IGETCAN - Immunologie intégrative des tumeurs et génétique oncologique

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Integrative Tumor Immunology and Genetic Oncology

ITIGO

Under the supervision of the following institutions and research bodies:

Institut National de la Santé Et de la Recherche Médicale - INSERM

Université Paris-Sud

December 2013

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,

- Mr. Pierre COULIE, 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:	Integrative Tumor Immunology and Genetic Oncology
Unit acronym:	ITIGO
Label requested:	INSERM
Present no.:	UMR-S753
Name of Director (2013-2014):	Mr Salem CHOUAIB
Name of Project Leader (2015-2019):	Ms Fathia MAMI-CHOUAIB

Expert committee members

Chair:	Mr Pierre COULIE, Université Catholique de Louvain, Belgium
Experts:	Mr Yves-Jean BIGNON, Université de Clermont-Ferrand
	Ms Suzan CHAN, Université de Strasbourg (representative of INSERM CSS)
	Ms Piona DARIAVACH, Institut de recherche en Cancérologie, Montpellier
	Mr Pedro ROMERO, University of Lausanne, Switzerland

Scientific delegate representing the AERES:

Mr Daniel OLIVE

Representatives of the unit's supervising institutions and bodies:

Mr Christian AUCLAIR (representative of Doctoral School Cancérologie ED n°418)

Mr Etienne AUGE, Université Paris-Sud

Ms Isabelle HENRY, Institut National de la Santé Et de la Recherche Médicale

1 • Introduction

History and geographical location of the unit

The INSERM unit UMR-S753 existed previously as unit U 487, created in 1998 and renewed in 2002 and in 2005, with Mr Salem CHOUAIB as its director. It was built up from the "Contrat Jeune Formation (CJF-94-11)" also created at IGR in 1994 and directed by Mr Salem CHOUAIB. U 487 "Cytokines and Tumor Immunology" contained a single team until 2007 and acquired new teams when it became U 753 in January 2008. The unit is located at the Institut de Cancérologie Gustave Roussy (IGR), for the main part at the first floor of the "Pavillon de recherche 1", with other laboratories and offices occupied by Mr Stéphane RICHARD's team located at the second floor of the "Pavillon de recherche 2". An ATIP-Avenir will soon join their lab. He was recently recruited by IGR and candidate for an INSERM CR1 position.

Management team

The unit was directed during the 2008-2013 contract by Mr Salem CHOUAIB, who leads one of the research teams. The unit consisted in 3 teams, led by Mr Salem CHOUAIB, Ms Fathia MAMI-CHOUAIB and Mr Stéphane RICHARD. Starting from january 2015 the unit will include only 2 teams: "Antitumor immunity and microenvironmental plasticity" led by Mr Salem CHOUAIB and Ms Fathia MAMI-CHOUAIB, and "Genetics and biology of Renal Cell Cancer" led by Mr Stéphane RICHARD. There is an administrative assistant, and a research unit council which meets twice a year and is composed of the research team leaders, permanent researchers and teacher-researchers, representatives of the technicians, engineers and students, and the director.

AERES nomenclature

SVE1_LS6

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	3
N2: Permanent researchers from Institutions and similar positions	4	3
N3: Other permanent staff (without research duties)		
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	9	9
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	5	5
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**21**	**20**

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

2 • Assessment of the unit

Strengths and opportunities related to the context

High scientific quality of the participating teams attested by the number and level of publications.

National and international recognition of the team leaders and of other team members.

The tumor immunology theme benefits from the recent clinical successes of immunomodulatory antibodies, increasing the unit's attractiveness for clinicians and for funding agencies.

The recruitment of 1 CR2 position is a clear asset of the unit.

The RCC genetics team is an european leader on hereditary predisposition to renal cancer.

The unit is very competitive in fund raising at the national level and at the international level outside of Europe (Qatar).

Multiple opportunities of collaboration and effective collaborations, with IGR as well as with other laboratories in France.

Productive links with Poland.

Weaknesses and threats related to the context

Diversity of topics addressed in the tumour immunology team.

The unit could be more competitive in fund raising at the european level.

Too few permanent positions for young investigators.

Small size of the RCC genetics team.

Difficulty around bioinformatics (lack of experienced staff), as in most other research centers.

Recommendations

Try to stabilize permanent positions for young scientists (Mr Medhi KHALED, ATIP-Avenir).

Try to establish more links between immunology and genetics, considering the available expertises.

It should be possible to increase the visibility at the european level, for funding purposes.

3 • Detailed assessments

Assessment of scientific quality and outputs

The unit covers two fields in oncology: immunological aspects of lung cancer and melanoma and genetics of renal cell carcinoma. The two teams have to be commended for the success of their undertakings in these two fields that are quite competitive at the international level. The groups have made several important discoveries that were published in very good or top journals in these fields of biology such as Nature Immunology (1 article), J Exp Med (2 articles), PNAS (2 articles), Cancer Res (11 particles) or J Clin Oncol (2 articles). The total number of publications from the unit is 27 from the group of Ms Fathia MAMI-CHOUAIB, 66 from the group of Mr Salem CHOUAIB, 40 from the group of Mr Stéphane RICHARD, 10 from the group of prof. Jérôme THIERY and 8 from the group of Mr Medhi KHALED.

Assessment of the unit's academic reputation and appeal

The team leaders are invited to participate in international conferences as invited speakers, and to give seminars in laboratories in France and abroad. They participate in numerous scientific committees for french or foreign research institutes, and for funding agencies or charities (including but not limited to INSERM, AVIESAN, Italian Association for Cancer Research, Weizmann Institute, British Council, INCA, ARC, European Commission, AFSAPS, IGR steering committee, Qatar Foundation). They are also participating in the editorial board of several scientific journals. Another sign of the U 753 appeal is the recruitment of postdocs with 17 fellows having joined the unit during the last contract.

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

Two patents have been filed during the 5-year contract. One MATWIN project was ranked n°1, resulting in discussions with 3 pharmaceutical groups. There are ongoing discussions for a possible biotechnology company to be created around the preprocalcitonin tumor antigen. One team leader is the academic member in a network of biotechnology companies with an anti-invasive cancer program. Another team leader was selected for a national video projection on the Pantheon's walls in Paris for “1000 researchers speak about future” in october 2010.

Assessment of the unit's organisation and life

The organization of the unit is based on two independent groups of quite different sizes, team 2 being notably smaller. The topics are also quite different, immunology versus genetics. However Mr Salem CHOUAIB has a charismatic leadership and is quite experienced in directing the unit and protecting its different parts.

During the meeting of the experts committee with staff scientists, it was apparent that the trainees had a strong sense of community and enjoyed a high level of interactivity both in their working lives and socially wise. Thus this is a well integrated and coherent group. There were no conflicts detected. The doctoral students are examined by a thesis committee twice during their thesis work. The latter takes four years in average. In addition, all of them were very pleased with the level of scientific supervision and it was clear that the team leaders are widely available to them and are good mentors. In terms of problems and limitations, they were unanimous in identifying insufficient funding to cover consumables as one of the major limitation. This often has led to making tough choices in competitive research projects. They also stated the need for a dedicated fund that may support travelling to international meetings. In summary, this is a well integrated group of trainees who are strongly motivated and have a very dynamic community life. There were neither major reservations nor issues to be raised. The scientific environment is rich and provides a stimulating atmosphere for their research work.

During the meeting of the experts committee with engineers, technicians and administrative staff it appeared that in general, the personnel were happy and there was a good ambiance within the group. The staff felt integrated in their projects: they planned their own experiments and worked independently, and they were co-authors in the publications. There appears to be good communication and respect within the unit and the staff had access to annual training opportunities and other technical support. They have weekly meetings with their laboratory heads and felt that the door was always open for discussion, including that of the unit director. The annual evaluation is conducted individually with the unit director and everyone is satisfied with this situation, although some have expressed a wish to conduct the interviews in the presence of the laboratory head in order to discuss perspectives in more detail.

Assessment of the unit's involvement in training through research

12 PhD students successfully defended their thesis during the 5-year contract. It is an indicator of the good quality of the tutoring of students in the unit, even more so considering that only 5 scientists have their HDR, 2 of which having obtained it during this contract. Moreover, 12 postdoctoral students have worked in the unit during the contract.

During the meeting of the experts committee with the representatives of the supervising bodies of the unit, the important participation of the unit to the Doctoral School was mentioned and praised, particularly for the immunological projects carried out in the École Doctorale de Cancérologie ED n°418.

Assessment of the strategy and the five-year plan

In the proposed project the unit will contain 2 teams instead of 3: the teams lead by Mr Salem CHOUAIB and Ms Fathia MAMI-CHOUAIB will merge, while the team lead by Mr Stéphane RICHARD remains unchanged. The proposed director will be Ms Fathia MAMI-CHOUAIB who is a strong scientist. This transition should be smooth and efficient.

The proposed project is the evolution and the continuation of the past activities and results of the unit. It remains focused on the immunology of lung tumors and melanomas, and on the genetics of renal cell carcinoma. Team 1 will pursue its investigations on the role of integrin CD103 in regulating intratumoral T-cell immunity, on the use of the preprocalcitonin tumor antigen that they dicovered to develop active immunotherapy against lung and thyroid cancers, and on various aspects of cellular biology within tumor cells that contribue to establish a resistance of the tumors to immune attack. The latter theme will be more focused on consequences of intratumoral hypoxia. Team 2 will continue to build up on its large expertise on the genetics of renal cancer with projects on new genes involved in familial RCC syndromes, on the physiopathology of inherited RCC with a functional genetic approach and on the elucidaton of the genetic causes of sporadic RCC.

The experts committee feels that this five-year plan is sound, consistent with the expertises of the teams and likely to stengthen the innovative contribution of U 753 to basic research as well as to translation of basic findings into the clinics. The propitious location of the unit on the IGR campus is a great help for reaching these objectives due to the scientific skills of neighbour research groups, the state-of-the art technological platforms available and of course the collaboration with the clinical departments of IGR.

4 • Team-by-team analysis

Team 1: Antitumor immunity and microenvironment plasticity.

Name of team leader: Mr Salem CHOUAIB & Ms Fathia MAMI-CHOUAIB

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	4	3
N3: Other permanent staff (without research duties)	5	5
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	5
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**14**	**13**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	10	
Theses defended	11	
Postdoctoral students having spent at least 12 months in the unit	12	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	4	3

• Detailed assessments

Assessment of scientific quality and outputs

The work of the unit is focused on cancer immunology. The scientific production has been excellent with 77 articles since 2008, including 12 reviews. A large part of the work is conducted directly on human cells, including materials derived from cancer patients. This is an asset of the unit. Part of this work involves human clones of tumor-specific cytolytic T cells, which very few groups are capable of producing and maintaining over long periods of time.

This provides the group with reliable tools generating reproducible results, another asset in the field of human antitumor T lymphocytes.

The work is organized around two themes:

- theme 1: Tumor antigens and T-cell reactivity.

The research has been focused on human T-cell immunity to lung carcinomas. Worldwide, very few groups are active on this dificult topic. One major reason is the extreme paucity of human lung carcinoma cell lines, which are absolutely needed to carry out detailed analyses of the anti-tumor T-cell response of lung cancer patients. The main results obtained by the team are the following:

A) Using a lung carcinoma cell line obtained by the team and autologous lymphocytes stimulated by this cell line, they discovered a tumor antigen recognized by a cytolytic T cell (CTL) clone. It is an antigenic peptide presented by HLA-A2 molecules and derived from the preprocalcitonin gene product (Proc Natl Acad Sci 2008 105: 10119). An important and original observation is that this antigenic peptide is derived from the signal sequence of the protein and that its processing is therefore independent from proteasomes and from TAP. As a matter of fact, the presentation of this antigen by the tumor cells is increased when TAP is inhibited or absent (J Immunol 2011 187: 5532). It is a very interesting result because inhibition or loss of TAP is considered to be one of the mechanisms whereby tumor cells escape CTL recognition. Thus this preprocalcitonin peptide is the first example of a human tumor antigen whose presentation is, on the contrary, increased by TAP loss. It is therefore a good candidate for cancer immunotherapy, with a patent filed in 2007 and granted in 2011.

B) Using tumor-specific CTL clones and the corresponding autologous lung tumor cell line, the team demonstrated that CD103, standing here for the αEß7 integrin, was required for tumor cell recognition (J Exp Med 2007 204: 559). Flow-based adhesion assay indicated that engagement of CD103, together with TCR, enhances the strength of the T cell-target cell interaction. Electron microscopy analyses showed that the integrin-dependent mature cytotoxic immunological synapse associated with target cell killing displayed a much more cohesive ultrastructure than in the absence of integrins (Cancer Res 2013 73:617). Moreover, CD103 signaling mediated by immobilized recombinant E-cadherin is sufficient to induce polarization of cytolytic granules, a prerequisite of efficient target cell lysis (Cancer Res 2011 71: 328).

C) They found recently that TGFß1 induces CD103 expression on T cells and identified the promoter regions in gene ITGAE, encoding this integrin α chain, that are responsible for this response to TGFß. Inasmuch as TGFß is considered to be an important immunosuppressive factor active in tumors, this observation is surprising and interesting.

D) Collaborating with the group of in Cochin Institute, they observed that in tumors the extracellular matrix surrounding tumor cells limits the contacts that T cells can establish with their potential target cells. Chemokines such as CCL5, when produced by the tumor cells, can nevertheless attract T cells and allow contacts between lymphocytes and tumor cells (J Clin Invest 2012 122: 899). The chemokine receptor CCR5 is involved in this migration, and its recruitment at the immunological synapse is increased by the interaction of CD103 with its ligand E-cadherin (Cancer Res 2009 69: 6249).

- theme 2: Molecular basis of tumor resistance to specific lysis.

Here the research is characterized by the integration of cellular biology concepts or tools into the vast problem of tumor resistance to T cell attack, one of the major if not the major area of research upstream of clinical cancer immunotherapy. The main contributions are the following:

A) The team pinpointed morphological changes of tumor cells as a mechanism of escape from CTL recognition. Starting from gene expression profiling of cells that were sensitive or resistant to the cytolytic activity of T cells, they observed that the activation of the Focal Adhesion Kinase was associated with sensitivity to lysis (J Biol Chem 2008 283: 31665). Pursuing this line of research, they found that morphological changes reminiscent of those observed in EMT (Epithelial-Mesenchymal Transition) were associated with resistance to the cytotoxic activity of TNFa. This proved to require the phosphorylation of the actin cross-linker L-plastin (J Cell Mol Med 2010 14: 1264). Moreover, EMT in human breast cancer cells was also associated with resistance ot CTL-mediated lysis, through autophagy induction (Cancer Res 2013 73: 2418).

B) Previous work by the group had shown that P53 was activated in cells undergoing apoptosis induced by granzyme B, released by cytolytic T cells or NK cells. Subsequently, their results indicated that the genotoxic stress-activated gene SMG1, which is upregulated in granzyme B-treated cells, was involved in granzyme B-mediated cell death (J Mol Med 2011 89: 411). Finally, in patients with soft tissue sarcoma, treated with isolated limb perfusion with

melphalan and TNF, higher levels of mutated P53 were found to be associated with a poor histological response to the treatment.

C) Using an original in vitro system of coculture of autologous tumor cells, endothelial cells and CD8 T cells in a collagen matrix, the team observed that endothelial cells were killed by tumor-specific T cells, following a cytosolic exchange of antigenic peptides from the tumor cells to the endothelial cells through the connexin CX43 (J Immunol 2009 182: 2654).

D) A large effort has been devoted to understanding the links between hypoxia and immune resistance in tumors. The team showed that hypoxia had an inhibitory effect on CTL- and NK-mediated tumor cell lysis. Hypoxia was associated with STAT3 phopshorylation, and silencing of STAT3 inhibited HIF-1a and restored tumor cell susceptibility to lysis (J Immunol 2009 182: 3510). Hypoxia induced autophagy, and inhibition of autophagy through hydroxychloroquine restored CTL activity in a preclinical model of anti-melanoma vaccination (Cancer Res 2011 71:5976). They found that transcription factor Nanog was involved in the tumor cell resistance to lysis induced by hypoxia (J Immunol 2011 187: 4031), as well as miR-210 (Cancer Res 2012 72:4629). They identified a link between hypoxia, autophagy and degradation of granzyme B in tumor cells, leading to a decreased susceptibility to lysis by NK cells (Proc Natl Acad Sci USA 2013 in press).

Assessment of the unit's academic reputation and appeal

The team is active in national (19) and international collaborations with joined grants obtained from INCa-DGOS, INCa (several programs), ANR, ARC and Cancéropôle.

One of the team member awarded a Contrat d'interface for translational research and a Prize of scientific excellence, both by INSERM. One team leader was nominated as a member of the Tunisian Academy of Sciences, and is an advisor to the general director of INSERM for the Gulf and North African countries.

Team members have established strong links with Poland since 1998, organising joined workshops and training promising polish researchers. They have also been very active in organizing and maintaining links with the Sharja Biomedical Research Center in the United Arab Emirates. More recently they have established links with Qatar, through the Qatar Foundation. One of the team leaders is scientific director of the Cancer Research Center of the Qatar Biomedical Research Institute.

The team is appealing as demonstrated by the fact that since 2008 they have attracted 17 post-doctoral researchers. One INSERM CR2 position was obtained in 2012 and one Contrat Avenir from INSERM in 2013. It is worth noting that these two positions were obtained by scientists who had been in this group in the past, and therefore decided to come back.

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

One patent on a tumor antigen derived from the preprocalcitonin gene product was granted in december 2011 (PCT: WO 2009/0108742010). There are ongoing discussions with 2 pharmaceutical companies to develop a vaccine containing this antigen. The MATWIN (Maturation and Accelerating Translation With INdustry) project 'Proof of concept of a novel cancer vaccine approach in lung cancer based on the immunogenic potential of a new tumor antigen' (Principal Investigator: Ms Fathia MAMI-CHOUAIB) was ranked n°1. There are ongoing discussions with INSERM-Transfert-Initiative and Genopôle for potential creation of a biotech company.

One patent on the use of inhibitors scinderin or ephrin-A1 was filed in 2007, with an european application scheduled in 2013.

There are links and collaborations with several biotechnology companies and the OSEO consortium which is a network of biotech working on a cancer anti-invasive program.

Assessment of the unit's organisation and life

In this team the organization and recruitment appear excellent and productive. Two promising scientists have been recruited over the last two years (CR2 and Contrat Avenir). Over the current period the group, was organized in two teams. For the next contract, they will merge into a single team. It makes sense because there are more and more themes that are common to the two groups.

The proposed director for the next term is one of the two team leaders for the current contract while the current director will become the deputy director. It will foster even more interaction between the two groups.

Assessment of the unit's involvement in training through research

Over the last period, the training activity was excellent. Eighteen PhD students defended their thesis and 10 PhD students have started and continue to work for a thesis since september 2009. One HDR was granted to a member of the group in 2012. Sixteen students have defended their Master 2 thesis. Members of the teams have teaching activities in fundamental and tumor immunology for Master 2 and PhD students at Universities Paris 11, Paris 7, IGR and École Pratique des Hautes Études in Dijon.

Assessment of the strategy and the five-year plan

The general objective remains to explore various means to increase the clinical efficacy of cancer immunotherapy, mainly for lung cancer and melanoma. The project will be developed along two axes:

1. Tumor antigens and T-cell reactivity.

2. Impact of tumor microenvironment on tumor resistance and its role in shaping tumor plasticity and stroma reactivity.

The first axis includes a further dissection of the role of integrin CD103 in regulating intratumoral T-cell distribution, migration and effector functions. The influence of CD103 in early T-cell signaling and cytotoxicity will be studied in lung tumor slices and xenograft models. There will be a search for the signaling proteins involved in CD103 activation and a study, in a mouse tumor model, of the in vivo role of CD103 in T-cell retention within epithelial tumors. Finally, the prognosis value of CD103 expression on human lung TILs will be assessed. The team will also pursue the cancer vaccine approach in lung cancer with the preprocalcitonin tumor antigen, in a preclinical mouse model.

The second axis addresses the crosstalk between effector cytotoxic cells and stroma components with the aim of attenuating tumor resistance to immune effectors. One project deals with the nontranscriptional function of p53 in regulating cell death and its role in cancer- associated fibroblasts. Another will make use of the 3D model developed by the group, to dissect the role of CX43 in the interactions between tumor cells and their stroma. A third project deals with hypoxia- induced immunosuppression using in vitro models and in vivo spontaneous cancer models. It will benefit from the "ATIP-Avenir" group that will focus on the interaction between MITF and hypoxia during melanoma progression. Finally the group will pursue a translational research on the anti-leukemic potential of NK cells in AML patients.

Overall, several items of the project should generate original findings with fundamental and clinical interest. Several tools and established collaborations are an asset for the success of the project.

Conclusion

- **Strengths and opportunities:**

The organization of the team should favor efficient synergy between the researchers coming from the two former teams, as they share complementary expertise and common scientific questions.

The ability to succeed in getting external sources of funding has to be mentioned.

The project is sound and based on solid data obtained by the team.

- **Weaknesses and threats:**

The team would be greatly stengthened by another permanent position for a young scientist.

The projects are still somewhat diverse.

Some projects are intrinsically risky, such as the preprocalcitonin vaccine development.

- **Recommendations:**

Try to strengthen scientific links with team 2.

Team 2: Genetics and biology of renal cell carcinoma.

Name of team leader: Mr Stéphane RICHARD

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)	4	4
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**7**	**7**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	1	2

• Detailed assessments

Assessment of scientific quality and outputs

This team is focused on inherited renal cell carcinomas.

The scope is original in France, as well as in Europe as only a few teams are working on this topic.

The team is a nice mix of clinicians and researchers.

The main realizations are:

- the demonstration that germline mutations in PHD2 are responsible for rare forms of congenital polycythemia;

- VHL mutations are perfectly correlated with a gradient of VHL dysfunction in hypoxia signaling pathways: it supports for the first time in human the new quantitative concept of tumor suppression that was recently suggested;

- the genetic alterations of VHL-associated ccRCC are similar to their sporadic counterparts;

- participation in 3 major international collaborative studies on PBRM1, BAP1 and MITF.

The scientific production in peer review journals, with one member of the team as first or last author is as follows: N. Engl. J. Med., BMC Cancer, Ophtalmology, J. Med. Genet., Eur. J. Hum. Genet. J. Urol., Hematologica, J. Clin. Oncol.

Assessment of the unit's academic reputation and appeal

The team is nationaly well-known and is a leader on hereditary predisposition to renal cancer (coordination of the 3 INCa networks on the topic). It participates in all major international networks on inherited renal cancers, which is essential in human genetics research, and has published with these networks.

They recently organized the Birt-Hogg–Dubé international symposium.

They chair the annual «European Kidney Symposium» and the biennal "National Congress meeting ARTuR on kidney cancer".

No post-doc was hosted by the team. The recruitment of full time researchers concerned only technicians from 2011 to 2013.

One prize in 2011 for a PhD student.

Reviewer for 9 different international journals.

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

The team leader was selected for the national video projection on the walls of the Pantheon Mausoleum in Paris for “1000 researchers speak about future” in October 2010, under aegis of the Dept of Research, then for the exposition “50 researchers from medical domain” at the Department of Health, 1st december 2010 to 1st february 2011.

Assessment of the unit's organisation and life

The team, with a single scientific theme, is very well organized with coherent objectives. Its members have access to platforms and biological ressources thanks to the clinicians and to IGR.

Budget for research is quite good and many grants are awarded.

Organization within the team is good and appropriate with no obvious problems.

Within the U 753 INSERM unit, it would be easy and natural to develop links between the teams in the hypoxia/antitumor immune response, considering the VHL/HIF pathway. Thus far it has not been possible, for a big part because of the departure of 2 members from Mr Stéphane RICHARD’s team in 2010. It is to be hoped that in the future it will be possible to combine the remarkable expertises of the unit in tumor immunology and in genetics.

Due to intense clinical activities and responsibilities at IGR since 2011, one of the team members was not able to pursue his research activity within the team.

Assessment of the unit's involvement in training through research

2 HDR in the team: nice capacity to coach PhD students.

One thesis in 2010 and one in co-direction in 2013: 2 papers as first author in peer-review journals for each of them. One is now in post-doc and is expected to come back in 2015.

1 PhD student started in 2010.

There is education and training of many master students.

Senior scientists of the team are mainly from the university and therefore deeply involved in training students (mainly from EPHE).

Assessment of the strategy and the five-year plan

The team aims at:

1. Searching for new mutated genes responsible for unexplained familial RCC syndromes by a candidate gene strategy and exome sequencing, followed by functional analysis of the novel identified mutations.

2. Understanding the physiopathology of inherited RCC using a functional genetic approach in 3 different models:

I) effects of various stimuli on DNA damage response in patients with/without Von Hippel-Lindau tumor suppressor gene,

II) role of the MITF/SUMO network in RCC carcinogenesis,

III) analysis of novel missense FLCN variants identified in patients affected with Birt-Hogg-Dubé syndrome or isolated renal cancer.

3. Characterizing genomic profiles of hereditary and sporadic RCC:

I) identify additional events and associated candidate genes to elucidate the different steps of VHL renal tumorigenesis by exome sequencing and by transcriptome and miRnome analysis,

II) use CGH-array and gene expression microarray on sporadic pRCC to provide better insight into pRCC biology and subclassification for the identification of potential therapeutic targets.

This project is a logical and sound follow-up of the previous achievements of the group.

The team has collaborations and platforms available for this project.

Good recurring funding is available.

The project is original and should produce new interesting results.

The project looks feasible even though it is ambitious as it combines/requires human tumors samples, DNA from families, animal models, in vitro experiments and clinical research. One difficulty might be bio-informatics to interpret all the “omics” results. It requires dedicated human power with a highly specialized know-how and a strong training for each topic: exome sequencing, sumoylome, transcriptome, miRome, proteome ...

From the project presentations and discussions with scientists, the links with team 1 were not obvious.

Conclusion

- **Strengths and opportunities:**

Excellent interactions between clinicians and scientists in this translational research program, and excellent access to human samples and patients.

Good level of funding.

Excellent scientific environment at IGR, including technical facilities.

Very good integration in national and international networks.

Opportunity to stengthen the team with a potential recruitment in 2015.

- **Weaknesses and threats:**

The size of the team, with only a few full-time scientists and the recent departures of some of them, is small considering the ambitious objectives of the project. It should be stengthened with post-doctoral fellows (the Qatar Foundation might be an opportunity to fund such position(s)) and possibly permanent full-time researchers (this should be the case with a promising fellow in 2015). Interesting publications but rely often on collaborations.

The absence of a bio-informatician in the team is an important issue. It appears to be the case also at the level of IGR. It will a problem when choices have to be made between several methodologies or for the interpretation of large amounts of data generated by the project's multiple “omics”.

- **Recommendations:**

Try to strengthen human ressources at the level of permanent scientists.

Try to have in-house bioinformatics.

Try to strengthen links and interactions with team 1.

5 • Conduct of the visit

Visit date:

Start: 12/20/2013 at 08.30 am

End: 12/20/2013 at 04.30 pm

Visit site: INSERM unit 753, Pavillon de Recherche 1

Address: 114 rue Edouard Vaillant, 94805 Villejuif

Conduct or programme of visit:

08.30 am	Meeting of the experts committe with the AERES scientific delegate (DS) (closed-door)
09.00 am	Presentation of the unit's past activities and project
10.00 am	Presentaion of team 1, with research themes 1 and 2
11.35 am	Presentation of team 2
01.00 pm	Lunch
02.00 pm	3 parallel meetings with personnel
02.30 pm	Discussion with representatives of the managing bodies
03.30 pm	Discussion with the head of the unit
03.45 pm	Private meeting of the experts committe
04.30 pm	End of visit

Specific points to be mentioned:

Mr Eric SOLARY, representing Institut Gustave Roussy, was present during the visit.

6 • Supervising bodie's general comments

UNIVERSITÉ PARIS SUD

Comprendre le monde, construire l'avenir®

Le Président de l'Université Paris-Sud

à

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
AERES
20, rue Vivienne
75002 Paris

Orsay, le 18 mars 2014

N/Réf. : 50/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007655

Monsieur le Directeur,

Vous m'avez transmis le 24 février dernier, le rapport d'évaluation de l'unité de recherche – Immunologie intégrative des tumeurs et génétique oncologique - N° S2PUR150007655 et je vous en remercie.

L'université se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions.

Vous trouverez en annexe les éléments de réponse de Monsieur Salem CHOUAIB, Directeur de l'unité de recherche.

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

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Nom de l'unité: Integrative Tumor Immunology and Genetic Oncology (Immunologie intégrative des tumeurs et génétique oncologique)

Acronyme: **ITIGO**

Nom du directeur pour le contrat en cours: **Salem CHOUAIB**

Nom du directeur pour le contrat à venir: **Fathia MAMI-CHOUAIB. Directeur adjoint: Salem CHOUAIB**

Assessment of the unit: Integrative Tumor Immunology and Genetic Oncology (present N° UMR-S753)

General comments:

We thank the AERES visiting committee for the fair assessment of our research unit. We are pleased that the committee found our teams of high scientific quality, nationally and internationally recognized and very competitive in fund raising and collaborative work undertaken. We are also pleased that the committee found our group of trainees well integrated, strongly motivated and has a very dynamic community life.

Responses to:

I. Assessment of the unit "Weaknesses and threats related to the context**"** (page 5)

1. Diversity of topics addressed in the tumor immunology team.

1. The immunology group has planed to reduce the number of topics addressed and to concentrate on three major topics:

i. The influence of the tumor microenvironment in regulating the antitumor immune response (mainly the role of TGF-β1 by inducing CD103 integrin expression and hypoxia).

ii. Development of a Cancer vaccine approach in lung cancer based on the preprocalcitonin tumor antigen.

iii. Elucidation of the impact of hypoxic stress on tumor plasticity and immune heterogeneity in particular hypoxia-induced immunosuppression using *in vitro* models and *in vivo* spontaneous cancer models.

2. The unit could be more competitive in fund raising at the European level.

2. The unit will apply for European funds including Horizon 2020.

3. Too few permanent positions for young investigators.

3. We are aware that our unit needs more permanent positions for young investigators in spite of the reduced number of positions offered by public research organizations (INSERM, CNRS and Universities). We have identified two potential young researcher candidates, which are currently post-docs in France or US, for permanent position competitions (concours) at INSERM and CNRS in the near future.

4. Small size of the RCC genetics team.

4. Regarding the small size of the RCC genetics team, efforts will be made to increase the size of the group. An expert in molecular geneticist, Brigitte Bressac-de Paillerets from the Biology department of Gustave Roussy, as well as

an experienced Uropathologist, Sophie Ferlicot, from Faculté de Médecine Paris-Sud will join the group by January 2015. In addition, another permanent teacher-researcher from EPHE is expected during the next 5-year contract. This team will also recruit a post-doc and a technician to reinforce its research.

5. Difficulty around bioinformatics (lack of experienced staff), as in most other research centers.

5. The difficulty around bioinformatics is not specific to our unit, but general to most research centers in France. Gustave Roussy is aware about this lack and has already recruited a bioinformatician to reinforce its Genomics and Bioinformatics plateform.

II. Recommendations (page 5)

1. Try to stabilize permanent positions for young scientists (Mr Mehdi KHALED, ATIP-Avenir).

1. Mehdi KHALED is currently the unit candidate for a permanent position at INSERM and CNRS, and he has a good chance to get a CR1/2 position. He was already preselected for oral presentation by INSERM commission CSS5 and CNRS Section 24 for 2014 CR1 competition.

2. Try to establish more links between immunology and genetics, considering the available expertises.

2. Stronger links between immunology and genetics teams have already started mainly by investigating a potential role of HIF-2α in regulating RCC susceptibility to NK cell-mediated killing *(Messai et al., submitted)*. Collaborative works between team 2 and themes 1 and 2 of team 1 will also be initiated to reinforce these interactions.

3. It should be possible to increase the visibility at the European level, for funding purposes.

3. The visibility of the unit will be increased at the European level by applications for European funds including Horizon 2020

III. Assessment of the unit's organization and life (page 6)

1. Insufficient funding to cover consumables and need for a dedicated fund that may support travelling to international meetings.

1. Fund raising at the national and European levels to cover consumables and travelling to international meeting for the unit young researchers will be requested namely from the Ligue (labellisation), INCa (an intention letter has been accepted for 2014), ARC, Leg Poix…

Team 1 : Antitumor immunity and microenvironment plasticity.

Specific comments:

We are pleased that the committee found the scientific production of team 1 excellent and that a large part of its work is conducted directly on human cells, including materials derived from cancer patients, or involves human clones of tumor-specific cytolytic T cells, which very few groups are capable of producing and maintaining and which provides the group with reliable tools and corresponds to an asset of the unit.

Responses to:

I. Assessment of scientific quality and outputs (conclusion, page 11)

We would like to mention the last contributions of theme 2 from team 1: E) this theme established a link between hypoxia-induced Nanog and TGF-ß1 and point to a role of this transcription factor in hypoxia-driven immunosuppression *(Hasmim et al cutting Edge J.Immunol 2013)*. This theme also showed that hypoxia causes an up-regulation of PD-L1 on MDSC by direct binding of HIF-1α to a hypoxia-response element (HRE) in the PD-L1 proximal promoter *(Noman et al JEM 2014)*.

1. The team would be greatly strengthened by another permanent position for a young scientist.

1. We are planning to recruit another permanent position young scientist to strengthen theme 1 from team 1 research. A permanent technician will also be hired to reinforce this group. Recently, a post-Doc, who obtained a fellowship from the "Fondation pour la Recherche Médicale", has joined theme 1 starting from March 2014.

2. The projects are still somewhat diverse.

2. Despite its apparent diversity, our research is focused on only the following themes:

i) influence of the tumor microenvironment on shaping the antitumor immune response.

ii) role of CD103 in potentiating intratumoral T-cell immunity.

ii) development of a cancer immunotherapy approach based on the preprocalcitonin (ppCT) tumor antigen and

iv) elucidation of the impact of hypoxic stress on tumor plasticity and immune heterogeneity, in particular hypoxia-induced immunosuppression, using *in vitro* and *in vivo* cancer models.

3. Some projects are intrinsically risky, such as the preprocalcitonin vaccine development.

3. We are aware that the development of a cancer vaccine will be long and will require a lot of investments, but this is a general issue for all the groups working in this field. The ppCT antigen has however several assets as compared to the tumor antigens currently used in lung cancer vaccine approaches (such as Mage-A3 by GSK and MUC-1 by Transgene and Merck-Serono): i) it is a shared lung tumor antigen, largely expressed in NSCLC, which induced a spontaneous CTL response in a NSCLC patient with long-term survival; ii) a strong patent application with a very good international research report (patent granted in December 2011); iii) it includes a TAP-independent epitope, derived from ppCT signal sequence, which represents an alternative target that permit CTL to destroy TAP-impaired tumors and thus overcome this mechanism of tumor escape from the immune system that we showed to be frequently used by NSCLC, iv) we demonstrated the immunogenic potential of ppCT in several NSCLC patients and in HLA-A2 transgenic mice, and identified 3 additional ppCT-derived epitopes processed by TAP-dependent and -independent pathways. Moreover, our group has strong interactions with national and international teams with worldwide-recognized expertise in the field and benefits from a Comprehensive Cancer Center (IGR) environment. Our project also benefits from financial supports of Gustave Roussy, INCa-DGOS…, which will help to be successful. Finally, this project benefits from the recent clinical successes of immunomodulatory antibodies in lung cancer. A phase 1b clinical trial combining ppCT-based approach with anti-PD-1 antibodies (successfully used at Gustave Roussy) is planned with clinicians from the thoracic Department.

Team 2: Genetics and biology of renal cell carcinoma

Specific comments:

We are pleased that the committee found that the team 2 is nationally well-known (as attested by the coordination of two INCA "Clinical Expert National Centers for Rare Cancers" an one "National Oncogenetic Network for Rare Cancers"), is an European leader on hereditary predisposition to renal cancer, it participates in all major international networks on inherited renal cancers and has already published with these networks.

Responses to:

I. Assessment of the unit's academic reputation and appeal (page 13)

1. No post-doc was hosted by the team

1. The team leader is aware that there is an urgent need to recruit post-docs. Funds from national and international organisms will be requested shortly to this aim.

II Assessment of the unit's organization and life (page 13)

1. Within the U753 INSERM unit, it would be easy and natural to develop links between the teams in the hypoxia/antitumor immune response, considering the VHL/HIF pathway.

1. Links between teams 1 and 2 will be developed mainly in the hypoxia/antitumor immune response, considering the VHL/HIF pathway.

2. It is to be hoped that in the future it will be possible to combine the remarkable expertises of the unit in tumor immunology and in genetics.

2. We will certainly combine in the near future our expertise in tumor immunology and genetics by developing common scientific programs.

III. Assessment of the strategy and the five-year plan (page 14)

1. One difficulty might be bio-informatics to interpret all the "omics" results. It requires dedicated human power with a highly specialized know-how and a strong training for each topic: exome sequencing, sumoylome, transcriptome, miRome, proteome ...

1. The team leader is aware about the difficulty related to bio-informatics in order to interpret all the "omics" results. Collaboration with the IGR bioinformatic platform has been established and will be reinforced by recruiting a dedicated post-doc with a highly specialized know-how. External collaboration will also be developed for these aims (exome sequencing, sumoylome, transcriptome, miRome, proteome).

2. From the project presentations and discussions with scientists, the links with team 1 were not obvious

2. Discussions between Team 1 & 2 members will be organized in order to reinforce the links between scientists within the unit. Collaborative work between team 1 and team 2 was initiated in 2013 and is focused on the impact of VHL mutation in shaping RCC microenvironment and the antitumor immune response. Two papers were cosigned by team 1 and team 2 in 2014 (British J Cancer and Cancer Research). The impact of VHL mutation on the antitumor response and acquisition of the tumor resistant phenotype will be pursued.

IV. Conclusion (page 15)

1. Opportunity to strengthen the team with a potential recruitment in 2015.

1. As the unit is now also under the official EPHE supervision, recruitment of an additional teacher/researcher from EPHE should be possible to strengthen the team.

2. It should be strengthened with post-doctoral fellows and possibly permanent full-time researchers

2. The team is planning to recruit a promising follow in order to be potentially recruited as a full-time INSERM researcher.

3. Interesting publications but rely often on collaborations.

3. The team was pleased to actively participate in three major collaborative works published in Nature and Am J Hum Genet, but it has also a number of its own publications reporting original results, including some in high impact journals.

4. The absence of a bio-informatician in the team is an important issue. It appears to be the case also at the level of IGR. It will be a problem when choices have to be made between several methodologies or for the interpretation of large amounts of data generated by the project's multiple "omics".

4. As mentioned above, a bio-informatician will be recruited at the IGR level and may be also within the team to help make choices between the different methodologies.