to promote green and open science.

RECOMMENDATIONS TO THE UNIT

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

The synergy with the CECS is extremely important for the unit. In this respect, the choice of a new director for the CECS represents a major strategic decision. The committee fully supports the idea of recruiting a clinician, which would help to maximise the transfer of results to the clinic.
The committee encourages the continuation of efforts to promote greater transparency regarding the advancement of CECS staff and communication with AFM-Telethon.
The committee also supports a greater role for the IAB, which is intended to become the sole body for evaluating I-STEM on behalf of AFM-Telethon, in drawing up its scientific strategy.
Participation in an international conference should be systematic for PhD students and postdocs, and should also be encouraged for ITAs who wish to do so.
Students/postdocs and technical staff should have representatives on the Institute Council.
It would also be important to appoint a referent for psychosocial risks.

Recommendations regarding the Evaluation Area 2: Attractiveness

It would be of great benefit to the unit to recruit a junior team through an international call. This would bring in new ideas and enable to exploit I-STEM's exceptional technological resources and expertise to support an ambitious project with a significant fundamental component.
Participation in European networks should be increased in order to continue to raise the Institute's visibility.
The number of doctoral and postdoctoral students could be increased and, to this end, stimulating interaction with Parisian university hospital centres (CHU) in order to attract medical students seems an interesting avenue.

Recommendations regarding Evaluation Area 3: Scientific Production

The committee recommend continuing to invest in more fundamental work to further improve the profile of scientific publications signed as lead authors. In future, to give priority to journals recommended by the French Academy of Medicine.

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

The committee recommend continuing to work with Inserm and AFM-Téléthon to optimise the exploitation of patents and the strategy for moving into phase 3 of clinical trials. It seems that there is a clear potential to increase the number of Cifre PhD contracts.

TEAM-BY-TEAM OR THEME ASSESSMENT

Team 1: Cell-based innovative therapies

Name of the supervisor: Ms Christelle Monville

THEMES OF THE TEAM

Team 1 is focused on the study of genetic and non-genetic diseases affecting the skin and retina. Their work spans from disease modelling and mechanism to the development of therapeutic approaches (cell therapy and pharmacological approaches) including preclinical and clinical studies.
In 2018–2023, T1 was focused on:

1. Genodermatoses (sickle cell disease, diabetes, Vitiligo, epidermolysis bullosa simplex, neurofibromatosis type 1): disease modelling/mechanisms, cell therapy and pharmacological approaches;
2. Wolfram syndrome: disease modelling/mechanisms and pharmacological approaches;
3. Retinopathy (Retinitis pigmentosa, Age-related Macular Degeneration, Alstrom Syndrome): disease modelling/mechanisms and cell therapy.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

A – Recommendations on scientific production and activities (criterion 1)
"Scientific production of the members building new team 1 could still be improved in terms of the number of articles and patents. The international visibility of the new team leader should be improved as well as the appeal of the team by recruiting foreign PhD students, postdocs and hosting invited professors."

T1 has substantially improved the number of articles (from 26 in the previous period to 45 in 2018–2023) and patents (11 patents).

The international visibility of the new team leader has not substantially improved (e.g. 9 to international events in 2018–2023 compared to 16 in 2013–2018).
T1 has increased the number of PhD students.

C – Recommendations on scientific strategy and projects (criterion 3)
The team should improve the design of pluripotent cell-derived human tissues, notably skin, for superior transplantability.
T1 has developed and demonstrated the functionality of prevascularised dermo-epidermal substitute in vitro and in vivo after transplantation in immunodeficient mice. T1 has also generated more complex retina tissues containing not only RPE but also photoreceptors and endothelial cells.

Collecting new grants is now urgently needed to support these many projects.
The team was able to collect 17M through grants and industrial collaborations.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	10
Sous-total personnels permanents en activité	**16**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	1
Sous-total personnels non permanents en activité	3
Total personnels	**19**

EVALUATION

Overall assessment of the team

Scientific production is very good to excellent but the number of publications is relatively low, with not many manuscripts published in top journals. The national visibility is excellent; T1 efforts in raising funding for basic and preclinical studies. International visibility is very good but it should be improved by recruiting scientists abroad and by participating in international/European consortia.
Non-academic activities are outstanding in terms of patents and clinical trials, having a unique expertise to perform both basic and preclinical studies to bring their discovery to the clinics.

Strengths and possibilities linked to the context

The Key strength of T1 is their work ranging from disease modelling and mechanisms to developing therapeutic approaches (cell therapy, pharmacology), including preclinical and clinical studies.
(Scientific production)
T1 had very good to excellent scientific output, publishing 39 manuscripts (12 involving PhD students as authors), with 25 as first, last, or corresponding author (5 led by PhD students). These include papers in Biomaterials, J Invest Dermatol, Stem Cell Reports, Scientific Reports, and the American Journal of Human Genetics.
Non-academic activities are outstanding. Of note 1 clinical trial has started using a drug product developed by the team (for retina disorders), the work contributed to the launch of a clinical trial for patients with Wolfram syndrome in 2021, and two clinical trials are planned (for skin ulcers). Moreover, T1 has filed eleven patents and collaborated with numerous industries.
T1 has an excellent visibility: T1 had numerous (mainly) national collaborations with academic labs, hospitals and companies and T1 has an excellent capacity to raise grants. T1 has obtained national funding (national agencies and charity associations) for a total of > 8 M (3.3 M funding from BPI France for the Genesis project) and almost 9 M from industrial collaborations (e.g. URGO for the Genesis project). The team leader has obtained the Prix La Recherche in 2019.
International visibility is very good with 22 oral communications (9 at international conferences), and 32 poster presentations (12 at international conferences).
Between 2018–2023, team 1 has focused on:
Genodermatoses (sickle cell disease (SCD), diabetes, vitiligo, epidermolysis bullosa simplex, neurofibromatosis type 1): disease modelling, cell therapy, and pharmacological approaches.
First axis: Cell therapy for skin damage

- Developed HESC-derived keratinocyte-based epidermal substitutes for SCD leg ulcers
- Produced vascularised skin substitute for diabetic foot ulcers (Generated melanocytes from HIPS for pigmentation disorders
- Second axis: Pharmacological approaches
- Modelled epidermolysis bullosa simplex using HIPSC neurofibromatosis type 1 to study bone defects Wolfram syndrome: Modelled disease using HIPSCS to generate mutant neurons, improving pathological phenotypes retinopathies (Retinitis pigmentosa, AMD, Alstrom Syndrome):
- Developed retinal pigment epithelium (RPE) tissue from HESCS (Optimised Stream via automation, enhanced RPE characterisation, and cryopreservation 3D retina reconstruction combining RPE and photoreceptors.
- Made a disease modelling of Alstrom Syndrome using HIPSCS to generate RPEs and retinal organoids

Weaknesses and risks linked to the context

The number of publications associated to the projects specifically led by the team and described in the self-evaluation document is relatively low, as well as the quality of the journals. In particular, for some members of the team, the publication rate is low.
International visibility could be better. There were 22 oral communications at conferences, of which nine were international conferences with the PI as an invited speaker (16 in 2013–2018)
There is no EU or international grant has been obtained. Most of the collaborations are with French groups.

Analysis of the team's trajectory

Programs of the genodermatoses sub-team:
Program 1: Cell therapy foreskin diseases
(1) Pace focuses on preclinical and clinical studies using HESC-derived keratinocyte-based epidermal substitutes to treat sickle cell leg ulcers. (2) the team will develop non-invasive quality controls via two projects: (i) Single New QC project aims to identify markers secreted during keratocyte production from HIPSCS as non-destructive controls (NGS platform (ii) Stellar project uses holographic imaging to track keratocyte differentiation. The Vitilips project aims to study and treat Vitiligo using HIPS to produce melanocyte stem cells with better regeneration potential than mature melanocytes. Clinical-grade melanocyte production will be optimised.
Program 2: Pathological and pharmacological modelling programs
(1) Vitili Pharm project focuses on optimising melanocyte stem cell production and studying molecular mechanisms to test pharmacological treatments in a novel Vitiligo *in vivo* model (2) 3D XerodermiPSC project aims to develop an in vitro 3D model containing keratinocytes, fibroblasts and melanocytes, derived from HIPSCS to study skin cancers mechanisms in xeroderma pigmentosum type C.

Programs of the retinopathy sub-team:
Program 1: Amelioration of cell therapy for retinopathy (1) Improve the Stream product to treat patients with retinitis pigmentosa by (i) up-scaling the production of RPE cells in a closed system; (ii) developing non-invasive quality controls during the production and in vivo assay of the final product; (iii) developing and validating a cryopreservation method.
(2) The retina project aims to develop a more complex retina system containing both RPE cells and photoreceptors in 3D using a polymeric scaffold and to develop a 3D blood-retinal barrier tissue containing RPE and endothelial cells.
Program 2: Alstrom syndrome modelling to identify therapeutic targets:
(1) Mutant RPE cells and organoids will be generated to analyse the pathophysiology of the disease and test pharmacological approaches.
Both sub-teams will leverage studies conducted from 2018 to 2023 and aim to develop more complex 3D/organoid models. However, the rationale for grouping retinopathy and skin disorders remains unclear, and the interaction between sub-teams could be better defined. Some diseases studied in the previous period are no longer part of the new program (epidermolysis bullosa, neurofibromatosis type 1). A new focus is planned on xeroderma pigmentosum type C.
The program on Wolfram disease will no longer continue, as the PI leading the project has moved to T2.
Team composition and funding: The team comprises eighteen members: one postdoc, one PhD student, two Professors, two CR, six IE, two IR, two technicians, one maître de conference and one physician. Although the workforce involved in the different lines of research is not detailed, funding sources are very clear for each project with excellent efforts in raising funds (collaboration with 5 companies, public and private foundation funding).

RECOMMENDATIONS TO THE TEAM

The committee suggests that team 1 increase its international visibility by applying for European/International grants, by attending more international conferences, and by recruiting scientists from abroad (including PhD students and postdocs).

In the new team, only one postdoc and one PhD student are included (with 3 team members holding an HDR degree). The committee recommends that the team should recruit more postdocs and PhD students.

The committee suggests that the number of publications and the quality of journals to publish their work be increased.

Team 2: Therapeutic Development for Neuromuscular Diseases

Name of the supervisor: Mme Cécile Martinat

THEMES OF THE TEAM

The « therapeutic development for neuromuscular diseases" team aims at deciphering the pathophysiology of different monogenic diseases using stem cells as a model for disease modelling and drug discovery. During the past period, the team was organised around four main topics:
- Physiopathology of muscle and motoneurons
- Disease of the myelinated fibres
- Pharmacology of muscular dystrophies
- Neuroplasticity and therapeutic development.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Criterion 1: As raised by the team leader (who is also the lab director), attractiveness remains an issue, mostly due to the geographic localisation of the centre.
The team has considered previous recommendations and made significant efforts to augment the lab visibility. This is in visible through collaborative programs involving members of the team. The LGMD group (group 2) has been very active in raising competitive funding (H2020 program). The PI leading the DMD project has left (retirement) and the project in its previous form was halted but the team will now focus on intellectual health in patients with DMD.
Efforts for hiring postdocs should be pursued.
Criterion 2: The team involve a large number of CECS members.
Efforts for hiring postdocs should be continued. Regarding the hosting of sabbatical researchers, funding was recently obtained from Evry University of the host, a visiting researcher for a few months.
Criterion 3: The strategy of the team remains largely focused on the use of stem cells.
Their expertise in this filed is clearly a force and efforts in developing innovative models should be pursued and expanded (organoids, bioprinting, ...) as it is a clear strength.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	2
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	19
Sous-total personnels permanents en activité	**25**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	1
Post-doctorants	1
Doctorants	6
Sous-total personnels non permanents en activité	**8**
Total personnels	**33**

EVALUATION

Overall assessment of the team

By taking advantage of the promises offered by disease-specific human pluripotent stem cells (HIPSCS), team 2 develops original lines of research in competitive fields. The team has produced excellent research towards the comprehension of several monogenic diseases while contributing to technological development and drug discovery. Its national and international visibility is excellent. It is involved in several scientific councils. It has been obtained substantial funding in highly competitive programs. The team participates in multiple outreach activities.

Strengths and possibilities linked to the context

The team has a long-standing expertise in the field of neuromuscular disease and stem cell research. This expertise allows proposing excellent integrated science aimed at improving comprehension of physiopathological mechanisms of several monogenic diseases and develop specific disease-modifying therapies. Moreover, it has produced new methodologies, in particular for stem-cell differentiation that are highly relevant to the field.

The scientific output of the team is very good with 72 publications (69/72 in open access journals, 34 in FLC position and 26 involving PhD students) in high impact journals such as Stem Cell Research, Nature communications, JCI insight, iScience, Scientific reports. Five patents were filled during the past period with one under licence.

The team takes full advantage of the excellent cutting-edge platform available on-site both for the development of its own lines of research or for collaborative programs including with the private sector. International visibility is excellent with twenty invitations to national or international conferences or institutes (mainly for the team leader).

Involvement in European and national networks is excellent to outstanding.
Non-academic links are excellent with very tight links with patients' associations.
A few prizes have been obtained during the period, in particular, the "Ordre National du Mérite" awarded to the team leader who is also the lab director.

Funding is substantial with successful applications to multiple highly competitive call, in particular during the last year of the contract with 3.319k€ granted in 2023 (PIA4 and H2020 program to group 1 and group 2 leaders respectively).

Group 1 led by the unit director is mainly focused on understanding the cellular and molecular mechanism underlying neuromuscular disorders (NDM) by focusing more specifically on three diseases, DM1, SMA and ALS. The strategy of the team was to develop cellular models for each of the respective diseases by using HIPSC as a model. By using high-throughput screening the team has contributed to the understanding of the molecular defects occurring at the molecular junction in different of these diseases. The group recently identified a new drug, Metformin that is currently investigated as possible therapy for DM1 (clinical trial). The team also identified other molecules that might lead to the development of a cure in other indications such as ALS/FTLD.

Group 2 led by a permanent researcher (Research Director) at CECS is mainly composed of permanent and non-permanent CECS staff members. The PI holds an HDR and supervises PhD students. Group 2 provided an extensive description of the past and future research project that are mainly focused on drug discovery or drug repurposing through drug screening or hypothesis-driven discovery in rare and ultra-rare diseases using induced pluripotent stem cells as the disease model. During the past period, group 2 has developed research programs aimed at identifying drug candidates for premature ageing syndromes and will now focus on neuromuscular diseases.

Group 3 led by a permanent Research Director at CECS is composed of four permanent CECS staff member. A. Benchoua holds a HDR and supervises one PhD student (who will defend in 2025). Group 3 conducts fundamental research aimed at deciphering the physiological and pathological development of the central nervous system to identify new therapeutic options in Phelan Mc Dermid (PMS) or Lesch-Nyhan disease. The team also develops a research program on Dystrophinopathies. The team is involved in a phase I/II clinical trial on PMS.

Weaknesses and risks linked to the context

Of the three academic researchers (1DR, 1 MCU, 1CRCN) that composed the team, one has recently left, leaving the team leader who is also the head of the lab as the only full-time permanent academic researcher of the team -group 1.

The team is internationally renowned and should try to attract more postdocs, including postdocs from abroad. The excellent level of funding and the access to cutting platform should improve the attractiveness of the team and the interest for young researcher to join a dynamic environment.

The distribution of tasks and priorities could have been described in more detail for groups 2 and 3.

Training of PhD should be encouraged, as there are five "HDR" in the team.

Analysis of the team's trajectory

In the upcoming contract, group 1 aims at developing a novel strategy including 3D cell culture models toward the explorations of NMDs and establish a specific DM1 transcriptomic atlas in order to identify markers of disease progression towards the identification of druggable targets. Furthermore, the team will develop organoid-based strategy to investigate function and dysfunction of the neuromuscular junction in diseases (DM1 and SMA), but also the brain dysfunction in DM1. The development of therapeutic approaches remains a constant preoccupation of the team and the main outcome of all research program.
The workforce involved in the different lines of research is indicated and distribution of tasks seems well balanced with regard to the expected outcomes.

Group 2 recently reoriented its research program toward the identification of therapies for Limb girdle muscular dystrophies and Glycogenosis storage disease, with a focus on autophagy for several of the research program. The group leader has been actively involved in European networks and the European H2020. As a PI, he recently created the Dreams consortium funded by the H2020 research framework. This international consortium involving academic researchers and private stakeholders aims at taking advantage of the "shared molecular etiology" concept for drug discovery for rare diseases. For group 2, the workforce involved in the various lines of this ambitious research program is not indicated.

Group 3 is involved in the INOVAND IHU on children's neurodevelopmental trajectories and will more specifically focus on Autism and neurodevelopmental disorders by bringing its expertise in HIPSC-based disease modelling.

RECOMMENDATIONS TO THE TEAM

The team that is internationally renowned provides an excellent scientific environment. The committee suggests attracting more postdocs, including postdocs from abroad.

The committee also encourages the team to recruit permanent academic research as a large proportion of team members belong to CECS.

The committee recommends to maintain or increase efforts in publishing in top-notch journals.

CONDUCT OF THE INTERVIEWS

Date

Start: 30 October 2024 at 8 a.m.

End: 30 October 2024 at 18:00

Interview conducted: online

INTERVIEW SCHEDULE

8:00 - 8:15 Testing Zoom connections

8:15 - 8:30 Closed session Expert Committee (EC) – Scientific Officer (SO)

Assessment of the Unit, Scientific Plenary session

8:30 - 8:40 Presentation of the EC to the staff members by SO

8:40 - 9:25 Presentation of the unit by Cécile Martinat (30 + 15 min questions)
Attending: EC, SO, all the unit members

Presentation of the teams

9:25 - 10:20 Cell-based innovative therapies for Monogenic Ectodermal Diseases – Christelle Monville
- Axe 1: Rétinopathies (Christelle Monville)
(18 min presentation + 5 min questions)
Attending: Team members, EC, SO, director of the Unit

- Axe 2: Genodermatosis (Christine Baldeschi)
(12 min presentation + 5 min questions)
Attending: Team members, EC, SO, director of the Unit

Axe 3: Wolfram syndrome (Laetitia Aubry)
(5 min presentation + 5 min questions)
Attending: Team members, EC, SO, director of Unit

+5' private discussion with the PI (Christelle Monville); attending: EC+SO

10:20-11:15 Team 2–Therapeutic development for Neuromuscular Diseases, Cécile Martinat
- Axe 1: Motoneuron Diseases (Cécile Martinat**)**
(18 min presentation + 5 min questions)
Attending: Team members, EC, SO, director of the Unit

- Axe 2: Pharmacology of muscular dystrophies (Xavier Nissan)
(12 min presentation + 5 min questions)
Attending: Team members, EC, SO, director of the Unit

Axe 3: Neuroplasticity and therapeutic (Alexandra Benchoua)
(10 min presentation + 5 min questions)
Attending: Team members, EC, SO, director of Unit

11:15-12:00 Break – Closed session with EC and SO

12:00-12:30 Closed session with researchers and professors
Attending: Researchers except group leaders, EC, SO

12:30-1:30 p.m. Lunch Break

1:30 p.m.-2 p.m. Closed session with thesis students and postdocs
Attending: PhD students and postdocs, EC, SO

2 p.m.-2:45 p.m. Closed session with technical and administrative personnel
Attending: Technicians, Engineers, Administrative staff, EC, SO

2:45 p.m.-3:30 p.m. Break – Closed session with EC and SO

3:30 p.m.-4 p.m. Closed session with the representatives of supervising bodies
Attending: expert committee, representatives of Institutions, SO

4 p.m.-4:30 p.m. Closed session with the head of the unit
Attending: Unit Direction, expert committee, SO

4:30 p.m.–18:00 Meeting of the Committee – Finalization of the report (closed hearing)

PARTICULAR POINT TO BE MENTIONED

N/A

GENERAL OBSERVATIONS OF THE SUPERVISORS

**DIRECTION DE LA RECHERCHE,
ET DES RELATIONS INTERNATIONALES**

1ère Vice-présidente de la Recherche
Christelle MONVILLE

2nd Vice-président de la Recherche
Guillaume TIFFON

Affaire suivie par : Carole TROUSSIER

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Evry, le 11 Férvier 2025

A l'attention de la Présidente
du comité d'experts HCERES

Rapport d'évaluation HCERES du Laboratoire I-Stem (DER-PUR260024984)

Madame la Présidente du comité d'experts HCERES,

Nous avons pris connaissance avec le plus grand intérêt du rapport détaillé du comité d'experts HCERES concernant l'activité du Laboratoire I-Stem (Institut des cellules Souches pour le Traitement et l'Etude des maladies Monogéniques) dont les tutelles sont l'université d'Évry Paris Saclay et L'INSERM, dans le cadre de la campagne d'évaluation 2019-2023 vague E.

Nous tenons à remercier le HCERES et tout particulièrement le comité de visite, qui malgré une tenue en distanciel de l'évaluation, a eu une écoute bienveillante ainsi que pour l'efficacité et la qualité du travail d'analyse conduit.

Nous avons reçu avec satisfaction votre appréciation positive concernant d'une le fonctionnement de notre laboratoire avec la complémentarité des équipes de recherche et les plateformes technologiques; d'autre part l'attractivité reconnue et les résultats : la progression tant qualitative que quantitative des publications, brevets, essais cliniques ainsi que la capacité de l'unité à lever des fonds ; enfin le lien de l'unité avec le grand public et la société à travers de nombreux évènements (conférences dans les collèges et lycées, Téléthon, article de presse et interviews, débats sociétaux).

Notre objectif pour le prochain mandat est de poursuivre ces dynamiques qui demeurent au cœur de nos priorités, tout en prenant en compte les points d'amélioration soulignés par le comité. Nous porterons ainsi une attention plus particulière à l'orientation de nos publications, en favorisant des recherches plus mécanistiques au service de notre

recherche translationnelle. Nous souhaitons également renforcer l'attractivité de notre unité en recrutant de nouvelles équipes de jeunes chercheurs et en poursuivant l'effort de recrutement de chercheurs post-doctorants internationaux. Illustrant ce point, nous avons recruté l'année dernière une jeune scientifique en tant que CRCN au concours Inserm et que notre laboratoire présente un deuxième candidat cette année au concours; enfin nous poursuivrons le dialogue avec nos tutelles pour permettre le renforcement des postes techniques et soutenir durablement nos activités de recherche.

Bien cordialement,

Vincent BOUHIER
Président
Université Évry Paris-Saclay

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