agence d'évaluation de la recherche
et de l'enseignement supérieur

Department for the evaluation of research units

AERES report on unit:

Immunology, Dermatology and Oncology

Under the supervision of the following institutions and research bodies:

Université Paris 7 – Denis Diderot

Institut National de la Santé Et de la Recherche Médicale

Centre National de la Recherche Scientifique

January 2013

agence d'évaluation de la recherche
et de l'enseignement supérieur

Research Units Department

President of AERES

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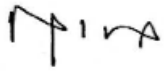
Department Head



Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).
This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.
NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1 : Scientific outputs and quality ;
Criterion 2 - C2 : Academic reputation and appeal ;
Criterion 3 - C3 : Interactions with the social, economic and cultural environment ;
Criterion 4 - C4 : Organisation and life of the institution (or of the team) ;
Criterion 5 - C5 : Involvement in training through research ;
Criterion 6 - C6 : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report (and, when necessary, its in-house teams) received the following grades:

- Grading table of the unit: Immunology, Dermatology and Oncology

C1	C2	C3	C4	C5	C6
A+	A+	A	A+	A	A+

- Grading table of the team: Pathophysiology of CTCL and Immunity

C1	C2	C3	C4	C5	C6
A+	A+	A+	A+	A	A

- Grading table of the team: Oncogenesis of Melanoma

C1	C2	C3	C4	C5	C6
A+	A	A	NN	A	A+

- Grading table of the team: Epithelial pathophysiology, stem cells and tissue repair

C1	C2	C3	C4	C5	C6
A+	A+	A	NN	NN	A+

Evaluation report

Unit name:	Immunology, Dermatology and Oncology
Unit acronym:	
Label requested:	UMR-S
Present no.:	U976
Name of Director (2012-2013):	Mr Armand BENSUSSAN
Name of Project Leader (2014-2018):	Mr Armand BENSUSSAN

Expert committee members

Chair:

Mr Alain TAIEB, Université de Bordeaux

Experts:

Mr Vladimir BOTCHKAREV, Bradford University, United Kingdom

Ms Silvia DEAGLIO, Torino University, Italy

Mr Jean-Philippe LACOUR, Nice University (CNU representative)

Mr Miguel LOPEZ BOTET, Pompeu Fabra University, Barcelona, Spain

Ms Fathia MAMI-CHOUAIB, Gustave Roussy Institute, Villejuif (CoNRS representative)

Ms Annie SCHID-ALLIANA, Nice University (INSERM representative)

Mr Maarten VERMEER, Leiden University, The Netherlands

Scientific delegate representing the AERES:

Mr David DOMBROWICZ

Representative(s) of the unit's supervising institutions and bodies:

Ms Isabelle HENRY, INSERM representative

Mr Benoît SCHLEMMER, Paris Diderot University representative

1 • Introduction

History and geographical location of the unit

This unit was previously located at Hôpital Henri Mondor in Creteil since 1996 (INSERM U448, U 659, UMR_S 841, creation and recreation under the same director, Mr A. BENSUSSAN). The current unit INSERM UMR-S 976 was created in 2009 at Hôpital Saint Louis, the historical Centre for Dermatology in France. Following an international call for applications from the host institution, Paris-St Louis Hospital/University Paris 7 Diderot, a new management was implemented combining research and clinical teams. Ms M. BAGOT, who was closely associated to the research unit since its creation at Hôpital Henri Mondor was appointed as Chair in charge of the merged clinical departments of Dermatology of the site and is acting as vice-director of the unit and co-team leader for team 1.

The new application (starting 2014), takes into account the request of the St Louis Hospital to include reconstructive surgery and regenerative medicine in association with dermatology and dermato-oncology, in parallel with the clinical activities located in the Hospital (plastic surgery, burn unit). The recruitment of a third team (Mr D. ABERDAM, epithelial stem cells, previously head of INSERM U898 in Nice) matches this goal. The founding unit has also recruited since 2009 a group to work on melanoma (leader team 2, Mr N. DUMAZ) besides cutaneous lymphoma, which was the core topic of the initial group.

As a consequence, the team has grown in size, and its proposed structure for the current evaluation includes 3 distinct teams.

- Team 1 pathophysiology of cutaneous T cell lymphomas (CTCL) and cutaneous immunology
- Team 2 oncogenesis of melanoma
- Team 3 epithelial pathophysiology, stem cells and tissue repair.

Management team

The director (Mr A. BENSUSSAN) works in close collaboration with Ms M. BAGOT, who heads Saint-Louis Hospital Dermatology department and the French national cancer institute INCa's sponsored national reference centre for cutaneous lymphomas. They have implemented a management plan according to the Institution's ambitious roadmap (1) develop a centre of excellence for skin disorders and skin biology, including cutaneous oncology beyond lymphomas and chronic inflammatory skin disorders, (2) add regenerative medicine in the research theme to foster collaboration with the burn/reconstructive medicine department at St Louis Hospital, with (3) overall a strong emphasis on translational programmes and industrial collaborations.

INSERM has provided help with the recruitment of an administrative manager in the unit.

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	5 (1.4)	9 (2.6)	5
N2: Permanent researchers from Institutions and similar positions	6	15 (13.6)	6
N3: Other permanent staff (without research duties)	7 (6.6)	9 (8.6)	5
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	5	4	5
N6: Other contractual staff (without research duties)	2		1
TOTAL N1 to N6	**26** (22)	**38** (29)	**23**

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit*	5	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	12	22

2 • Assessment of the unit

Strengths and opportunities

- Balanced structuration for a main focus on Dermatology research including a multidisciplinary team (dermatologists, plastic surgeons, ophtalmologists, immunologists, cell and molecular biologists) with strong interaction between clinical and research groups. The close collaboration with clinical departments (dermatology, plastic surgery, ophthalmology) fosters existing and future translational research from discovery of novel phenotypic markers (e.g CTCL, melanoma), in vitro investigation of functional consequences, to drug development and clinical trials.
- Recognised expertise of individual members and team leaders: CTCL, melanoma genetics, skin ESC and iPSC.
- Existence of education tracks for M.D. Ph.Ds in Dermatology and Master degrees in Dermatology/ Democosmetics.
- Influx of a new team with excellent credentials and of talented young scientists.
- Generation of unique monoclonal antibodies with potential use in cancer immunotherapy.
- Good to excellent list of publications both for basic research and clinical research.
- Industrial valorisation (several patents, teams 1 and 2) and industrial partners.
- Very good funding profile (National institutes and Charities, EU, Industry).
- Strong local partnership with the Institute of Hematology (IUH) of Hospital Saint-Louis, a major international player in the field which should foster collaborations around lymphomas/leukemias, and gives access to research platforms.
- Implication and leadership (in top 5 at international level for CTCL according to visit committee) in national and international collaborative research (EORTC, Genomel, p63).

Weaknesses and threats

- Animal models: the visiting committee has specifically investigated this aspect which was acknowledged as a weakness by the team leader, because specific models are lacking for CTCL. For melanoma, patient-derived tumour xenografts are available and human-based alternative preclinical assays are implemented (histocultures, circulating tumour cells). The animal house facilities for mouse studies are of good standing. Team 3 has generated relevant mouse models transiently hosted at other institutions.
- Interaction between teams around a major common theme are lacking. This aspect needs to be addressed in the five year plan.
- It has been noted that the number of academics working in CTCL is planned to decrease in the next 5 years raising questions about sufficient clinical backup available in the future for this field. Another weakness is the human resources in pathology for both human and animal studies. The vice-president of the host university has however informed the committee that this aspect of recruitment is a priority.

Recommendations

- Strengthen scientific interactions between the 3 teams: immunology of melanoma, cancer stem cells, reconstructed skin models are some possibilities for stronger interaction, but choices are difficult in very competitive areas and niches which combine added value of expertise of each team should be priorised.
- Increase collaboration with the strongest local partner (Institute of Hematology), with obvious common research interests.
- Besides scientists, plan balanced recruitment of pathologists and clinical researchers in accordance with major research fields, especially CTCL, immunodermatology, melanoma, regenerative medicine for adequate backing of research plans.
- Put more emphasis on drug discovery and therapy especially for CTCL, chronic inflammatory skin disorders and regenerative medicine.

3 • Detailed assessments

Assessment of scientific quality and outputs

The 3 teams work on original projects and have made valuable progress in the field of CTCL, melanoma and stem cells over the last 5 year period. The unit members regularly publish in very good specialized and more general international journals.

Of note, in the 143 listed papers 2007-2012 for **Teams 1-2**

- best specialty journals in **dermatology** and **immunology** with members as first/last authors (5 J Invest Dermatol, 10 Blood, 7 J Immunol, 1 Immunity, 1 Immunol Rev) and **cancer** 2 Oncogene, 2 Clin Cancer Res, 1 J Clin Oncol, 1 JNCI, 1 Lancet Oncol
- High impact **general scientific publications** with members as first/last authors : 1 Nat Struct Mol Biol, 1 J Exp Med and in collaboration 4 PNAS, 1 JCI
- Collaborative papers in the **most prestigious medical journals** : 3 N Engl J Med (melanoma trials, 1 JAMA (Kaposi HHV8)

For the newcomer Team 3 of a list of 29 papers for the same period (corresponding to restructuration and moving from Nice to Paris with concomitant direction of Israel Institute of Technology stem cells lab)

- General scientific publications with members as first/last authors: 1 PNAS, 6 Cell Death Differ, 3 Stem Cells
- Collaborative papers 1 Mol Cell, 1 PNAS, 1 J Cell Biol, 1 J Invest Derm

For Teams 1-2 major grants have been obtained at National (ANR, INCa, PHRC) and European levels, plus industrial contracts, totalizing more than **3,200 K€**. Of note, DGOS-INca funding 500 K€, European grant Euro-Trans-Bio 200 K€. For 2007-12 11 patents obtained of which 5 patents licenced and 4 with ongoing licensing. For Team 3, 2 ANR and one INCa grants as coordinator, and partnership in PF7 Epistem, and Erare2 SkinDEv, plus industrial support.

Assessment of the unit's academic reputation and appeal

As judged by the visiting committee, the overall reputation of the unit is rated good to excellent. Individual members are partners of international networks (EORTC, Genomel, Biogenomel, SkinDev). It is reflected by the status of associate editors in major specialty journal of several team members, numerous national and international scientific collaborations. The CTCL group is considered as top 5 at the international level. The organization of international congresses (13th International Congress of Immunology, Rio de Janeiro, 2007. 3rd European Congress of Immunology, Glasgow), international speaking invitations, international missions of expertise (US, Israel, Italy), nomination at scientific governing committees (INSERM), and presidence of the French Society of Immunology (2007-9) underline the visibilty of the unit's leader and co-investigators.

The appeal is recognizable by the number of doctoral and postdotoral students trained during the last 5 years (16) the ongoing addition of a reputed team (Team 3) and the high standard of young scientists currently recruited by the unit.

Assessment of the unit's interaction with the social, economic and cultural environment

The unit director has been awarded two distinctions for the creation of a Biotechnology startup company (OREGA-Biotech) and interacts with several industrial partners (Innate Pharma, Galderma, l'Oréal, Johnson & Johnson…) with potential influence in the economic and health care.

The royalties from licensing to the industry of several monoclonal antibodies has produced royalties managed by INSERM (average 400 K€/year).

Both the unit leader and his academic co-investigators have been successful to disseminate their knowledge by participating to several academic programs and student training.

As witnessed by the committee auditions, the doctoral and postdoctoral trainees have been able to find positions in academic or industry jobs.

Assessment of the unit's organisation and life

The visiting committee has interviewed separately 3 groups of staff members: scientists, doctoral and postdoctoral trainees, and technical staff, and concludes that the unit is well organized.

The unit has easy access to biological materials from CTCL and melanoma patients due to a good organization from the clinic to the laboratory, situated at a short distance, and due to the presence of clinical trainees and staff resulting in good interaction for research goals. The research platforms of the site are easily accessible with good technical supervision.

Bimonthly lab meetings are organized for all the unit members. Laboratory council (*Conseil de Laboratoire*) is organized twice a year. Monthly meetings with the unit director of all the ITA staff are also organized.

Visiting scientists are coming on a regular basis and other scientific meetings are scheduled within the institution, but also in other places in the Paris area and all the unit members have an easy access to all the information, via websites, newsletters and billposting on the lab's noticeboard.

The committee has not found evidence of conflicts for access to financial support of team members. Overall, the recurrent institutional funding is around 25-30% of the unit's budget. The recurring institutional credit lines have been submitted to a substantial drop as in other French laboratories (159 to 105 K€ from 2010 to 2011) due to the change in structuration of French funding agencies but other sources have compensated the loss. Each team has been able to obtain good level funding, which is allocated according to unequivocal internal rules. The recurrent funding given by INSERM and Diderot University is used for purchasing consumables or equipment shared by all teams.

In addition, multiple patent licensing (royalties donated to INSERM around 400 KE/year) generates stable resources which can be allocated to specific needs.

Assessment of the unit's involvement in training through research

The visit committee concludes after site visit and discussion that the students are well supervised and guided. The unit belongs to doctoral schools (*Ecoles Doctorales)* Paris 7 and Paris 12. 12 doctoral students from Universities P7 and P12 have been trained during the past 5 years. All students have been granted scholarships.

For predoctoral students, 5 M1 students and 13 M2 students from several Paris Universities (P5 P7, P11, P12, P13, Ecole Pratique des Hautes Etudes) have been supervised during their bench training in the lab. A special attention is given to predoctoral training for M.D.s and to encourage the most motivated to enter a Ph.D. program. The director and co-director are involved in national and international training networks and education programs.

Assessment of the five-year plan and strategy

The creation of a skin research center in Saint Louis hospital to associate dermatology and plastic surgery in an ambitious project has been clearly stated by the host institutions. The proposed projects are a logical extension of previous research conducted individually by the 3 teams and tries to implement the roadmap defined in 2009.

This reinforced unit has good capacity for adaptation and several researchers either from Saint-Louis or Faculty of Medicine in Nice have joined or will join the unit in 2014 to fill the regenerative medicine/epithelial biology gap. All the unit members work on original projects in close relationship with the clinic and benefit from several available platforms at Saint Louis Hospital, especially from the major research partner Institut Universitaire d'Hématologie. As it is, the strategy is a good mix of basic and applied research including a wealth of academic and non-academic partnership.

As underlined above (recommendations) the recruitment of M.D. Ph.Ds is a priority for a balanced development of translational projects, and the strengthening of collaboration between teams around common goals cross nurturing expertise is strongly recommended.

4 • Team-by-team analysis

Team 1 : Pathophysiology of CTCL and Immunity

Name of team leader: Mr Armand BENSUSSAN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	5	1	1
N2: Permanent EPST or EPIC researchers and similar positions	6	8	6
N3: Other permanent staff (without research duties)	7	6	6
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	3	3
N6: Other contractual staff (without research duties)	2	0	0
TOTAL N1 to N6	**26**	**19**	**17**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	12	8

• Detailed assessments

Assessment of scientific quality and outputs

Over the last 5 years, Team 1 expertise has been consolidated in the field of CTCL, especially diagnostic biomarkers. It has identified KIR3DL2 (CD158k) as a biological marker for CTCL. Additional biomarkers, such as NKp46 and T-plastin, have also been discovered. Novel aspects are investigated concerning innate immunity related to the development of CTCL, via KIR receptor activation and a role for environmental triggers such as CpG DNA fragments interacting with TLR9. In collaboration with an italian team, team 1 showed that KIR3DL2 on NK cells is also a ligand for CpG-ODN and that after complex internalization CpG-ODN can encounter its ligand TLR9 in early endosomes. The work on CD 160 has produced an unexpected advance in angiogenesis. An anti-CD160 mAb, produced by the team in collaboration with Philippe LE BOUTEILLER, displays anti-angiogenic properties and corresponds to a promising candidate for cancer immunotherapy. Therapeutic developments using anti KIR Mabs are under investigation using in vitro and in vivo models. The development of 3D reconstructed models with the input of Team 3 may provide interesting insights into pathophysiology especially the role of innate immunity agonists.

The investigation of NF-kB signalling in CTCL and cutaneous inflammation driven by necroptosis is a novel promising axis, as well as the part on regulatory B cells, and altogether this part needs to be developped to foster interaction between groups implicated in chronic inflammatory disorders and those focusing on CTCL;

The scientific production is of good to excellent quality. Team 1 regularly publishes in specialized and more general international journals of high impact factor. best specialty journals in **dermatology** and **immunology** with members as first/last authors (5 J Invest Dermatol, 10 Blood, 7 J Immunol, 1 Immunity, 1 Immunol Rev). For high impact **general scientific publications** with members as first/last authors : 1 J Exp Med, 1 JCI, 2 PNAS and in collaboration 2 PNAS.

The ratio between the number of researchers and publications is balanced.

Patents (filed and licensed) illustrate the concern and competence of the unit for tranferring results to the industry. Competitive funding, both national and european, has been obtained.

Assessment of the unit's academic reputation and appeal

Researchers of team 1 have a strong and internationally recognized expertise in several aspects of cutaneous T cell lymphoma (CTCL) biology acknowledged by a solid publication record and involvement in national and international networks (EORTC, EuroTransbio). The CTCL group is considered as top 5 at the international level. The organization of international congresses (13th International Congress of Immunology, Rio de Janeiro, 2007. 3rd European Congress of Immunology, Glasgow), international speaking invitations, international missions of expertise (US, Israel, Italy), nomination at scientific governing committees (INSERM), and presidence of the French Society of Immunology (2007-9) underline the visibilty of the unit's leader and co-investigators.

The appeal is recognizable by the number of doctoral and postdotoral students trained during the last 5 years (15).

Assessment of the unit's interaction with the social, economic and cultural environment

This part has been detailed above for the whole unit appreciation. To summarize, the team has solid partnerships with non-academic partners (Innate Pharma, L'Oréal…). with potential influence in the economic and health care. Team 1 director is a co-founder of a start-up in biotechnology (AREGA-BIOTECH in 2010). This team has produced several unique mAbs with promising transfer potential in to the clinic. Several biomarkers associated with CTCL have been patented and/or licensed and team has developed with Innate Pharma a diagnostic Kit for Sesary Syndrome based on anti-CD3, anti-CD4 and anti-KIR3DL2 labeling. Director and co-director regularly disseminate their knowledge by participating to scientific programs as well as student training, and have published reviews of their work in scientific journals.

Assessment of the unit's organisation and life

See previous comments on the whole unit, which apply here.

Assessment of the unit's involvement in training through research

See previous comments on the whole unit, which apply here.

Assessment of the five-year plan and strategy

The proposed goals have a clear translational scope, being based on the expertise of the team and, in general, on previous achievements that are well described. Presentation of the objectives is systematic and clear, including relevant unpublished information which contributes to justify their scientific interest and rationale. The intricate relationships between innate immunity, inflammation and initiation of lymphoma has not been sufficiently highlighted in the research plan and can be developed further given the expertise of the recruited scientists.

The previous comments on the whole unit for recruitment of clinician-scientists and pathologists applies to team 1

Conclusion

- Strengths and opportunities

Team 1 has a long-standing and solid experience in the characterization of human leukocyte receptors, successfully oriented towards translational research in the diagnosis and therapy of CTCL with outstanding ability to transfer results to the industry. A diagnostic kit has been developed with Innate Pharma. It has the opportunity to develop immunotherapeutic strategies in CTCL by targeting KIR3DL2 such as by using chimeric mAb. Team 1 has also a very good experience with CD160 structure, expression regulation and functions.

The team has also a good experience with Treg cells, in particular $CD39^+$ Treg, and their immunosuppressive function via production of adenosine. Targeting CD39 using an anti-CD39 mAb generated in the laboratory offers immunotherapeutic opportunities mainly in melanoma and HIV infection.

- Weaknesses and threats

- CD160-GPI and NK/T lymphoma parts of the project are still exploratory and needs to be further developed.
- A preclinical CTCL mouse model is lacking.
- Team 1 has undertaken several collaborative studies on Treg, Breg, mast cells etc… in which it is much less competitive than in CTCL.

- Recommendations

Overall, the goals proposed for the next five years are satisfactory. Yet, the team together with the Dermatology Dpt., should eventually consider the opportunity to explore strategies aimed at progressively broadening the scope of their synergistic research in Immunodermatology to bridge innate immunity, inflammation, and CTCL initiation.

Stronger scientific interaction with the other teams, in particular team 2, should be developed in the five-year plan.

Given the needs for novel therapies in CTCL, give more priority to drug discovery and therapy, such as immunotherapy based on KIR3DL2.

4 • Team-by-team analysis

Team 2 : Oncogenesis of Melanoma

Name of team leader: Mr Nicolas DUMAZ

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		5	4
N2: Permanent EPST or EPIC researchers and similar positions		3	1
N3: Other permanent staff (without research duties)		2	1
N4: Other professors (PREM, ECC, etc.)		0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		0	0
N6: Other contractual staff (without research duties)		0	0
TOTAL N1 to N6		**10**	**6**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		8

• Detailed assessments

Assessment of scientific quality and outputs

The team leader is a scientist (CNRS) with a strong expertise in the field of melanoma signaling. He will be assisted by two senior clinicians/researchers (PU/PH), with respectively expertise in melanoma clinical research/oncodermatology and dermatology oncogenetics. Team 2 has been emerging over the last 5 years and consists of ten researchers (scientists or academics), including seven from the former sub-group 'Oncogenesis of Melanoma' of the unit developing a project articulated around two major axes: signaling and genetics combined with a strong translational axis.

The signaling axis, directed by the team leader, has focused on the role of RAS/RAF/MEK/ERK (MAPK), PI3K/AKT and cAMP pathways in melanocyte transformation and melanoma proliferation and invasion. The aim has been to understand how these pathways are activated or inhibited in melanocytes and melanoma and how they interact to regulate melanoma growth. This study has led to the identification of new potential melanoma therapeutic targets (Kit, CRAF, PDE4).

Besides this fundamental work, a translational study has been conducted, in collaboration with the Department of Dermatology of the Institut Gustave Roussy, to understand the development of squamous cell carcinomas (SCC) associated with the use of Raf kinase inhibitor (Sorafenib) in the treatment of melanoma.

The publication's record in relation with this work is very good: 6 articles in good to very good international journals (Small GTPase; Clin Cancer Res; Nature Structural and Molecular Biology, Oncogene, Plos One, Arch Immunol Ther Exp, mean IF=6,5) reporting original findings and 2 reviews. This work has also led to a patent, a licence agreement of a cell line with Sanofi-Aventis and a collaboration agreement with L'Oréal.

The melanoma genetics axis, more clinically oriented, is directed by one of the 2 senior scientists, Dermatologist and Professor of Genetics. The research has been mainly oriented on the study of genes involved in predisposition to skin cancers (basal cell carcinoma, melanoma) and genes involved in melanoma progression.

This research has allowed to identify new genetic biomarkers in skin cancers (4 patents filed) as well as genetic factors involved in melanoma progression.

Since 2007, the scientific production of this axis has been good with 19 publications in Genetics and Dermatology journals reporting original findings (mean IF=4,2) and 2 reviews.

Along with these two axes, one the senior scientists (Head of Onco-Dermatology Department of Hôpital St Louis, Paris) has mainly conducted her research in collaboration within INSERM U940 where she contributed, through a translational study, to highlight the key role of the CD147/EMMPRIN molecule in the melanoma angiogenesis and lymphangiogenis. The number of publications of this senior scientist is impressive with more than 60 papers in the last 5 years as senior author or co-author, among which about 90% have an IF >4. Most of the publications arise from clinical activity, many of them are in prestigious (New Engl J Med (3), J Clin Oncol (2), Lancet Oncol) or very good (Plos Pathog, Clin Cancer Res, Blood, Clin Infect Dis, J Natl Cancer Inst…) journals.

Assessment of the unit's academic reputation and appeal

It seems premature to assess the academic reputation and appeal of this new team as a whole. However, the visiting commmittee has made observations regarding individual members.

The team leader was awarded (2011) a translational research contract with 'Assistance Publique-Hôpitaux de Paris' and has raised numerous funds from various national sources (Ligue Nationale Contre le Cancer, Société Française de Dermatologie, Fondation de France, INCA, PHRC), which is the marker of a national recognition. Besides, the team leader has an adequate visibility, as attested by invitations to meetings (mostly national), in the last ten years, by his activity as reviewer for AACR publications and for grants delivered by AICR (UK) and Ministry for Education University and Research of Italy.

Moreover, other researchers of the team are implicated in important national or international genomic and clinical research networks (Genomel, BioGenomel, Melancohort, INCA, PHRC). One of the senior scientist is recognized for his expertise in oncogenetics applied to dermatology at the National and European level, and has produced an important contribution to the diagnosis of xeroderma pigmentosum with the discovery of founder mutations for XPC and XPA in Maghreb families. The other senior scientist is recognized as a leader in melanoma and cutaneous oncology clinical research by her peers at the national and international level.

Assessment of the unit's interaction with the social, economic and cultural environment

The socio-economic output of the three PI together is good for a young team with filing of 4 patents (without licensing) and a licence agreement with an industrial group.

Assessment of the unit's organisation and life

It is also too early to evaluate adequately the management of the team. However, the team leader was able to organize a well-structured team, well-balanced in terms of the ratio of scientists/researchers whose skills and expertise in the biology and translational aspects of melanoma are complementary. Nevertheless, it should be noted, from the bibliographic analysis, that all the researchers of this team have had, in the past, little interactions with the team leader. There is a relative imbalance between the high number of senior researchers (scientists or clinicians) and the low number of junior ones. This should be corrected by the scheduled arrival of three postdocs in 2014.

Assessment of the unit's involvement in training through research

The involvement of the team members in educational activities is quite good due to the high number of professors (5). Moreover, most members of the team are involved in the training of pre-doctoral (master degrees) and Ph.D. students.

Assessment of the five-year plan and strategy

Based on published results and expertise, this new team proposes a bench-to-bedside research program centred on melanoma biology. Three major axes will be developped with a clearly-defined common objective to discover new targets for melanoma treatment and novel biomarkers for melanoma susceptibility.

The axis dedicated to the study of signal transduction addresses melanomas not yet eligible for new targeted therapies, namely Ras mutated, acral and mucosal melanomas. The goal is clearly defined and derives logically of the previous work of the team leader. The program of this axis is ambitious. The program of this axis being ambitious, the team could be strengthened to ensure a high level of competitiveness in the field.

The second axis, aimed at characterizing genetic biomarkers involved in melanoma susceptibility and progression, is a continuation of the past work of one of the senior scientist. Given the size of the group, the feasibility of the project is correct, especially since the researchers implicated have already in the past, collaborated and co-published together.

The third axis aims to identify, in melanoma microenvironment, novel therapeutic targets involved in tumour progression. In this context, the project focuses, on the one hand, on translational studies of two molecules, EMMPRIN and FERMT3, overexpressed in melanoma and known to induce MMPs expression and, on the other hand, on the role of kallikreins, a family of proteases. While the relevance of the various projects is very good and well-structured, the adequacy between manpower and real time implication for the clinicians to develop these projects is questionable, especially since these clinicians are also involved in an important pharmacology research project.

The whole project is fully relevant and of importance in the field. Nevertheless, the three axes are articulated in a series of 12 sub-topics, which, in view of the team's size, seems excessive to maintain a high competitiveness.

The access to clinical samples and to a preclinical platform are clearly added values.

Conclusion

- Strengths and opportunities

The team has a good experience in translational cancer research leading to contribution in the discovery of new biomarkers. The group has been able to fund its research by grants obtained from competitive calls such as INCa and PHRC. The addition of the group of one of the senior scientist who is publishing at a high level and brings in the collaboration with a preclinical screening platform (pharmacogenomics) and access to large national cohorts and biobank (Melbase) as well as phase I trials is a major asset for this team.

- Weaknesses and threats

The number of post-docs and full time researchers involved in basic projects is too low in a very competitive field. Dispersal is a major risk for the competitivity of the team. It was not obvious at the visit that all sub-groups of this team fully benefit presently from the expertise each other but they seem keen to develop synergistic projects.

- Recommendations

It would be wise to clearly better define priorities in the project and to allocate adequate resources accordingly.

4 • Team-by-team analysis

Team 3 : Epithelial pathophysiology, stem cells and tissue repair

Name of team leader: Mr Daniel ABERDAM

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		3	
N2: Permanent EPST or EPIC researchers and similar positions		4	
N3: Other permanent staff (without research duties)		1	
N4: Other professors (PREM, ECC, etc.)		0	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		1	
N6: Other contractual staff (without research duties)		0	
TOTAL N1 to N6		**9**	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		6

• Detailed assessments

Assessment of scientific quality and outputs

Knowledge of the mechanisms that control stem cell maintenance and activity during postnatal life is highly important for better understanding their role in organ regeneration and tumorigenesis. The research program of the team ("Epithelial Pathophysiology, Stem Cells and Tissue Repair") focuses on delineating the molecular mechanisms that control stem cell activity in the skin and other organs during development and postnatal regeneration.

The advantage of this highly successful program is a unique focus on the transcription factor- and microRNA-regulated mechanisms that control stem cell activity in the developing and regenerating tissues. Following this route, the team has made several important discoveries that reveal an important role for micro-RNAs in fine-tuning the genetic programs regulating in adult stem cells by lineage-specific transcription factors.

The data generated by the team during the last five years (2008-2012) are summarized in 21 original publications and reviews on different aspects of stem cell biology and tissue regeneration. It is important to note that this output was generated while the team was moving from Nice to Paris, with a strong interaction with Israel Institute of Technology, where the team leader has served as co-director of a stem cell lab under the auspices of INSERM and Technion. The 21 listed research papers are published in highly-ranked and prestige scientific journals, such as Proceedings of National Academy of Science USA (1), Mol Cell (1), J Cell Biol (1), Trends in Biochemical Sciences (1), Stem Cells (3), Cell Death and Differentiation (6), Journal of Investigative Dermatology (1), which is an important indicator of the high-quality research generated in this lab. General scientific publications with members as first/last authors.

Assessment of the unit's academic reputation and appeal

The team leader and his team have an undisputably high academic reputation in many different areas of bio-medical sciences, such as developmental biology, stem cell biology, investigative dermatology,etc. The team is very productive and continuously generates high-quality data, which always receive positive feedback from the colleagues.

The strong academic reputation of the team is also evident from the fact that the team leader serves as a member of the Editorial Boards of several international journals including Stem Cells that publish a high-quality reports on the modern aspects of stem cell biology and tissue regeneration, and that he has been appointed since 2006 co-director a joint Israeli-French lab on stem cells located at the Israel Institute of Technology (Technion).

Assessment of the unit's interaction with the social, economic and cultural environment

The team actively interacts with social, economic and cultural environment via:

1. Communication with broad groups of researchers working in different areas of experimental biology and medicine throughout the project, demonstrating how complex approaches used for this study can lead to deeper understanding and progress of the research.

2. Publishing the results of this project in open-access high impact peer-reviewed journals and book chapters available for broad audience.

3. Engaging with the public audience directly through the institutions funded by the project and indirectly through the print, broadcast and online media to promote further understanding of developmental/stem cell biology and ageing in driving progress in these areas.

4. Communication with the pharmaceutical/cosmetic industry in exploring the application of different small molecules for modulation of skin regeneration and ageing.

5. The application to the rare disease p63 mutated ectodermal dysplasia group as a model is important for this group of patients and beyond for skin aging, bone development, and further dermocosmetics development in skin aging and hair biology.

6. Implication in ethical law on stem cells at French Senate and National hearings.

Assessment of the unit's organisation and life

The team consists of several sub-groups and includes 10 full-time research positions. The activity of members of the team is concentrated around five research projects focused on both fundamental and applied aspects of the molecular control of stem cell activity and tissue regeneration. Because of the appropriate combination of the experienced and young researchers working on different projects, the unit looks as very sustainable, capable of generating high-quality data and has a strong potential for further development. The addition of young investigators coming from plastic surgery and ophthalmology is expected to expand the applied research branch of the group and to develop translational projects locally in Saint-Louis Hospital.

Assessment of the unit's involvement in training through research

In Nice and Marseille, the team leader has been teaching on Stem Cells 2005-2012, and he has trained a team in Israel with the nomination of an assistant professor who is now taking the lead at Technion's stem cells lab.

Assessment of the five-year plan and strategy

The five-year plan presented by this unit consists of five distinct projects, which are closely linked to each other and also connected to the projects proposed by other groups (Team 2). The general focus of the five-year program is to delineate molecular mechanosms that control stem cell activity in epithelial tissues (skin, cornea) in normal and pathological conditions including EEC syndrome.

The major advantage of this program is a focus on integration on the transcription factor- and microRNA-regulated mechanisms that control stem cell activity in the developing and regenerating tissues. The team will study the role of microRNAs in the modulation of the genetic program regulated by p63 trahscription factor in epithelial stem cells and their progenies (Project 1), as well will define a role of microRNA-184 in the control of keratin 15 expression in keratinocyte stem cells (Project 2). These two projects are closely linked to Project 3, which will further study the role of NFAT as one of the important regulators of stem cell activity.

Project 4 will help to translate the results obtained in Projects 1-3 towards better understanding the role of epithelial stem cells and their progenies in the pathobiology of the ectodermal dysplasia EEC syndrome. Mr D. Aberdam's team will apply an iPS technology already established and extensively used in previous studies towards the correction of the EEC syndrome. Finally, the role of p63 and its target gene IGFBP-7 in the control of melanoma growth and progression will be studied in Project 5 as a part of collaboration with Team 2.

Overall, this five-year research program looks as very focused and balanced in terms of the combination of fundamental and applied aspects of the research, use of novel methods and approaches to understand biological roles of the transcription factor- and microRNA-mediated mechanisms of gene expression in epithelial stem cells and their progenies. All research methods and techniques required for execution of this program are available in the laboratory, which, together with high levels of expertise of the team members, suggest for a feasiblity of the proposed studies and high probability for the succes.

Conclusion

● Strengths and opportunities

1) The team leader and his team are highly regarded by the international scientific community in terms of the excellent productivity and strong academic reputation in developmental and stem cell biology.

2) Research unit has an appropriate combination of the experienced and young researchers working on different projects of stem cell biology and pathophysiology, which makes the team as very sustainable and having a strong potential for further development in the new environment, especially with surgeons of the burn and plastic surgery department.

3) Research plan is very focused and balanced in terms of the combination of fundamental and applied aspects of the research, use of novel methods and approaches to understand biological roles of the transcription factor- and microRNA-mediated mechanisms of gene expression in epithelial stem cells and their progenies.

4) All research methods and techniques required for execution of this program are available in the laboratory, which, together with high levels of expertise of the team members, suggest a good feasiblity of the proposed studies and high probability for success.

● Weaknesses and threats

The only minor weakness of the program is the availablity of the animal models for the research at Saint-Louis site. However, animals have already been bred at other facilities in Strasbourg and Orléans and should be available for research using new animal housing facilities in Paris to resolve this issue.

● Recommendations

To further support this highly productive team and their unique research program, which success will ultimatetely help to better understand mechanisms controlling stem cell activity in normal and pathological conditions and develop new approaches to modulate their functions for the needs of regenerative medicine and stem cell-based therapy. Strengthening links with other teams should result in higher impact outcomes for the whole unit.

5 • Conduct of the visit

Visit date:

Start: January 22nd, 2013, at 8.30

End: January 22nd, 2013, at 18.00

Visit site: Hôpital Saint-Louis, Paris

Institution: INSERM, CNRS, Paris 7 University

Address 1, avenue Claude Vellefaux 75475 Paris Cedex 10

Specific premises visited: None

Conduct or programme of visit:

08h30-08h40 :	Welcome of the committee
08h40-09h00 :	Closed-door meeting of the committee
09h00-09h10 :	Introduction of the committee members and presentation of evaluation procedures and role of AERES
09h10-9h35 :	Project and achievements of UMR_S 976
	Armand BENSUSSAN
09h35-10h00 :	Discussion
10h00-10h25 :	Presentation Team 1
	Martine BAGOT & Armand BENSUSSAN
10h25-10h50 :	Discussion
10h50-11h05 :	Coffee
11h05-11h30 :	Presentation Team 2
	Nicolas DUMAZ, Nadem SOUFIR & Céleste LEBBÉ
11h30-11H55 :	Discussion
11h55-12h20 :	Presentation Team 3
	Daniel ABERDAM & Sébastien JAULIAC
12h20-12h45 :	Discussion
12h45-13h00 :	Meeting of the committee with the institutional representatives
13h00-14h15 :	Lunch + Posters
14h15-14h45 :	Parallel meetings of the committee with a. researchers and teachers b. students and post-docs c. Technical and administrative staff
14h45-17h45 :	Closed-door meeting of the committee, Equerre Bazin, Hôpital Saint-Louis

6 • Statistics by field: SVE on 10/06/2013

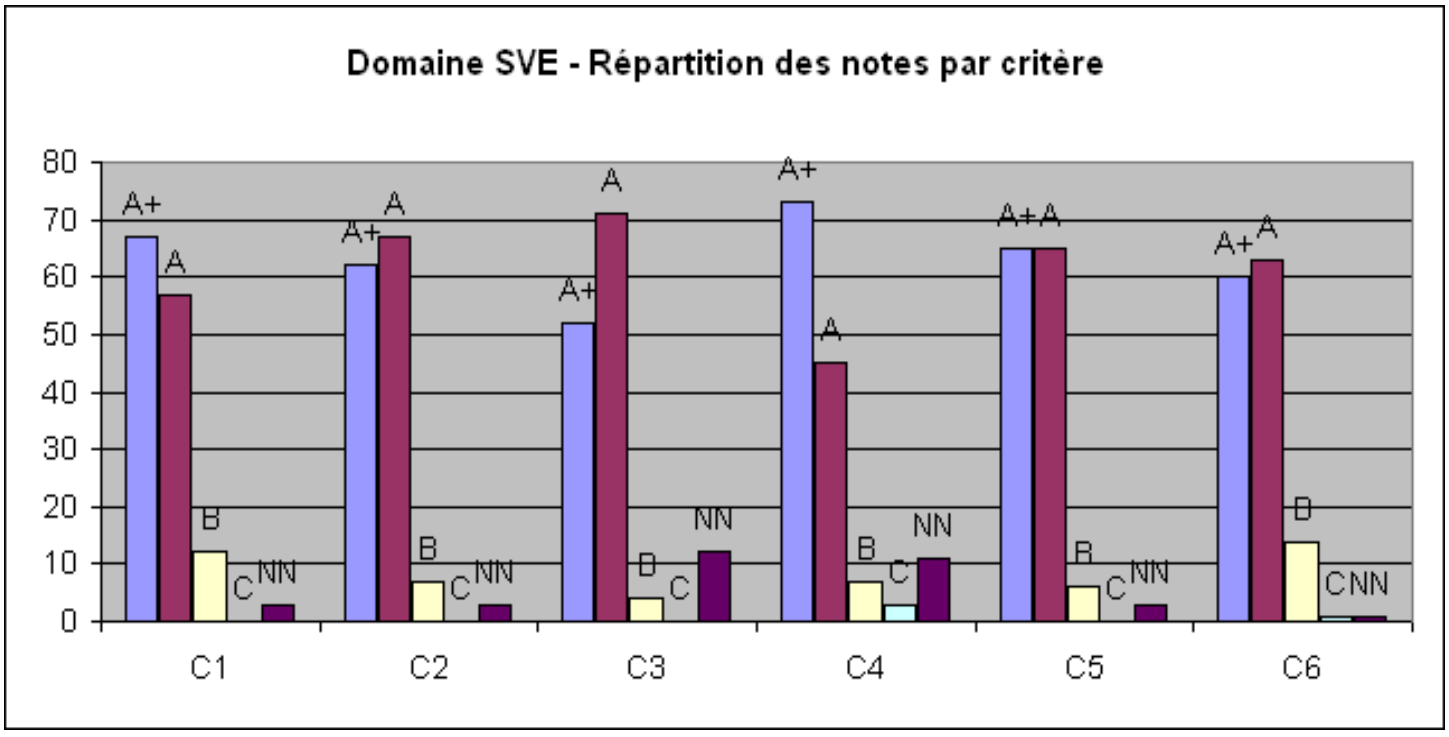
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



7 • Supervising bodies' general comments

Le Président

P/VB/RL/MCF – 062
Paris, le 5 avril 2013

A Monsieur Pierre Glaudes
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 Paris

Objet : S2PUR140006401 - IMMUNOLOGIE, DERMATOLOGIE, ONCOLOGIE - 0751723R

Monsieur le Directeur,

Je tiens en premier lieu à remercier les membres du comité de visite de l'AERES pour la production du rapport sur la situation de l'unité « Immunology, Dermatology and Oncology ».

L'excellent niveau de publications et la position de leader au niveau national et international sur le champ, entre autres, de la génétique des mélanomes, y sont mentionnés, ce dont je ne peux que me réjouir.

En terme de postes dont le comité s'inquiète de la diminution au prochain contrat, il a été dit au cours de la visite du comité, que le maintien, voire le renforcement de l'unité est une priorité, et de manière générale, l'université continuera d'apporter un fort soutien pour, à la mesure de ses moyens, conforter ce laboratoire et l'association avec l'INSERM.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de toute ma considération.

Vincent Berger

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Dr. Armand BENSUSSAN
Directeur
Email : armand.bensussan@inserm.fr

Paris, le 2 Avril 2013

Nous n'avons aucun commentaire significatif concernant le rapport d'évaluation de l'AERES concernant l'activité et le projet notre unité Immunologie, Dermatologie & Oncologie.

Armand BENSUSSAN