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

Department for the evaluation of research units

AERES report on unit:

Services de recherches en Hémato-Immunologie

CEA-DSV-iMETI-SRHI

Under the supervision of the following institutions and research bodies:

Commissariat à l'énergie atomique et aux énergies alternatives

Université Paris 7 – Denis Diderot

January 2014

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Ms Laurence AMIOT, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the experts committee, the composition of which is specified below.

The assessment contained herein are the expression of independent and collegial deliberation of the committee.

Unit name:	Service de Recherche en Hémato-Immunologie
Unit acronym:	CEA-DSV-iMETI-SRHI
Label requested:	Unité mixte CEA-Paris7
Present no.:	
Name of Director (2013-2014):	Mr Edgardo CAROSELLA
Name of Project Leader (2015-2019):	Mr Edgardo CAROSELLA

Expert committee members

Chair: Ms Laurence AMIOT, Université de Rennes 1

Experts: Mr François LEMOINE, Centre de recherche d'Immunologie et Maladies infectieuses CIMI-Paris (representative of the CNU)

Mr Thomas VAUVERT, University of Copenhagen, Denmark

Scientific delegate representing the AERES:

Ms Annick HAREL-BELLAN

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

Mr Eric QUEMENER, CEA

Mr François SIGAUX, University Paris 7 (representative of doctoral school B2T n° 273)

1 • Introduction

History and geographical location of the unit

The "Service de Recherches en Hémato-Immunologie" (SRHI) or Department of Blood Immunology Research was created in 1991 as a consequence of the Chernobyl accident; it is located at Hôpital Saint-Louis (AP-HP), within the "Institut Universitaire d'Hématologie (Bâtiment Lailler)" in Paris. The research unit on haematopoietic stem cell biology was part of this department. The research conducted by the SRHI has, since 1992, focused on the description of the function of the Human Leukocyte Antigen (HLA)-G molecule. The service is at the moment one of the four units of the Institute of Emerging Diseases and Innovative Therapy (iMETI), which is connected with the Life Sciences Division of CEA. The research performed by SRHI focuses on immune tolerance conferred by the molecule HLA-G.

Management team

The management team includes the director of the unit, three senior scientists in charge of the three themes in the unit laboratory, and two clinicians associated to the unit.

AERES nomenclature

SVE_1

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		1
N2: Permanent researchers from Institutions and similar positions	5	4
N3: Other permanent staff (without research duties)	7	5
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	4	4
N6: Other contractual staff (without research duties)		1
TOTAL N1 to N6	**16**	**15**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	4	5

2 • Assessment of the unit

Global assessment fo the unit

The SRHI has, since the 1990's, performed internationally recognized, high quality basic and clinical research in the field of immune regulation, with a very strong focus on the Human Leukocyte Antigen (HLA) class Ib molecule, HLA-G. When the unit started in this area, not much was known regarding HLA-G and its functions. It was discovered as a non-classical HLA molecule, expressed in the placenta and first studied in relation to the maternal tolerance to semi-allogenic fetus. The focus at SRHI has primarily been on the role of HLA-G in (organ) transplantation and in cancer immunology. In this regard, the unit has been the internationally leading laboratory for the last decade. The unit still focuses on HLA-G function in cancer and in transplantation. For several years, the research was mostly basic, and the complexity of the functions of the HLAG molecule, both at the cell surface and as a soluble protein, was elucidated both in immune regulation and in immune suppression related to cancer and post transplantation. Studies were mostly descriptive and did not elucidate the fundamental immunological mechanisms. During the last five years, however, the research at the unit seems to have become more innovative and with greater emphasis on therapeutic applications, which is also reflected by the eight patents that were filed. The research unit has a quite large international network (especially collaborations with Brazilian and Spanish research groups), and a wide range of student origins, some of them from international origins. The unit has produced seven theses during the last five years. Finally, SRHI has clearly the ambition of being the leading force in the International society for HLA-G research", and has organized six international conferences and workshops with several hundreds participants every third year since 1998.

Strengths and opportunities related to the context

- High degree of specialization and specific knowledge on HLA-G molecules,
- Strong intellectual properties on HLA-G molecules,
- National and International leadership on HLA-G,
- Interactions between clinicians as well as with start-ups, which are good opportunities to develop clinical research as well as clinical applications.

Weaknesses and threats related to the context

- Even if the three axis of the project can be connected with a senior researcher, the composition of the workforce (doctoral and/or post-doctoral, students, autonomous researchers, engineers, technician) is not described in details.
- The strategies to define the different priorities and to raise funds are not described in details.

- In a more general way, focusing all research activities on a single gene and its product could be a weakness, as 1) only parts of the pathophysiology in specific diseases are investigated, and not the disease entity in itself; 2) it can be difficult to obtain a steady flow of very original and ground-breaking results when the research is centered on a very specific topic.

Recommendations

- It seems as a good strategy to focus on two clinical settings: cancer and transplantation. However, the research activities might benefit of focusing on a moderate number of models and deciphering more deeply the mechanisms involved in the specific pathologies.
- On the other hand, for therapeutic perspectives the unit needs to stay focused on therapeutic tools based on HLA-G.
- The ambitious project appears too large with regard to the current number of scientists and to the funding. Therefore, the unit would benefit from better defining priorities and from better delineating the interactions between researchers. The role of each researcher should be better defined in the projects, as well as the means to raise financial support.
- In spite of its scientific appeal, the strategy for hiring senior scientists and post-doctorants should be discussed.
- If the unit grows, the logistic should be reinforced.

3 • Detailed assessments

Assessment of scientific quality and outputs

The major topic of this research unit is focused on the biology of HLA-G molecules. The unit has, during the last five years, made a range of original and new findings with an important international impact:

- Studies of in house animal models that show the *in vivo* importance of HLA-G in immune escape of solid tumours would allow a clarification of some of the immunological mechanisms involved;
- A range of studies demonstrating the involvement of HLA-G in trogocytosis (transfer of membrane parts between cells), thereby enabling the in situ generation of temporary suppressor cells;
- Study of in house animal models demonstrating the importance of HLA-G expression for graft survival *in vivo;*
- Development of synthetic HLA-G-related molecules that have a functional effect *in vivo* and have the potential for therapeutic applications.

The team has clearly a worldwide leadership on HLA-G molecules concerning its effect on immune and non-immune cells, and their clinical impact in transplantation and oncology as immunosuppressive molecules. HLA-G molecules have also important therapeutic relevance in cell therapy and anti-tumour immunotherapy. Most of these studies and activities build upon paradigms and theoretical concepts that are well known in this specific research field.

In order to conduct their studies and specific projects, the unit has set several national and international collaborations. Most of the studies build upon well-established methodologies, although in the context of the specific animal models and the development of synthetic molecules for therapeutic use, the unit collaborates with labs of other disciplines.

The unit has along the years often published in high-impact, international scientific journals. Since 2008, the unit has produced 72 publications and 44 of them are in a leadership position, together with five book chapters. The quantitative evaluation of publications is summarized in the two following tables

Table 1: Evaluation of different items from *Web of Sciences* of ISI - Web of Knowledge (biblioinserm)

Web of science items	1998-2014(February)	2008-2014 (February)
Citation report	358	107
Sum of times cited without self citations	7 039	1 151
Number of citing articles without self-citations	3 293	787
h-index	55	19

The repartition of the publications for the period (2008-2013) *in leadership position* are summarised according to the impact factor in the table 2:

Table 2: Quantification of the publications during the period 2008-2013 according to the impact factor.

	<3	3<Impact factor <5	5<Impact factor<10	Impact factor>10	Total
Number of publications	23	17	27	5	72

Their publications allowed writing the history of HLA-G, as this team is at the origin of all the cutting edge publications in this domain since the discovery of this gene by Geraghty in 1987.

Assessment of the unit's academic reputation and appeal

SRHI has organized an international conference on HLA-G every third year in Paris, since 1998, two during the last contract (2009, 2012). The events gathered several hundred researchers from all over the world, and it is without doubt a great opportunity for the unit to meet other scientists in the field, to follow the developments in this specific research field, and to make interesting and strategic collaborations in a fruitful network.

The unit is engaged in several collaborative projects with other national and international research units. In particular, SRHI had a scientific cooperation with the Brazilian research organization CAPES.

The team has raised different national, EU and worldwide (Brazil) grants.

Researchers from the unit have been guest editors of three different medium-impact journals, and are reviewers for a variety of scientific journals (45), some of them being high-impact journals.

Members of the unit have given a variety of invited oral presentations (57) at different kinds of international scientific meetings during the last five years, and the unit is thereby well known and well recognized in the scientific communities.

The unit director received in 2009 the “Blaise Pascal Medal in Medicine” in Bologna, Italy, and was appointed as a member of the “Real Academia de Medicina y Cirugia” in Spain in 2013. The unit director is involved in different reports for the Ministry of Research, as well as with the Academy of Science.

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

Senior researchers from the unit have participated in different national and international conferences with broad scientific and/or philosophical scope, such as “Un regard sur l’Homme contemporain à travers la science, la morale et la politique”. Thus, researchers from the unit contribute to a broad reflection on their specific scientific findings in a social and cultural context.

The unit has also participated in a variety of radio broadcastings (7) and in newspaper articles presenting the research to a lay public.

The unit seems to interact with the social and cultural environment, and aims at translating basic science results into therapeutic applications.

Moreover, the unit is in partnership with a start-up, Invectys (Pasteur Institute). The research at SRHI has, so far, leaded to eight patents submitted since 2009, on possible therapeutic use of manipulating HLA-G expression in transplantation and cancer.

Assessment of the unit's organisation and life

SRHI is organized into three research themes, each led by one of the three senior scientists. Each research theme focuses on different types of projects and aspects of HLA-G research.

Scientific seminars are run once a week; these weekly seminars are open to all research institutes and each scientist in the unit can present scientific results; on some occasions, the meeting is a joint meeting between clinical staff and researchers at the SRHI, or corresponds to presentations by external researchers in the department – and not necessarily about HLA-G. The last type of meeting is important for expanding the scientific vision.

There are also regular internal meetings in the unit in order to establish new strategies and to organize the different projects (resources, investments etc).

Assessment of the unit's involvement in training through research

The team is affiliated to ED 273 and ED 516 doctoral schools.

Since 2008, 7 PhD students have obtained their diploma.

Between 2008 and 2013, there have been 5 post-doctoral students (3 Brazilian CAPES scholarships), 7 doctoral students (4 in collaboration with Brazil) and 4 Master students.

The team is involved in different teachings, at the level of master and university diploma, in cell therapy (DU, UP7). The team is also involved in teaching in doctoral schools.

The unit has also participated in lectures and courses organized by international universities (3 in Denmark, 1 in Brazil and 1 in Italy). Furthermore, the unit has participated in international PhD examining boards (2 in Brazil and 1 in Spain).

Thus, the unit participates in student training programs, and a large fraction of the scientific members of the unit were students until now.

However, the teaching activity is moderate, due to the fact that the senior scientists have no teaching duties.

According to the head of the doctoral school (N°273, B2T), there was no problem in the unit and all students have completed their PhD.

Assessment of the strategy and the five-year plan

The scientific aim of SRHI in the future is to continue research related to the tolerogenic properties of HLA-G in the context of transplantation and cancer. The plan is to pursue this in three ways:

- Advance the understanding of the biology of the HLA-G molecule
- Studying the clinical relevance and implications of HLA-G in transplantation and in oncology
- Exploring therapeutic applications

Part 1 is focused on HLA-G biology (expression, regulation, polymorphisms) and particularly the interaction between HLA-G and its ILT2 receptor in order to study their role on the proliferation and differentiation of B lymphocytes as well as iNKT cells. Part 2 is focused on the clinical relevance of HLA-G, its immunomodulatory functions, in particular in lung transplantation, and its relevance in oncology. Part 3 focuses on the development of therapeutic applications.

General assessment of the strategy: in general, the different projects are a logical continuation of SRHI's previous and ongoing research activities and maintain the research focus. Moreover the link with the clinicians is reinforced through the association of clinicians to the unit.

Most of the projects are original, have not been performed before and includes development of new model systems, but some projects are variants of previously published investigations (e.g. some of the HLA-G polymorphism studies).

Most of the studies are at low risk and will produce results. The projects related to therapeutic applications are at higher risk, as it can be difficult to predict their final outcome and the feasibility of the project. Nobody knows anything regarding possible side effects associated with the use of HLA-G or synthetic analogs as therapeutic compounds. However, in general, the project is coherent with the past activities and seems to be feasible. Furthermore, the following comments can be made:

- It seems as a good strategy to focus on two clinical settings: cancer and transplantation. However, the research might benefit of focusing on a moderate number of models in order to explore more deeply the mechanisms involved.
- On the other hand, in order to pursue therapeutic objectives, the unit needs to remain focused on therapeutic tools based on HLA-G.
- As the project is ambitious, it appears too large with regard to the current number of scientists and the current funding. Therefore, it would benefit from better defining both the priorities and the interactions between researchers. The role of each researcher in the projects should be better defined, as well as the means to raise financial support.
- In spite of its scientific appeal, the strategy for hiring senior scientists and post-doctorants should be discussed.
- If the unit grows, the logistic should be reinforced.

4 • Conduct of the visit

Visit date:	Thursday, 30th January, 2014
Start:	Thursday, 30th January, 2014 at 09:00 AM
End:	Thursday, 30th January, 2014 at 05:00 PM
Visit site:	SRHI- Service de Recherches en Hémato-Immunologie,
	1 avenue Claude Vellefaux - 75010 Paris, 2nd floor of the building Lailler
Institution:	Institut des maladies émergentes et des therapies innovantes (iMET), CEA
Address:	Saint-Louis Hospital, 1 avenue Claude Vellefaux, Paris

Conduct or programme of visit:

09.00-09:15: Welcome (closed-door) Visiting committee with the AERES Scientific advisor (the role and procedures of AERES)

09:15-09:30: Mr Edgardo D. CAROSELLA, director of the unit: administrative general presentation of the unit

09:30-11:00: Presentation of the scientific programs and research results by the 3 PIs of the unit themes

- Mr Joël LEMAOULT
- Mr Philippe MOREAU
- Ms Nathalie ROUAS-FREISS

11:00-11:30: General discussion

11:30-11:45: coffee break

11:45-12:00: Discussion with the scientists including associated medical scientists (Pr. DESGRANDCHAMPS and Dr. Olivier BRUGIÈRE)

12:15-12:30 Discussion with students and post-docs

12:30-12:45: Discussion with technicians

12:45-13:00: Discussion with administrative personnel

13:00-14:15: Lunch

14:15-15:00: Discussion with the representative of the managing bodies

14:15-14:30: CEA, University Paris 7- René Diderot

14:30-14:45: École doctorale

14:45-17:00: Private meeting of the visiting committee (in presence of the AERES scientific advisor)

17.00: End of the visit

5 • Supervising bodies' general comments

DE LA RECHERCHE À L'INDUSTRIE

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Monsieur Pierre GLAUDES
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

Fontenay-aux-Roses, le 31 mars 2014

Objet : Rapport AERESE2015-EV-0912281K-S2PUR150008188-006350-RT Service de Recherches en Hémato-Immunologie

N/Réf. : DSV/DIR/2014-126/ADLC/guc

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport d'évaluation du Service de Recherche en Hémato-Immunologie dirigé par le Dr Edgardo CAROSELLA, dont le CEA et l'Université Paris-Diderot exercent la tutelle. Le comité de visite a réalisé un remarquable travail d'évaluation et souligne la qualité de l'interface entre recherche fondamentale et application clinique sur la molécule HLA-G développée par cette unité.

Le CEA se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions. Les points d'améliorations suggérés par le Comité seront discutés avec le directeur d'unité dans un esprit constructif pour l'avenir de la recherche au CEA et à l'université.

Vous trouverez joint à ce courrier les éléments de précisions que Monsieur Edgardo CAROSELLA a souhaité apporter au Comité à la lecture du rapport.

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

Gilles BLOCH

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Le Directeur

Direction des Sciences du Vivant
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Service de Recherches en Hémato-Immunologie
Hôpital Saint-Louis

Directeur du service :
Edgardo D. CAROSELLA
Directeur de recherche

Paris, April 1, 2014

We thank the expert committee members for their constructive evaluation report which highlights that "during the last five years, the unit seems to have become more innovative and with greater emphasis on therapeutic applications, which is also reflected by the eight patents that were filled. … Finally, SRHI has clearly the ambition of being the leading force in the International society for HLA-G research." In this regard, the expert committee members notify the national and international leadership on HLA-G among strengths of the unit.

However, we would like to answer to weaknesses and recommendations pointed out by the committee members:

Weaknesses and threats from the Expert committee members:

The examining committee argues that focusing all research activities on a single gene and its products can, on the one hand, be an advantage, but that on the other hand, it can also be a weakness. We are fully aware of these facts and we would like to point out that we have already started to address them: (1.) The inclusion of a clinical department within our unit now enables us to better focus on and to study specific diseases more in depth, as was presented in the context of bladder cancer. (2.) Even though our main research topic is the HLA-G molecule, we do not focus on it exclusively. In particular, we have long sought to diversify the topics of our studies, by expanding them to other molecules that may be related to HLA-G: HLA-G receptors, HLA-G active forms (dimers and peptides), immunosuppressive drugs, other tolerogenic molecules, and to specific cell subsets that may be related to HLA-G such as regulatory cells. Furthermore, we also expanded our research on HLA-G functions to non-immunological ones, especially those targeting hematopoietic and mesenchymal stem cells (erythroid and osteoblast differentiation).
Thus, even though we agree with the examining committee, we feel that these issues have been properly addressed.

Recommendations from the Expert committee members:

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1) "It seems as a good strategy to focus on two clinical settings: cancer and transplantation. However, the research activities might benefit of focusing on a moderate number of models and deciphering more deeply the mechanisms involved in the specific pathologies."
As reported by the committee, we have chosen to study two clinical areas such as cancer and transplantation. In both contexts, we described for the first time the involvement of HLA-G: in melanoma (Paul et al., PNAS 1998) and in heart transplantation (Lila et al. Lancet 2000), respectively. Then, over the past years, we have validated our initial observations in other types of cancer and transplantation, which constituted an important issue prior to pursue with clinical applications.

More recently, we have initiated more in-depth studies in order to explain the mechanisms implemented. This is well exemplified in our work with haematological malignancies: indeed, we described an unexpected antitumoral role of HLA-G when tumor cells express HLA-G receptors and we went further by precisely delineating the mechanisms involved in malignant B cell inhibition through cycle shutdown and blockage of signalling pathways. We also initiated a new in-depth study, focused on the role of HLA-G in another immunologically relevant cancer, i.e. bladder cancer. Finally, one of our studies is focused on the molecular and cellular pathways that are involved in the tolerogenic functions of HLA-G in the context of lung transplantation. Therefore, we have already initiated studies deciphering more deeply the mechanisms involved in these clinical settings.

2) "On the other hand, for therapeutic perspectives the unit needs to stay focused on therapeutic tools based on HLA-G.
We thank the committee for this recommendation which corresponds to one of our current priorities.

3) "Nobody knows anything regarding possible side effects associated with the use of HLA-G or synthetic analogs as therapeutic compounds."
We agree with the observation of the committee members and we are aware of the studies which are required in order to address the very important issue of the potential side-effects of HLA-G as therapeutic compounds. These validations will be performed by experts, following official procedures for obtaining approval of the competent authorities in health. This part will be done by the Start-up Invectys which is associated with our department.

4) "As the project is ambitious, it appears too large with regard to the current number of scientists and the current funding."
We are in complete agreement with the committee that our projects would require a larger staff, and we expect to recruit very soon from national and international institutions.

Sincerely yours,

Edgardo D. Carosella