



Vaccins anti-cancer et immunorégulation

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Cancer Vaccine & Immune regulation

From the

Université de Nantes

INSERM

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INSERM

Le Président de l'AERES

Didier Houssin

Section des unités
de recherche

Le Directeur

Pierre Glorieux

February 2011



Research Unit

Name of the research unit : Cancer Vaccine & Immune regulation

Requested label : UMR_S INSERM

N° in the case of renewal

Name of the director : Ms. Danila VALMORI

Members of the review committee

Committee chairman

Mr Roland LIBLAU, Université de Toulouse 3, Toulouse

Other committee members

Ms. Nathalie CHAPUT, Institut Gustave Roussy, Villejuif

Ms. Clotilde THERY, Institut Curie, Paris

Ms. Paola NISTICO, Regina Elena Cancer Institute, Rome, Italy

Ms. Maria-Pia PROTTI, San Raffaele Scientific Institute, Milan, Italy

Mr. Antoine TOUBERT, Hôpital Saint-Louis, Paris, INSERM CSS representative

Mr. Jérôme ALEXANDRE, Hôpital Cochin, Paris, CNU representative

Observers

AERES scientific advisor

Ms. Ana-Maria LENNON-DUMENIL

University, School and Research Organization representatives

Ms. Christine TUFFERAU, INSERM

Mr. Regis BATAILLE, Cancer Center Rene Gauducheau

Mr. Jean-Michel ROGEZ, Université de Nantes



Report

1 • Introduction

- **Date and execution of the visit**

The site visit of the “Cancer vaccines and Immune regulation Team” took place over 2,5 hours on February 15th, 2010. The organization allowed the visit to go smoothly. The committee had enough time to listen to the presentations and discuss their scientific content, assess the research of the 2 groups, and discuss with the students around their posters and also in a more informal manner.

At the end, the review panels met to exchange their views and to organize the preparation of the final report.

- **History and geographical localization of the research unit, and brief presentation of its field and scientific activities**

The 2 PIs of the research unit moved to France from Columbia University Medical Center in New York in 2007. They have since established the first basic research laboratory in the Nantes Cancer Center. Initially associated with INSERM Unit 892 (CRCNA) located some 15 km away, the “Cancer vaccines and Immune regulation Team” has decided to develop an independent INSERM unit in order to increase the visibility of their cancer vaccine program. This decision has been taken with the full support of the acting Director of the Nantes-Angers Cancer Center. The research team remains closely associated with international programs and consortia, such as the Cancer Vaccine Collaborative and the Ludwig Institute for Cancer Research.

Their main field of activity is to develop active immunotherapy programs for cancer patients using cancer-testis antigens. This implies developing the immunomonitoring tools as well as in-depth investigation of qualitative aspects of the T cell response in humans, areas in which the team has invested major efforts during the last 4 years.

- **Management team**

As foreseen, the team will include 10 staff members (scientists, teaching scientists, clinicians, technicians and students). The unit is managed smoothly hand in hand by the 2 PIs. Given the small size of the unit at the present stage, the financial and administrative management of the team goes without problems.

The trainees have easy access to the 2 PIs and communication is fluid among the team members. Concerning scientific animation, internal laboratory meetings are organized on a weekly basis. These include journal clubs given by students and post-docs. As scientific seminars are very rarely organized at the Cancer Center, the trainees are encouraged to participate to national or international congresses or to attend the IFR seminar series.



- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3	3
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	1
N7: Number of staff members with a HDR or a similar grade	2	2

2 Overall appreciation on the research unit

- Summary

The team researchers presented an ambitious and very well structured program on cancer vaccines and immune regulation. Since they moved to Nantes in 2007, they were able to set a laboratory that is fully equipped with state of the art instruments for cellular and molecular immunology. For development of their program they recruited a good number of technicians, PhD students and post-docs and they also have planned further recruitments in the near future. The scientific approach and data presented are solid and sound. The research already produced a large number of high-quality publications and a patent. The program is very well funded both nationally and internationally. The location of the laboratory within the Cancer Center favours interactions with clinical and surgical oncologists essential for both preclinical and clinical studies. These collaborations add to others previously established both national and international. In addition, the future attraction within the Cancer Center (as already planned by the Director) of other research units will increase, the opportunities for daily basis interactions with researchers of the same or other fields of interest, especially for PhD students and post-docs.

- Strengths and opportunities

- The two PIs seem to synergize perfectly. The technicians, engineers and students are blooming and happy in this team. Management is harmonious with discussion and consensus decisions ;
- The demonstrated capability to set a new fully equipped laboratory and attraction for PhD students and post-docs ;
- A competitive and comprehensive preclinical and clinical program in cancer vaccines and immune regulation ;
- A strong connection with Ludwig Institute for Cancer Research and Cancer Research Institute through the joint international cancer program (i.e., the Cancer Vaccine Collaborative) ;
- Newly established collaborations with national research units and local clinical and surgery units within the Cancer Center (CLCC René Gauducheau) ;



- The research program is very well funded both nationally and internationally ;
- Excellent track record (i.e., publications and patents) especially in consideration of the time needed to set the laboratory.

- **Weaknesses and threats**

The main weakness is related to the isolation of this research team in the Cancer Center of Nantes. There is therefore an urgent need for the Cancer Center and Biomedical research authorities to increase its critical mass of scientists and further help this excellent team to recruit new staff ranging from technicians to researchers.

- **Recommendations to the head of the research unit**

Encourage the PhD students and post-docs to interact with other scientists, especially those from other immunology and cancer research Laboratories in Nantes. This could be readily initiated by facilitating their attendance to seminars organized by these distant laboratories.

- **Production results**

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	1
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	1
A3: Ratio of members who are active in research among staff members $[(A1 + A2)/(N1 + N2)]$	1
A4: Number of HDR granted during the past 4 years	2
A5: Number of PhD granted during the past 4 years	0

3 • Specific comments

- **Appreciation on the results**

Between 2006 and 2010, several articles published every year (with one of the 2 PIs as last author) in journals such as Clinical Immunology, Cancer Immunol Immunotherapy, or Journal of Immunotherapy (IF 3-4), plus at least one article in journals of higher impact factor such as J Immunol or Clinical Cancer Research, IF 6-7, or PNAS: IF 10. One patent has been filed on the NY-ESO1 immunodominant epitopes.

The team performs very strong translational research regarding NY-ESO1 in cancer patients and the rationale to use this antigen as a therapeutic cancer vaccine in cancer-bearing patients. More specifically, they have shown that vaccination using recombinant NY-ESO1 protein elicits a good CD8 T cell response in 50% of vaccinated patients, with HLA-B35 and/or -Cw3 positive individuals exhibiting more consistent responses. The CD4 T cell response against NY-ESO1 was also studied using, in particular, original His-tagged peptides/HLA-DR tetramers as investigation tools. The helpful development of such immunomonitoring tools should lead in the near future to great clinical research studies on the natural adaptive CD4+ immune responses in cancer patients.

Very strong more basic science for Th17 differentiation and lineage plasticity in humans and on Treg cells. In particular the team has identified human natural naive Treg cells based on CD25 and CD45RA markers. They went on to dissect the FoxP3+ T reg population and identify central memory and effector memory subsets. Interestingly, they identified a human memory Treg subpopulation that secretes IL-17 and expresses ROR α . Natural naive FoxP3 Treg



cells do not produce IL-17 but can be induced by cytokine cocktails including IL-1 α to acquire ROR γ t, produce IL-17 and down-regulate FoxP3. These very original data document, using human cells, the great plasticity that exists within the CD4 compartment and open wide possibilities in terms of manipulation of the CD4 functional subsets.

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

The team researchers presented an ambitious and very well structured program on cancer vaccines and immune regulation. Since they moved to Nantes in 2007, the 2 co-PIs have secured prestigious positions (PU-PH and DR with AVENIR contract).

They were able to set a laboratory that is fully equipped with state of the art instruments for cellular and molecular immunology. They have trained 1 post-doctoral fellow, 2 PhD students and 3 M2R students. Currently, 2 post-doctoral fellows, 1 PhD student and 2 assistant-engineers are being trained in the laboratory. Space is available for further recruitments.

The program is very well funded both nationally (ARC, INCa, Fondation de France, Région) and internationally (Ludwig Institute for Cancer Research, Cancer Research Institute, FEDER).

They have been invited to 14 lectures at international Workshop or Congress.

Their main field of activity is to develop active immunotherapy programs for cancer patients using cancer-testis antigens. The impact of the research, albeit hypothetical at this stage, may be considerable.

- **Appreciation on the strategy, management and life of the research unit**

Without revealing specific research aims, the overall goal of the team is to follow up their studies on the spontaneous and the vaccine-induced T cell responses to tumor antigens in cancer patients. In parallel, in-depth investigation of the relationship between Treg cells and other CD4 T cell subsets will be pursued and investigation of the specificity of Tregs cells present at the tumor site performed. These studies should lead in the very near future to early phase clinical trials in patients with ovarian cancer or breast cancer.

The potential of these studies in terms of implementation of new anti-cancer vaccines approaches associated with refined immunomonitoring is real. Identification of subsets of cancer patients with an immune repertoire allowing efficacious anti-tumor immunotherapy is an additional potential outcome of these studies.

Given the clinical environment, the accumulated know-how, and the international networks they are associated to, the feasibility of the projects presented by the 2 PIs appears solid.

The two PIs seem to synergize perfectly. The technicians, engineers and students are blooming and happy in the team. Management is harmonious with discussion and consensus decisions. There is however an urgent need for the Cancer Center and Biomedical research authorities to increase its critical mass of scientists and further help this excellent team to recruit new staff.

- **Appreciation on the project**

The general project on cancer vaccines and immune regulation is ambitious and very well structured. Most projects are in line with their previous work. However, new and cutting edge projects, in particular related to the lineage relationship between Tregs and other functional subsets of CD4 T cells, have emerged and will be actively pursued.

Several projects are developed in highly competitive fields but high gain is expected.



Intitulé UR / équipe	C1	C2	C3	C4	Note globale
VACCINS ANTI-CANCER ET IMMUNOREGULATION	A+	A+	A	A+	A+

- C1 Qualité scientifique et production
- C2 Rayonnement et attractivité, intégration dans l'environnement
- C3 Gouvernance et vie du laboratoire
- C4 Stratégie et projet scientifique



Statistiques de notes globales par domaines scientifiques (État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2_LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	42	5	20	26	36	59	5	17	29	239
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

* Les résultats SVE2 ne sont pas définitifs au 06/05/2011.

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
 - SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie
 - SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes
 - SVE1_LS3 Biologie cellulaire, Biologie du développement animal
 - SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie
 - SVE1_LS5 Neurosciences
 - SVE1_LS6 Immunologie, Infectiologie
 - SVE1_LS7 Recherche clinique, Santé publique
- **SVE2 Ecologie, environnement**
 - SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement
 - SVE2_LS9 Sciences et technologies du vivant, Biotechnologie
 - SVE2_LS3 Biologie cellulaire, Biologie du développement végétal

Nantes, le mardi 19 avril 2011

REF : JG/EP - 2011 RECH N° 512 .
SUIVI PAR : Jacques GIRARDEAU
Objet : Rapport d'évaluation - S2UR120001447
VACCINS ANTI-CANCER ET
IMMUNOREGULATION - 0440984F

LE PRÉSIDENT

à

Monsieur Pierre GLORIEUX
Directeur de la section des unités de
recherche
AERES

Monsieur le directeur,

Je vous prie de trouver ci-joint les observations de portée générale concernant le rapport d'évaluation de l'unité « VACCINS ANTI-CANCER ET IMMUNOREGULATION », dirigée par Madame Danila VALMORI, observations que j'approuve bien évidemment.

Je vous prie d'agréer, Monsieur le directeur, l'expression de mes sentiments les plus cordiaux.

Pour le Président de l'Université de Nantes
et par délégation
Le Secrétaire Général, Directeur Général des Services


Philippe DIAZ

Yves LECOINTE

Pr. Danila VALMORI

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UNIVERSITÉ DE NANTES

Re: AERES report “CANCER VACCINES AND IMMUNE REGULATION”

Nantes, April 19th 2011

To the members of the AERES committee:

Dear Colleagues,

We would like to thank you, on behalf of our team, for carefully reviewing our work. We are pleased of the positive appreciation of our research activities and our accomplishments since our moving to France in 2007. In particular, we appreciate that our research program on Cancer Vaccines and Immune Regulation has been valued as “very ambitious and well structured” and the productivity of the group has been appreciated. Setting up a comprehensive program going from basic to translational and clinical research in a new location has indeed required a considerable investment during the last years, involving setting up a new laboratory and constituting a new research team, but also developing a close collaboration with clinical oncologists and surgeons at the CRG and with research groups in France, while maintaining our international network activities within the Cancer Vaccine Collaborative. We are particularly proud of our research team and are pleased that the committee has well sensed the enthusiastic, dedicated and mutually supportive character of the team. The only concern raised by the committee is in relation to our location in an environment that is mostly clinical (the Cancer Center) with respect to the needs of our PhD and post-docs to interact with other scientists. We value this comment and are of course engaged in exposing our young scientists to the scientific community as much as possible. They are therefore not only encouraged to attend local seminars but they also present their results on a regular basis at conferences in France and abroad.

Again, thanks a lot for your time, encouragements and support of our research.

Sincerely yours,

Danila Valmori and Maha Ayyoub.