CPTP - Centre de physiopathologie de Toulouse Purpan UMRS U563 (absorbe UMRInra 1225 IHAP, équipe UPR 8241 LCC, EA2405, EA3038, equipe UMRD152)

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Centre de Physiopathologie de Toulouse Purpan (CPTP)

From the

Université Paul Sabatier Toulouse 3

INSERM UMR 563

Mai 2010

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Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	**Pierre Glorieux**

Mai 2010

Research Unit

Name of the research unit: CPTP, Centre de Pathophysiologie de Toulouse Purpan

Requested label: UMR INSERM

N° in the case of renewal: 563

Name of the director: Mr Roland LIBLAU

Members of the review committee

Chairperson

Ms Lucienne CHATENOUD, Necker Hospital, Paris

Mr Jean-Louis MEGE, Université de la Méditerranée, Marseille

Other committee members

Mr Luciano ADORINI, Intercept Pharma, Perugia, Italy

Mr Hai-Tao HE, CIML, Marseille

Mr Mauro PERRETTI, William Harvey Research Institute,London, UK

Ms Angela SANTONI, University " Sapienza" of Rome, Roma, Italy

Mr Burkhard BECHER, Institute of Experimental Immunology , Zurich, Switzerland

Mr Thomas MERTENS, University of Ulm, Germany

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Mr Bernt Eric UHLIN, Umea University, Sweden

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Mr Eric LEGIUS, Catholic University of Leuven, Belgium

Committee members nomminated by staff evaluation committees (CNU, CoNRS, INSERM and INRA CSS....)

Ms Sophie EZINE (CSS INSERM)

Mr Bruno POZZETTO (CSS INSERM)

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Mr Joel PESTEL (Section CoNRS)

Mr François TRON (CNU)

Observers

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Mr Jean-Pierre VINEL, Dean of Medical School, University Toulouse 3 Paul Sabatier

Research Organization representatives

Ms Christine TUFFEREAU and Ms Armelle REGNAULT, INSERM

Mr Stanley TOMASO, CNRS

Report

1 • Introduction

- Date and execution of the visit:

The site visit of the "Centre de physiopathologie de Toulouse Purpan" (CPTP) took place over two days on December 3 and 4, 2009. Because of the size of the center, including 14 teams, and also due to the multidisciplinarity of the research themes developed it was decided, when preparing the visit with the AERES representatives, that the experts' committee would split into two groups. The first would review the teams which work focused on Immunology and Inflammation and the second would review the teams which work focused on Infectiology and Genetics. A chairman was selected to lead each of the review panels; the two chairmen worked in close collaboration to collect the reviewers' comments and prepare the present final report.

This organization allowed the visit to go smoothly. Each committee had enough time to be able to listen to the presentations, assess the research of the groups, the environment for the PhD students and young research scientists as well as having time for the needed discussion. At the end of each team' presentation, a short discussion between the panel members took place to summarize the salient issues to retain.

Both review panels met at the end of all teams' presentations and once the meetings with the technicians, students and scientists from the center had been held, 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 CPTP was created by INSERM in 2002 as a multidisciplinary biomedical research center to gather different INSERM units, all located within the Hôpital Purpan campus, working in Immunology, Genetics, cell signaling and cancer. At that time, this was viewed as a pilot initiative to help developping/fostering the interaction/collaboration between the teams and, more importantly, providing the critical mass needed to define a site research strategy supporting and facilitating the establishment of the needed common core facilities. Five years later, in 2007, a scientific review of CPTP took place. The assessment was positive both considering the center as a whole and the individual teams and therefore the support to this whole operation was renewed. The development of CPTP since 2007 went along and in parallel with a more in-depth reorganization of the Toulouse biomedical research landscape, very actively supported by the Toulouse III University Paul Sabatier. Thus, a second INSERM research center, Institut de Médecine Moléculaire de Rangueil, was created in 2007 gathering the research units located in another medical campus of Toulouse, the one of Hôpital Rangueil. This center is devoted to research on metabolic diseases, cardiovascular diseases and cancer. In addition, a more long-term project was progressively established, which is now close to completion, and concerns the creation of a new building in Langlade devoted to cancer, gathering not only medical facilities but also academic and industrial initiatives. This building should open by 2013.

All this explains that the CPTP has devoted major efforts over the last two years to focus its research themes on what was viewed as the strengths of the founder teams namely, the pathophysiology of infectious, immune and genetic-based diseases. To implement at best these objectives, the center was able to attract senior scientists from other cities in France and also from other countries. In addition, the center has reorganized the fundamentals of the management team. Finally, in collaboration the teams within the Purpan campus and those in the Rangueil campus have significantly expanded the number of common core facilities to which they both have has now access.

The commitee acknowledged these important developments as well as the commitment of the Université Toulouse III Paul Sabatier in helping fostering this endeavour (the President of The University and the Dean of the Medical School were present at the beginning of the site visit).

- Management team:

As foreseen, the CPTP will include more than 200 staff members (scientists, teaching scientitsts, clinicians, research assistants, technicians and students). The management of the center is presented as follows. The center is managed by a triad including one Director and two deputy-Directors. These three persons are assisted by a board of team leaders (one leader per team). The Director, the deputy Directors and the board of team leaders constitute the core decision making body of the center. The Director and the deputy-Directors are nominated by the board of team leaders. The Directors and board members (i.e, management board) have in charge the management and all the aspects related to the scientific life of the center; they meet at least every three months.

A unit council composed by the Director, the deputy-Directors and 15 elected representatives (5 for each of the 3 following colleges: research scientists, research and administrative assistants, PhD students and post-doctoral fellows) meet regularly and make suggestions on organizational issues of the center, including prioritization of the use of the common facilitaties. The Director and the deputy-Directors are assisted in their administrative duties by an executive secretary.

The financial and administrative management of the individual teams is under the responsability of each of the team leaders assisted in their duties by the centralized management structure (the director, the deputy-directors and the executive secretary). Each team keeps financial control on their individual research grants but have accepted to provide a 5% tax (salaries and equipment excluded) of these grants to the center that are used to develop stategic scientific actions. The management board identifies, through consensus, what are the strategic scientific actions which need special support.

Concerning scientific animation in addition to the internal laboratory meetings organized by each individual team, different mechanisms have been established and are actively pursued to guaranty scientific exchanges between the members of the center. These include journal clubs, seminars delivered by students and post-docs to all scientists of the center, weekly seminars organized in the campus having as speakers invited scientists from other institutes in France, meetings held every two months in which senior scientists present their projects to the other teams for open discussion.

- Staff members (on the basis of the application file submitted to the AERES):

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	53	35
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	59	34
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 and 2.7 of the application file)	64	29
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	40	21
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	41	17
N6: Number of Ph.D. students (Form 2.7 of the application file)	88	36
N7: Number of staff members with a HDR or a similar grade	82	40

2 • Overall appreciation on the research unit

- Overall opinion:

The committee felt overall that the center is productive, the research is of international standard and that there is evidence of established collaborative links both nationally and internationally. Among other parameters, this was seen from the competitive grant funding already in place and that applied for as well as from the publication records. Creating the premises to allow cross-fertilisation among the different research topics of the teams which progressively gathered/developed with those of the teams that constituted the initial core of the center was not an easy task. Yet, the committee acknowledged that the goal has been, so far, satisfactorily achieved. The committee was unanimous in that all scientific leaders involved in this endeavor have directed, and sometimes redirected, their work in order to establish the needed tools, methods, and collective know-how to develop the center along the scientific lines selected and described above. In particular, given the present development of biomedical research in Toulouse presented, it appears particularly well-suited to continue the efforts in focussing the themes of the CPTP on Immunology, Infectious diseases and Genetics. The capacity to attract young scientists as well as established seniors scientists, who committed in enriching the existing infrastructure along the scientific lines that have been selected, appeared both as a success of the administrative and scientific management options that have been taken over the past years and as a guarantee for positive future development.

At the end of the consensus discussion the review committe agreed in that over the fourteen teams included in the center five of them were scored as excellent and seven of them as very good.

- Strenghts and opportunities:

1) The publication record of the center has overall been very good and the quality of these publications has steadily improved over the past two-three years. A number of papers have been published in high impact journals such as Science, Nature Medicine, Immunity, Journal of Clinical Investigation, New England Journal of Medecine, etc.

2) Given the attractiviness of the research environment, the center has been able to recruit new teams and in particular very promising young researchers as assessed by the fact that their projects have been supported by competitive funding sources (such as AVENIR grants, ANR Jeunes Chercheurs, ERC starting grant).

3) The whole reorganization of the biomedical research in Toulouse with, in particular, the establissement of a new building in Langlade will facilitate in the future relocation of part of the personnel presently in Purpan, therefore providing more space for developing new groups.

4) The management system that has been established is very efficient and especially very focussed in providing support to new initiatives and creating the interaction needed between individuals to foster scientific collaborations.

5) The significant number of common core facilities are in place to guarantee the development of many of the projects proposed.

6) The close interaction with the medical school and the clinical centers in the hospital is a major strength in terms of development of clinical translational programs.

7) Active collaborations are being instituted with the other big research center in Toulouse located in the campus of Rangueil.

- Weaknesses and threats:

1) One important problem, that has been highlighted on several of the teams' presentations, is the insufficient space in the presently available animal facility. This is a very important common core as many research programs involve the use of animal models. The existing facility is well-organized and the personal in charge of it is competent. The major problem, however, is that the space is very much reduced as compared to what it should be given the number of the researchers who are interested in using this facility. This problem is very actively taken in charge by the management board and the Director emphasized that different measures have already been taken in order to get

help from the major support organisations (INSERM, the University) to solve the problem. A solution appears to be foreseen, in terms in expanding the surface available, within the next two to three years.

2) As it would be detailed in the specific teams' appreciations, the inclusion of some young researchers supported by AVENIR grants within given teams appears not totally adequate if one woudl like to keep as a priority a certain form of coherence between the research themes. This is essential to allow developping fruitful intra-team collaborations.

3) The review panel felt that there was a significant difference between the very productive and efficacious way in which the research areas related to Immunology and Infectious diseases were developed as compared to those presented by some of the teams focused on Genetics. Even though the panel understands the need and rationale underlying the choice of the main research themes, there is certainly room and need for improvement if the research on Genetics in the CPTP is meant to reach the same standards as the ones seen for Immunology and Infectious diseases.

- Recommendations to the head of the research unit:

Major recommendations from the panel to the Director of the CPTP are the following:

1) To continue the active discussion with the institutions (INSERM, University) providing the financial support to CPTP in order to reach, as soon as possible, a consensus on a practical way to proceed rapidly with the implementation of the animal facility.

2) To establish a programme of "brain storming" in the context of the managing board to decide how the programs devoted to Genetics may be reoriented in order to achieve a higher competitiveness, interaction among the groups and critical mass.

3) Some reorganization at the level of young researchers supported by AVENIR grants may be needed, taking into account the appreciation given to the individual teams concerned by this problem.

- Data on the work produced :

(cf. http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf)

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	68
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	6/6
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	62/68
A4: Number of HDR granted during the past 4 years	8
A5: Number of PhD granted during the past 4 years	47

3 • Specific comments on the research unit

The CPTP is a large biomedical research center including several teams developing different topics yet, centered around common themes namely, Immunology, Infectious diseases and Genetics.

In order to provide a fair overall appreciation of the results obtained it is of utmost importance to consider the historical background described above.

This is a relatively 'young' center that stemmed in 2002 from a pilot initiative INSERM decided to create in Toulouse by gathering a number of research groups located in the Hôpital Purpan campus.

It was obvious that this type of operation would need time so that the constituting teams would 'learn' to live, work and interact together and also attract additional groups to increase the critical mass.

Results were positive and year by year the 'core' teams succeeded in selecting the main research topics on which they would concentrate their efforts to build-up long-term projects taking into account their individual expertise and fields of interest.

As already mentioned, based on the past results, the publication record and visibility, the relevance and the impact of the projects presented, the committee scored 12 out of the 14 teams in the CPTP as excellent or very good. This is already an indication that the operation started 8 years back is a success.

The publication record of these teams is of high standard and, perhaps more importantly, some of these published data represent original and important contributions to the field.

A significant number of senior scientists and young investigators were attracted to the CPTP over the past 4 years and will join it over the next 2 years whose were all granted significant funding and, for the vast majority of them tenure research or university positions. This assesses more than any other parameter the attractiveness of CPTP.

Moreover as this was meant a 'biomedical'-oriented operation it is important to highlight that a great deal of energy was devoted to establish successful translational projects going, if one uses the conventional definition, from the 'bench to the bed side'.

All this operation, especially with its effectiveness which, as assessed by all indicators, significantly improved over the last 4 years was made possible by a thorough management design. Of course, as visible from the detailed appreciations of the individual teams, this is a never-ending effort which will need to be pursued in particular to support the young scientists and the innovative perhaps high-risk but sometimes high-gain projects to emerge. This is rendered more easy, given the management structure established, which involves the active participation of all team leaders in the decision making process; the Director and the deputy-Directors being also team leaders.

In conclusion the committee felt that CPTP is a very good research center which scientific production is of international relevance. It certainly represents an 'attracting' pole for both senior and young scientists from other centers both national and international.

4 • Appreciation team by team and/or project by project

4.1 Team 1 - Title of the team: Tolerance and autoimmunity

Name of the team leader: Mr Joost VAN MEERWIJK

- Staff members (on the basis of the application file submitted to the AERES):

	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)		1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)		2
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results:

The team has been working on two regulatory T lymphocyte (Treg) populations in the mouse: $CD4^+CD25^+Foxp3^+$ and $CD8^+CD28^{low}$ Treg cells. Data from the past five years show that the repertoire of $CD4^+Foxp3^+$ Treg is shaped in the thymus by a combination of cortical positive selection of autospecific precursors and lack of negative selection by medullary epithelial cells, but not by cells of hematopoietic origin. The resulting Treg repertoire is thus capable of preventing autoimmune responses without paralyzing adaptive immunity.

The team has studied polymorphic genes acting in a thymocyte-intrinsic manner and demonstrated that multiple genetic loci are involved in Treg development, some of which are linked to the MHC. Paradoxically, in the type 1 diabetes (T1D) prone non obese diabetic (NOD) mouse, relatively large numbers of Treg develop in the thymus. They could trace a responsible locus to a 7.4 Mbp interval centromeric to the MHC on mouse chromosome 17, which was distinct from previously identified genetic locations. Identification of the gene(s) involved may shed light on thymic Treg commitment and/or selection, and on the potential role of Treg developmental defects in susceptibility to autoimmune diseases.

Treg are good candidates for the induction of transplantation tolerance. The team has succeded in establishing a Treg-based protocol allowing effective prevention of chronic rejection of fully allogeneic skin and heart allografts.

The team has shown that $CD8^+CD28^{low}$ Treg cells are involved in the control of intestinal immune responses, demonstrating that coinjection of freshly isolated splenic $CD8^+CD28^{low}$ Treg can prevent colitis via IL-10 production. The transcription factor AIRE was shown to be involved in the generation of the $CD8^+CD28^{low}$ Treg repertoire, most probably modulating expression of antigens in the thymus.

Collectively, this body of work has successfully addressed important questions on Treg development, providing important contributions to the field. The work performed has clear elements of innovation and has followed a logical and coherent path of development.

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

In the past five years, the team has published 10 research papers. Among them, a Nature Medicine paper describing prevention of acute and chronic allograft rejection with $CD4^+CD25^+Foxp3^+$ regulatory T lymphocytes. The team leader as well as one of the senior scientists in the team have been invited to deliver lectures at several international meetings and have given seminars at various institutions in France and abroad. The team has therefore a good international visibility.

- Appreciation on the strategy, governance and life of the research unit:

The team comprised 2 researchers, 5 students, and two research assistants. The management of the group appears to be effective, and is facilitated by the relative small size of the team. Partnerships have been established with excellent research groups in different countries. The team has successfully applied for competitive funding, and has been able to raise considerable funds.

- Appreciation on the project:

The future plans of the team are articulated in several well-defined projects.

1) Increased Treg cell development in the NOD mouse. A first aim is the identification of mechanisms leading to increased Treg development in the NOD mouse, looking at the contribution of defined thymic cell types in Treg selection. Increased Treg development will then be linked to T1D susceptibility by adoptive transfer into NOD.SCID recipients. Identification of genes involved will be carried out by gene expression analysis, studies of associated gene polymorphisms, manipulation of gene expression, and mutagenesis experiments.

2) Following the past work demonstrating inhibition of acute and chronic rejection of heart and skin allografts by $CD4^+CD25^+Foxp3^+$ Treg cells, experiments will be carried out using drug-mediated preconditioning to achieve immunosuppression and partial myeloablation. The potential involvement of infections tolerance mechanisms will be clarified by Treg depletion in vivo. The immunocompetence of transplanted mice treated with different tolerogenic protocols will be analyzed by examining $CD4^+$ and $CD8^+$ T cell responses, and by monitoring the response to T. gondii infection.

3) Characterization of $CD8^+CD28^{low}$ Treg cells. This project includes several interconnected tasks aiming at defining further this Treg cell population. Main topics will be definition of Foxp3 expression and identification of novel markers, analysis of the repertoire (restriction, specificity, role of AIRE in IBD prevention), role in colitis prevention and oral tolerance, identification of effector mechanisms with emphasis on IL-10 targets and role of IDO.

Overall, the futures plans are shaped along two main lines of investigation. The first addresses the role of $CD4^+CD25^+Foxp3^+$ Treg cells in T1D development, and aims at advancing the potential use of Treg cells in clinical transplantation. The second will address repertoire selection and physiological role of $CD8^+CD28^{low}$ Treg cells. Both projects are feasible and the demonstrated expertise is expected to lead to a successful outcome. The projects integrate very well with other projects at the CPTP centre, and will contribute to its success.

- Conclusion :

The committee felt this is an *excellent* team.

– Strengths and opportunities:

The committee was impressed by the clear formulation of future research projects, the sound rationale in the experimental approach and the extensive background information available.

– Weaknesses and threats:

The only weakness/problem that was foreseen and discussed is that the field of regulatory T cells and in particular of $CD4^+CD25^+Foxp3^+$ regulatory T cells is a very competitive one.

4.2 Team 2 - Title of the team: Molecular dynamics of lymphocyte interactions

Name of the team leader: Mr Salvatore VALITUTTI

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	6
N7: Number of staff members with a HDR or a similar grade	3	4

- Appreciation on the results:

This is a well-established team well renowned at the national and international level in the competitive field of the study of immunological synapse (IS).

Over the past five years, the team has focused its research activities on the study of structural features and functional roles of the immunological synapse.

The major findings were:

1) That both T helper cells (Th) and cytotoxic T cells (CTL) engaged cell synapses are dynamic and adaptable structures. T helper cells can sense multiple antigen presenting cells (APC) simultaneously and selectively polarize their secretory machinery towards the APC offering the strongest stimuli. An important novel finding is that this polarization of Th cells towards APCs involves an atypical PKC¤ at the immunological synapse. The team has also addressed the role of regulatory T cells (Tregs) in the immunological synapse and found that Tregs inhibit polarization of the Th cell secretory machinery towards the APC, a phenomenon that is TGF-¤-dependent. On their side, CTLs can kill multiple targets simultaneously by rapidly addressing lytic granules towards different adjacent cells including 'innocent bystanders'. This process, however, does not appear efficient enough to destroy tumor target cells, at least in the experimental model which was used (a model of solid tumor namely, melanoma). The team also devoted interest to the potential involvement of mast cells. In fact, recent data from different groups has suggested that mast cells could serve in the various tissues where they are localized as 'non-conventional' APCs. The team could directly visualize that mast cells can form cognate associations with Th lymphocytes leading to bi-directional cell-cell interactions at the immunological synapse.

2) The team was able to obtain a permanent position from INSERM to recruit in 2006 a senior researcher who has significantly implemented the scientific investment by opening a new field that is the molecular control of actin cytoskeleton by the Wiskott-Aldrich syndrome protein (WASP) during activation of Th cells, Tregs and CTL. Results offer a molecular understanding of the abnormalities in immune-cell cooperation leading to the quite diverse symptoms observed in this rare immunodeficiency syndrome.

- 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 is renowned worldwide for its work and original contributions to the field of T cell biology and especially on the analysis of the function and fine dissection of the structure of the immunological synapse. The salient findings, described above, have led to various publications in high impact journals such as Immunity, J. Exp. Med., PNAS and Blood.

The team leader as well as the senior scientist recruited in 2006 have been invited speakers at various national and international meetings in their field (about 40 invitations as a whole over the last 5 years). Important fundings have been raised (EC/FP6, Marie-Curie Excellence, "labellisation" by "Ligue Nationale Contre le Cancer",..).

In addition, there are three university teachers in the group, who make very significant contributions to the immunology teaching at the University of Paul Sabatier. The team leader is a member of the Editorial Board for Immunology Letters and Self/Nonself - Immune Recognition and Signaling and, as well as the senior scientist involved in Wiskott-Aldrich syndrome research, serves as a regular reviewers for Nature Immunology, Immunity, PNAS, Blood, The Journal of Immunology, European Journal of Immunology and PlosOne.

- Appreciation on the strategy, governance and life of the research unit:

The team has recruited brilliant young researchers during the last 5 years. The team has also trained numerous students: 5 Master candidates, 9 PhD candidates and 5 post-doc fellows. They have brought with them new studying models and expertise. The committee felt that the new models and biological questions, some of which have a clear translational relevance, have been successfully integrated into the general themes of the group and therefore significantly increased the strength and critical mass of the team.

- Appreciation on the project:

For the coming years, the group aims at translating their knowledge and expertise on the study of lymphocyte activation dynamics by focusing at the visualization and investigation of immune response development in physiopathological situations.

The project includes in particular the analysis of interactions of human T/tumor cells during an immune response, both in vitro and in situ using tumor tissue explants. The committee recognises that this certainly represents a scientific challenge especially from the methodological point of view. However, the committee also acknowledges that this is indeed an important subject to address to get further insights into the field of anti-tumor immunity, a research subject in which the group has invested significantly and successfully over last years. In addition, the team is certainly very well equipped in terms of theoretical background, critical mass and technically sound and up-to-date methodologies to face such a challenge at the best level in the context of the international competition. Especially, at the technical level it is relevant to highlight at this point that the team leader has inspired and supervised the implantation in the center of a bi-photon microscope in the microscopy platform of the institute.

- Conclusion :

The committee felt this is an *excellent* team.

– Strengths and opportunities:

The committee was impressed by the clear formulation of future research projects, the sound rationale in the experimental approach and the extensive background information available.

The committee was also impressed by the original results which stemmed from the energy the team has devoted to apply their fundamental knowledge and practical expertise to the study of human diseases.

This endeavor has already provided relevant information on complex human pathology models which may help guiding novel therapeutic avenues in important conditions such as cancer and immunodeficiencies. Finally, the wish the team expressed to go for a more in depth analysis of in situ of the phenomena they have so far analyzed at a cell suspension level is certainly a worth high-risk high-gain effort.

– Weaknesses and threats:

The committee unanimously felts there were no weaknesses in the overall strategy conducted over past years and presented for the future.

4.3 Team 3 - Title of the team: Estrogens and calcium channels in the physiopathology of allergic and autoimmune diseases

Name of the team leaders: Mr Jean-Charles GUERY and Ms Lucette PELLETIER

- Staff members (on the basis of the application file submitted to the AERES) :

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
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)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	2
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results:

The research work of this solid team developed along the expertise of both leaders in the study of T cell biology and T cell differentation pathways involved in different immune-mediated diseases. Over the last few years the team concentrated on the dissection of the regulation of T helper (Th) cell activation and differentiation, and more particularly of Th2 cells, in experimental models of transplantation and allergic diseases. Each of these subjects was led by one of the team leaders.

Concerning allotransplantation the team showed that in absence of CD8+ T cell activation, Th2 cytokine production represents a default pathway driving alloreactive Th2-cell differentiation, which is deleterious for graft survival. They went on analyzing the mechanisms underlying the CD8 T cell-mediated regulation of allospecific Th cell development using as models allogeneic skin transplantation or subcutaneous immunization with allogeneic dendritic cells. The salient and original finding was that recipient CD8 T cells, once differentiated, rapidly eliminate allogeneic dendritic cells thereby inhibiting alloreactive CD4 T cell priming and Th2 development. Interestingly, they also bring one of the first demonstrations for a key role of NK cells in solid organ transplantation which, as CD8 T cells, by killing dendritic cells expressing allogeneic class I major histocompatibility (MHC) molecules, refrain the development of allospecific Th2 responses. This project, which results lead to publications in a high impact journal (Blood) will not be pursued further by the team. This is because the team leader in charge of this work has recently developed another project, which the committee felt as an interesting and promising one, dealing with the study of estrogen receptors on immune responses.

The interest of the team in allergic diseases came along the description of fundamental data related to T cell signalling showing that voltage-operated calcium channels (Ca_v1) were specifically up-regulated in Th2 but not in Th1 differenciated CD4 T cells. By sequencing the encoding full-length cDNAs the team confirmed that the sequence of Ca_v1 channel in Th2 cells is identical to some isoforms already described in other cell types. Furthermore, they showed that nicardipine, an inhibitor of dihydropyridine receptors, blocks Ca_v1 products thereby inhibiting, selectively in Th2 cells, the increase in intracellular calcium, the nuclear translocation of the transcription factor NF-AT and the

cytokine production. In addition, implementing the studies on the kinases involved in the regulation of Ca_v1 the results of the team pointed at Protein kinase G1 (PKG1) as a major regulator, as assessed by classical biochemical experiments and also showing, based on a collaboration with a group from Munich, that mice invalidated for PKG1 mounted defective Th2 responses while Th1 differentiation was normal. Interestingly enough, nicardipine was very effective at protecting BALB/c mice from ovalbumin-induced allergic asthma just as were antisense oligonucleotides blocking the expresion of (Ca_v1). These results open new therapeutic avenues for a pathological situation which frequency is steadily increasing in industrialized countries.

More recently, as meantioned above, one of the team leaders decided to approach another line of research which has been honed by several years of disappointing studies from different laboratories. This is the one on estrogen receptors (ER) and their dual effect on the immune system. The starting point is very relevant since it stems from the clinical observation that estrogens can be both 'bad' and 'good' on a series of autoimmune diseases, e.g. multiple sclerosis and rheumatoid arthritis. Incidentally, estrogens also have major actions on the vascular system, so that there is different susceptibility between females and males to related diseases. Using the experimental allergic encephalomyelitis (EAE) model in bone marrow chimeras the team already obtained original data showing that endogenous estrogens protect from EAE by signalling through ERα in non-hematopoietic cells, thereby limiting inflammatory cell recruitment into the central nervous system (CNS). Moreover, in a model of experimentally-induced myasthenia gravis the team obtained data showing that estrogen administration increased the pathogenic Th1 autoimmune response through ERα in hematopoietic cells. Finally, interesting recent results demonstrate the key role of estrogens in dendritic cell differentiation and suggest (using ER invalidated mice), at least in vitro, that the important signalling pathway is through ERα and not ERβ in that estrogen-dependent effect. These results provide the first molecular basis to explain the differential/paradoxical impact of estrogens on different clinical autoimmune diseases.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners:

The team leaders have an international standard of scientific production as assessed by their publication record. In addition, they have been able to establish collaborations with excellent teams to implement their research. The committee was unanimous in that both team leaders have published well, solidly and – as said above – this line of research is based on robust scientific grounds.

- Appreciation on the strategy, management and life of the team:

Although this team is smaller in size as compared to other within the center their level of scientific productivity is a good reflect of the capacity of the team leaders to manage their research work. All the data that have been obtained since 2005 were generated with the active participation of 6 Master students; 4 of them pursued their PhD training in the team. Since 2005, 5 PhD Thesis were defended and 3 are ongoing. The two main lines of research may certainly benefit in the future from further inter-connection. Two young investigators will join the team in 2010 and 2011.

- Appreciation on the project:

Two main projects are presented, in the direct continuation of the data obtained over the last years, and which were both ranked positively by the committee.

The one on ER seems very interesting since the team is now at the stage of solving the clinical condundrum, mentioned above, specifying the different cell targets behind the inhibitory effects of estrogen on autoimmunity and the target responsible for their activating/stimulating effects. This will be achieved using, in particular, newly generated experimental tools (in close collaboration with a group in P Strasbourg, leader in the field of estroden receptors) that are conditional knock-out mice in which ERα receptors will be selectively deleted in various tissues including the endothelium, myeloid cells, CD4 T cells and CD11c dendritic cells. All the mouse lines have already been generated and are presently being evaluated. Thus, the team proposes to go on establishing the role of ER activation in endothelium as a major mechanism behind the protective effects of estrogen in autoimmune settings. Again, this line of research can yield really exciting findings. This work will bring excellence. In addition, based on published data showing a role of interferon-producing plasmacytoid dendritic cells in systemic lupus erythematosus, the team embarked in a clinical translation approach. Results from a pilot clinical study show that in vivo treatment with estrogens in post-menopausal women potentiates TLR-mediated type I interferon production by plasmacytoid dendritic cells. On this basis the team wish to pursue studies to better dissect the disease-promoting effect of estrogens in systemic lupus erythematosus.

The second project of is the continuation of the work on Ca_v1 which can lead to important discoveries with a therapeutic potential. Further dissecting the functioning of this pathway in Th2 cells can unveil major fundamental discoveries. The committee felt this project was less advanced in its development as compared to the other one running in the team, and possibly riskier, but that it could greatly benefit from further simple and basic analysis for Ca_v1 expression in lung cells, using both mouse and human tissue samples, and from the know-how acquired in the estrogen receptor project. This being said there was no real expert on fundamental cell signalling in the committee and, as it appears, the data presented are really novel and tackling a pathway which is not yet widely studied by the immunological community.

- Conclusion :

The committee felt this is a very good team trustworthy of producing high level national/international research.

– Strengths and opportunities:

The committee was impressed by the straightforward presentation of the past work and how it connects with future research projects. Also the energy of this relatively small team in establishing high standard and fruitful collaborations was acknowledged. Finally, here too, the focus of the CPTP in establishing in the future robust lines of translational research was a visible wish addressed by the team. Both projects appeared as important 'niche research areas'. The potentiality for synergism – sharing tools and protocols – that would be beneficial to the development of each single project was also highlighted.

– Weaknesses and threats:

No weaknesses were highlighted, yet recommendations were formulated.

– Recommendations:

It was suggested that analysis of the expression of other nuclear receptors could be run in parallel, with respect to the estrogen receptor project. Perhaps, analysis of other nuclear receptor agonists could also be done, in selected experiments, both for comparative purposes and to identify potential new lines of research. Similarly, with respect to the calcium channel project, it was suggested to test (in the asthma model and in relation to Ca_v1 antisense oligonucleotides) mice deficient for specific leukocyte subset (e.g. partially reconstitued RAG-deficient mice). Exortation to explore Ca_v1 expression pattern in other lung cells, behind Th2 cells, was also underlined.

4.4. Team 4 - Title of the team: T cell differentiation and autoimmunity

Name of the team leader: Ms Sylvie Guerder

Avenir team: Mr Nicolas Fazilleau

- Staff members (on the basis of the application file submitted to the AERES):

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	3
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results:

The team leader is a well known researcher in the field of tolerance and autoimmunity who moved to the CPTP 4 years ago and had, thus, to hire a complete new laboratory. The team was implemented with 1 young investigator who joined the team leader. Therefore, it is obvious from the description of the work performed over these last few years that it was mainly focused on finishing past work, completing collaborative studies initiated in other institutions and preparing the experimental models for the project presented (see below), namely, mice invalidated for the thymus-specific serine peptidase (TSSP) backcrossed into the NOD background. Results obtained from the analysis of these mice suggest that TSSP contributes to the generation of peptides presented by class II major histocompatibility (MHC) molecules in the thymus and, thus, to CD4 T cell repertoire selection. By analysing $TSSP^{-/-}$NOD mice, the team observed that these double deficient mice are normal both in terms of thymic selection and immune competence. Interestingly, these mice are resistant to the development of autoimmune diabetes and mechanistic studies were performed to tackle the molecular mechanisms of this resistance. Results suggest that this may, at least in part, be due to a defective selection of the autoreactive T cell repertoire. The paper describing these data is presently under review in a prestigious high impact journal.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners:

The organization of the new team within the CPTP has impacted on the publication record of the team leader (2 papers as senior author in 4 years). The visibility of the team was therefore not optimal. The committee, however, acknowledged the presentation of the data generated from the established $TSSP^{-/-}$NOD mice that is presently submitted. Most of the published articles in high impact journals (Nature Immunology, Immunity) are from the young investigator who joined the team and was granted an AVENIR funding.

Very important fundings from various national and international sources (Association pour la Recherche contre le Cancer, Fondation pour la Recherche Médicale, European Foundation for the Study of Diabetes and Novo Nordisk, Juvenile Diabetes Research Foundation) have been raised by the team leader which is certainly a reflect of national and international recognition.

The team leader and the young scientist who joined the team are both involved in teaching.

The team leader has trained master students, 1PhD and 1 post-doctoral fellow.

- Appreciation on the strategy, management and life of the team:

The team leader has recruited two brilliant and promising young candidates, one has been granted an AVENIR support coupled to a CR1 position in 2008 to develop an independent project within the team together with a technician and a PhD student. Furthermore, another young scientist will join the team in 2010 back from a post-doctoral training in Berkeley. They will represent new forces to firmly establish the group.

- Appreciation on the project:

The team leader will pursue the in depth analysis of the TSSP$^{-/-}$NOD mouse model also in collaboration with other senior scientists from the center (one of the team 3 leaders). Main objectives are to identify the islet-derived autoantigens targeted by TSSP and the corresponding autoreactive T cell repertoire, to get further insights into the precise step in the MHC class II presentation pathway at which TSSP acts and to attempt extending to the human clinical situation the findings recovered from the mouse model.

The young investigator who joined the team with an AVENIR grant will develop an independent project in the direct continuation of his post-doctoral work, yet not in competition with the originating laboratory. This project is focused on follicular helper T cells with an accent on in vitro studies. The other young investigator who will join the team in 2010 and who is currently finishing a post-doctoral training in leading immunology lab in Berkeley will develop a new project on the role of CD4 T cells in anti-tumor responses. Both young candidates will be fostered in this group in order to accomplish their research.

The committee has acknowledged both the objectives and the goals defined by the team. The unpublished as well as the preliminary data have been perceived as very interesting and encouraging.

- Conclusion :

The committee felt this is a good team, with weaknesses in the past but very promising perspectives for the future.

– Strengths and opportunities:

The committee acknowledged the sound models that are in place and the attractive experimental rationale. Also the implementation of the team with two young and promising scientists was perceived as a major positive event.

– Weaknesses and threats:

The projects are sound yet very competitive and perhaps too many given the size of the group.

– Recommendation:

The team leader may need to implement the scientific management of the team in order to foster an eficient interaction between the investigators and to fix precise milestones at which results will be evaluated and strategic decisions will be made in terms of which research themes may be pursued, expanded or stopped. This will be essential to integrate at best within the team the potentialities of the young investigator with the AVENIR grant.

4.5 Team 5 - Title of the team: Inflammatory diseases of the nervous system: mechanisms and treatment

Name of the team leaders: Mr Roland LIBLAU and Mr Abdelhadi SAOUDI

- Staff members (on the basis of the application file submitted to the AERES):

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	10	6
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	4	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	9	4
N7: Number of staff members with a HDR or a similar grade	5	6

- Appreciation on the results:

The team is leaded by two senior investigators who are well recognised experts in the field of neuroimmunology both at the national and international level. One of the team leaders is the Director of the CPTP. The work performed over the past years followed an original, straightforward and competitive rationale along two major themes, each one coordinated by one of the team leaders.

The first topic is the fine dissection of the phenotypic and functional heterogeneity of pathogenic T lymphocytes that mediate the aggressive response affecting the central nervous system (CNS) in autoimmune demyelinating diseases as well as the analysis of the different sets of regulatory T cells (Tregs) that refrain disease progression. A long held dogma, essentially based on the analysis of some experimental models, was that CD4+ T lymphocytes and more particularly of the T helper (Th) 1 phenotype, producing interferon gamma, were the key players. This line of thinking has significantly evolved based on the data showing that other effector T lymphocytes including not only Th17 cells, producing interleukin (IL)-17, but also CD8+ T lymphocytes were involved in disease progression. The work of the team provided some seminal contributions on the role of pathogenic CD8+ T cells and also of their targets in the CNS using as tools different types of transgenic mice namely, mice expressing the influenza hemagglutinin (HA) transgene as a neo-self antigen in astrocytes, oligodendrocytes or neuronal cells and mice expressing an HA-specific T cell receptor (TCR) recognising the cognate peptide in the context of either major histocompatibility (MHC) class I (CD8 TCR transgenics) or class II (CD4 TCR transgenics) molecules. One major finding was that selective traffic of antigen-specific CD8 T cells into the brain occurs in vivo and is dependent on luminal expression of MHC class I molecules by CNS endothelial cells. This has implications for a variety of diseases in which antigen-specific CD8 T cell traffic into the brain is a beneficial or deleterious feature. The use of these models also led to the demonstration that not only negative selection but also the occurrence of antigen (HA)-specific Tregs are essential mechanisms for preserving self tolerance/ disease progression. Furthermore, a more careful analysis of the heterogeneity of regulatory T cells protecting from CNS autoimmunity revealed that invariant NKT cells, through their capacity to inhibit Th17 effectors appear as important players. Finally, it is important to highlight the very interesting more recent data that stemmed from collaboration with the group of H. Wekerle in Germany showing the paradoxical development of spontaneous experimental autoimmune encephalomyelitis (EAE) in transgenic mice expressing a myelin oligodendrocyte glycoprotein (MOG)-specific T cell antigen receptor (TCR) in the absence of MOG. In these Mog-deficient mice the autoimmune response by transgenic T cells is redirected to a neuronal cytoskeletal self antigen, neurofilament-M thus representing a form of molecular mimicry between two totally distinct self antigens.

The second topic deals with the genetic control of regulatory T cells and of CNS autoimmune inflammation studied using as a tool both an EAE model in the rat as well as a cohort of patients presenting multiple sclerosis. Using LEW and BN rats, that behave in opposite ways for their susceptibility to various immune-mediated diseases and, in particular, for EAE, and adopting a linkage analysis and genetic dissection, through derivation of a panel of congenic rats, the team identified a 120 Kb region on chromosome 9 that controls the levels of peripheral Tregs both CD4+FoxP3+ and CD8+FoxP3+. Within this locus they went on identifying a mutation in the first exon of the *Vav1* gene that encodes for a guanine nucleotide exchange factor for Rho family GTPases. The identified mutation leads to an amino acid substitution of the VAV1 protein; the protective variant is associated with higher numbers of FoxP3+ T cells, lower expression of VAV1 impacting on VAV1 signaling and segregates with susceptibility to EAE. In an important translational effort the team demonstrated, based on the analysis of various human cohorts (encompassing more than 12000 individuals), an association with multiple sclerosis of 2 single nucleotide polymorphisms (SNP) in the first *VAV1* intron.

As a whole this represents a very substantial contribution to the field that also well reflects the capacity of the team leaders to conduct innovative, high-risk/ high-gain projects with competence and perseverance.

The number of publications is well above average, the majority being published in very good to top-tier journals.

- 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 is a well established, internationally recognised group in the field of Neuroimmunology. Over the years, when they worked independently, both of the team leaders built fruitful and long-standing collaborations with high standard scientific partners not only in France but also worldwide. The fact that they decided to work together has reinforced their image in the community and certainly their capacity to demonstrate the synergism of their scientific view at the time each of them went on developing different aspects of the same research target that is the understanding of the etiology and physiopathology of autoimmune CNS diseases. Especially over the last years the two leaders have attracted strong financial support to the team through competitive funding including European FP6 and FP7 grants and grants from national agencies (ANR) and charities. The team leader who is the Director of the CPTP has organised various scientific meetings and served on national and international grant review panels as well as on editorial boards. The team leaders are actively involved in teaching to medical students and Master and PhD students. Another indicator, well reflecting the attractiveness of the team, is the recent recruitment of 3 young scientists providing them all the needed support to pursue their carrier; one of them got a tenured position in 2009 from INSERM, another is applying for a similar position and in the mean time was awarded a 3-year grant for young investigators from ANR.

- Appreciation on the strategy, governance and life of the research unit:

The team is highly integrative and the committee could value that members of the team from students, technicians to senior researchers appreciate the outstanding leadership. This is a tightly and highly efficiently run operation. This team stands out as role models in all aspects of management.

- Appreciation on the project:

The project presented by the team is in the direct continuation of the results they have obtained over the past few years, which are detailed above, with, in addition, some new projects that stem from the recruitment of young scientists having completed their post-doctoral training abroad and who joined back the unit to pursue an independent focus albeit always within the team main focus, i.e. the study of autoimmune-mediated CNS inflammation in both the murine models as well as in human patients.

Five major individual projects are proposed that are intertwining between fundamental and more translational research. These are: 1) a sustained effort in the device of transgenic models with targeted expression of neoantigens on well defined CNS targets such as astroglia, neurons. These will be used to unravel the mechanism of tissue damage, antigen exposure, T cell polarisation and collaboration and migration of different T cell subsets to the target; 2) to pursue the working hypothesis that autoreactive TCRs may cross-react through molecular mimicry against two distinct autoantigens, and not only as initially described against an autoantigen and a foreign (frequently an infectious-related) antigen. This project, that follows on the results recently published in Nature Medicine, plans to address if and how the target autoantigens play a synergistic role in aggravating the autoimmune phenomenon, whether these cross-reactive T cells are more pathogenic than autoreactive T cells for which only one autoantigenic specificity can

be detected and if, given the mimicry, the existence of cross-reactive T cell tolerance can also be demonstrated; 3) to dissect the role of Foxo3, a transcription factor controlling cycle progression, survival and death of different cell types, in EAE models. Foxo3-deficient mice, which are characterised by an increased number of dendritic cells expressing an increased ability to stimulate T cells and promote their survival, will be used as a tool; 4) to further understand the role of the mutation of VAV1 in T cell development and homeostasis using as a tool, knock-in mice carrying the protective mutation (that have already been developed), to define which are the down-stream genes that are a target of the mutation and to further pursue the genetic association studies in patients presenting neurological diseases such as multiple sclerosis and myasthenia gravis. The collaborations are already in place for the recruitment of the corresponding patients cohorts. Lastly, they have an active genetic group which plans to elucidate the feasibility of identifying pharmacokinetic biomarkers in the context of available therapies. This approach is again focused and highly comprehensive; and 5) to find reliable biomarkers to monitor immune-based treatments in MS patients through a combined approach using transcriptome analysis of anti-VLA4 (natalizumab)-treated patients, antigen microarrays for the high-throughput test of antibody self-reactivity and pharmacogenomics.

- Conclusion :

The committee felt this is an excellent team at the leading edge of Neuroimmunology research. The past and present performance is of the highest standard and all the prerequisites are in place to guarantee the feasibility of the projects proposed.

- Strengths and opportunities:

A particular benefit is the recruitment of young scientists building up their independent focus within the general topics of the team.

The benefit of having collected data that are clearly opening precise avenues of translational biomedical research and of having established strong collaborations with other teams in the CPTP that will bring-in their expertise in modern imaging techniques to open new fundamental avenues (Team 2).

- Weaknesses and threats:

No weaknesses were highlighted, yet recommendations were formulated.

- Recommendations:

The group is one of the largest in the CPTP and, with time, redundancies may become inevitable. Efforts will then need to be devoted to favor the budding of independent groups under the leadership of the present team leaders. At some point, depending on their creativity and energy, these groups should then be endowed with independence and the possibility to influence strategic decisions of the entire CPTP.

4.6 Team 6 - Title of the team: Immunity, pregnancy and therapeutics

Name of team leader: Mr Philippe LE BOUTEILLER

- Staff members (on the basis of the application file submitted to the AERES):

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results:

This is a well-established group with an international recognition in the field of reproductive immunology. During the past five years, the group has focused its research activities on the study of the role of NK cells and HLA-G in the immunological control of pregnancy.

The major findings are:

1) The identification of a specific pattern of NK receptors on decidual NK cells and their ability of triggering distinct functional responses (cytotoxicity vs cytokine/chemokine production).

2) The demonstration that soluble HLA-G is an inhibitor of angiogenesis and this inhibition is mediated by the interaction with CD160 receptor that is expressed by human $CD56^{dim}$ NK subsets. CD160 is also expressed by activated (but not quiescent) endothelial cells.

The group went on producing a monoclonal antibody to CD160 (CL1-R2) and demonstrated that engagement of CD160 by the monoclonal antibody triggered the activation of NK cell effector functions (i.e. cytotoxicity and cytokine production) and, interestingly enough, also induced the apoptosis of endothelial cells. Therefore the monoclonal antibody was endowed with two distinct activity of potential therapeutic relevance that are: immune stimulatory and anti-angiogenic capacities. Based on these observations the team invested major efforts to have the CL1-R2 developed in order to perform preclinical studies in two distinct indications that are: ocular neovascular diseases and tumor models. The results presented support the proof of concept of the beneficial effect of the monoclonal antibody in the two pathological conditions.

- 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 leader is internationally renowned for his work on HLA-G and reproductive immunology. He is has received many invitations to deliver lectures in both national and international meetings (total number of 11 times during the last 5 years). He has also been able, over the years, to establish a number of fruitful national and international scientific collaborations.

Since 2005, the major findings of the team led to a very good publication record; manuscripts appeared in Blood, J Immunol, Intl Immunol , J Reprod Immunol. Invited reviews on these topics have been published on Nature Medicine, Reproductive Biomedicine on line, Circulation Research, etc. In addition a patent has been licensed with a PCPT International extension.

Important funding has been raised including grant from the European community (EC/FP6), ANR-Research Innovation Biotechnology.

The team has trained numerous students: 3 Master candidates, 2 PhD candidates and 6 post-doctoral fellows.

- Appreciation on the strategy, governance and life of the research unit:

The team is a small one compared to others in the CPTP but the publication record and the international visibility of the team is a testimony of the efficient scientific management. The other young senior investigator who was given an INSERM CR2 tenure position is also very active. The committee noticed, however, that the main scientific interests of the team leader and of this other young investigator do not always appear well integrated (e.g. the research focus of the young investigator appears very much focused on anti-tumor therapy and less on the reproductive immunology topics). This situation, if pursued, could reduce the strength of the group as, at least presently, it is the reproductive immunology topic that provides a high international visibility to the group.

- Appreciation on the project:

For the coming years, the group research activity will address three main topics that are:

1) the analysis of uterine NK cell effector functions in response to pathogens with particular attention focused on plasmodium falciparum and cytomegalovirus.

2) the fine dissection of CD160-mediated signalling and.

3) a translational project focused on the clinical development of the novel anti-angiogenic therapy in cancer and ocular neovascular diseases using the anti-CD160 monoclonal antibody which has been produced and is available in humanised forms.

Both these topics represent the continuation of the previous studies performed by the team. The committee encourages close collaboration with other groups working in the CPTP in order to make the research focus shift towards the field of angiogenesis more successful.

At the same time the committee acknowledged the high quality research in the field of reproductive immunology that has been established by the team leader which is relevant as there are not so many laboratories investing in this field worldwide.

- Conclusion :

The committee felt this is a very good team. The past and present performance is of international standard in the field.

– Strengths and opportunities:

Both the fundamental and the clinically-oriented topics are of significance and are worth being actively pursued.

– Weaknesses and threats:

The group may need some implementation in the future, by recruiting young scientists if the two projects presently developed are to be pursued in parallel in an effective way. This will be essential to keep the international visibility in reproductive immunology and to cope with the huge academic and pharmaceutical competition in the field of anti-angiogenic agents for tumor therapy.

4.7. Team 7 - Title of the team: Mediators of inflammation, infection and inflammatory pain

Name of the team leader: Ms Nathalie VERGNOLLE

- Staff members (on the basis of the application file submitted to the AERES):

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	3
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)		2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	4
N7: Number of staff members with a HDR or a similar grade	1	2

- Appreciation on the results

The team leader was recruited in 2007, coming back from an institution in Canada (University of Calgary), supported by an AVENIR grant coupled to an INSERM tenure position. She has done tremendous work to establish the team, attracting qualified post-doctoral fellows and students. More recently, a young senior scientist from another institution in Toulouse has joined her team.

As assessed from the data presented, this is certainly one leading team, and at the international level there is no doubt that this Team is world leader in the area of Protease Activated Receptors (PARs) biology, with the particular focus of dissecting the role of PARs and proteases in innate immunity and pain response. Because of the expertise of the team leader in gastrointestinal (GI) pathologies, the analysis addressed three different GI pathological conditions namely, infectious diseases, inflammatory bowel diseases (IBD) and irritable bowel syndrome (IBS). Animal models recapitulating these clinical situations have been used, taking also advantage of a series of experimental tools the team leader had developed including genetically modified mice for the expression of PARs as well as PAR agonists and antagonists.

Salient findings were that: 1) the proteolytic activity released by the host following infection played a major role in the intensity of the consequent inflammatory response;2) PAR_1 and PAR_2 have an important role in IBD models arguing for the interest of these receptors as potential therapeutic targets; 3) proteases, through activation of PARs, can signal sensory neurons. Following on this line, the team further dissected the implication of proteases and PARs in sensory functions and pain pathways. Results demonstrated the interaction between PAR_2 with members of the transient receptor potential vallinoid (TRPV) family; one of these members, TRPV4, being a major component of visceral pain sensation; and 4) from a more translational point of view, the team identified the key role of PAR_2 in IBS-related symptoms (pain) arguing for its importance as a potential therapeutic target.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners:

Despite the short time, and the hurdles that a move from Canada would entail, the team leader has a very good publication record in high impact journals (>30 publications) with two major contributions with the papers published in the Journal of Clinical Investigation and Gastroenterology.

During this short period the team leader has established/maintained - possibly carrying some of them on from Canada – an impressive number of fruitful collaborations.

The committee acknowledged that the team leader was able to settle very well not only her team but also herself into the CPTP since she is one of the deputy directors of CPTP. In this position she has actively contributed and contributes to the overall strategy of the Centre. This is really impressive considering she may be the youngest team leader in CPTP.

Another indication that the team leader is a well renowned scientist in her field is the number of invitations to deliver lectures in international meetings (36 over the past 2 to 3 years).

- Appreciation on the strategy, management and life of the team:

The team leader has accomplished these tasks very efficiently both with respect to settling her team into CPTP, including setting up and validation of several experimental tools. Bringing back to CPTP a budding young scientist is also a positive strategic result. The additional move of a senior scientist from another laboratory in Toulouse is certainly beneficial, on several aspects.

- Appreciation on the project:

The Committee appreciated the well-structured presentation, where the vision of the team leader for the next 4 years was clearly expressed. Three main projects were presented with a great deal of breath, integration and translational efforts. The novelty of these projects was appreciated as well as the potential for integration/synergism between the research interests/tools of the team leader and the other senior scientist who joined the group.

Indeed, the great impulse to establish the translational potential of the protease/protease inhibitors in human tissue samples was deemed excellent. Three major projects are proposed:

1) Project I (protease/protease inhibitors) was very appreciated by the Committee. A minor issue raised was the large use of inflammatory bowel disease (IBD) experimental models, without clarification of the reasons behind the rationale for choosing a model over another. However, it was subsequently agreed that the team leader would be in perfect position to make the right selection when necessary in relation to the scientific question to be addressed. This project represents the main thrust of the research activities of the team in the years to come and there is high guarantee of making fundamental contributions due to the knowhow of the team leader and the options/directions presented. It is also the project that appears the more developed/implemented with several key components (animals, cells, clinical samples).

2) Project II (TRPV4) is a recently established one in the team, though underpinned by a Gastroenterology paper and supported by the activities of a young post-doctoral fellow who has the possibility of progressing in his career making this project his own, over time. Some minor comments on the relevance of studying pain were expressed, though it is clear that: a) pain is a fundamental symptom of inflammatory pathologies; b) the team leader has published, over the past few years, very important papers in the field and c) abolition of pain sensation in patients suffering from inflammatory bowel syndrome (IBS) (and IBD?) is a **major** goal in the clinical management of these pathologies.

3) Project III (enkephalins) is the newest project of the team and it is brought on by the recent arrival of the senior scientist from another laboratory in Toulouse. This project is clearly in its infancy since this scientist has essentially moved area of research, at large. However, it was noted that he brings a series of protocols and methodologies (predominantly molecular and cellular) that would synergise very well within the team with great potential for overspill benefits on the other projects too. The application of a new protocol for generation of anti-GPCR antibodies was discussed. In any case, the importance of defining, within the gut (experimental and translational), the potential for immune cell generation of enkephalins was very much appreciated by part of the Committee. However, fundamental questions such as how opioid receptors were going to be searched on hematopoietic cells were not clearly addressed.

- Conclusion :

The committee felt this team is a very good one. The past and present performance is of high quality and all indicators are present to guarantee the feasibility of the projects proposed.

– Strengths and opportunities:

This team benefits from several important strengths. One of them is the obvious energy and management capacity of the team leader to conduct at best her research. Another positive aspect of particular benefit is the recruitment of a senior scientist with complementary skills to implement the work. There is, in addition, a clear clinical translational effort incorporated in the research focus.

– Recommendations:

The two main projects address a large number of questions to be solved and, in many cases, were based on analysis on human biopsies. The committee suggests to the team leader to restrict some experimental approaches made on biopsies and to try to validate the experimental hypothesis on the potential role of studied molecules in animal models allowing dynamic and time-dependent experiments. Finally, the pain model must require special attention in its experimental development to be fully convincing.

4.8. Team 8 : Viral infection: persistence, host response and pathophysiology

Name of the team leaders: Mr Christian DAVRINCHE and Mr Jacques IZOPET

- Staff members (on the basis of the application file submitted to the AERES):

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	10
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	1
N7: Number of staff members with a HDR or a similar grade	6	6

- Appreciation on the results:

The overall relevance and originality of the research performed by this “team” as well as quality and impact of the results are high. This is true for the basic science projects as well as for the more clinical studies. The results cover a broad spectrum of scientific goals as well as different viruses (HCMV, HCV, HEV, HIV, EBV). One internationally most visible result has been the detection of chronic Hepatitis-E-virus infections in immunocompromised patients.

The number and quality of the publications and scientific communications is equally very high. The overall number of publications is impressive covering a really broad spectrum.

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

Eight members of the team have teaching duties of 50h to 200h per year attesting for strong interface with Toulouse School of Medicine. The team demonstrated good attractiveness by supporting 7 PhD defenses in the past 4 years, training 6 PhD students at present, recruiting young researchers, and planning to welcome two additional senior scientists in 2011, although weakness in recruiting post-docs from abroad could be mentioned. They

demonstrated also good insertion in national and European networks as participation in review panels (ANRS) and exert societal involvement as expertise in safety of health products (AFSSAPS).

A large number of internal, national and international partnerships are listed, which in part are documented by common publications, and interface with industry is proven by patent depository and research grants.

- Appreciation on the strategy, governance and life of the research unit:

The reason for building up this team in its present form was not completely clear to the committee. Any scientific interactions between the groups of the two team leaders were not clearly visible and the communication between the numerous members of this large team appeared to be less intense than possible. In addition, the different projects appeared somewhat heterogenous which may be explained in part by some more divergent clinical projects in the group working on HIV and HeV. The clear link between the two groups is that they deal with viruses. According to the reviewers this does not sufficiently support the construction of the present group as a coherent team, especially since another small virological team (Team 9) has been succesfully established and a strong cooperation between the different teams is not only possible but highly encouraged.

Overall, this team seems to be very large. The internal structure and interaction were not really transparent to the reviewers. This was also true concerning the structured ongoing scientific discussion within the whole team. Together with the partially divergent projects this might hamper initiatives aiming at the scientific motivation of the young researchers and graduate students within this team, although crosstalks between research projects focussing on different viruses may be a source of fertility.

- Appreciation on the project:

The team proposes a number of different projects, some of which are more orientated towards basic virology while others more towards pathogenesis or even antiviral therapy and clinical studies. The projects are dealing with HCMV, HIV, and HEV. Although the team did not propose a renewal project on HCV (which has been studied before) to reduce complexity, a future focussing of the projects might even strengthen the team(s). The outlined written new projects are mostly of great interest and promise high quality scientific work, although the work plan has not been very explicite in some of the projects probably due to the format (lack of space) of the written document. Overall the proposed projects surely are suited for several long term scientific projects accompanied by some determined clinical studies.

- Conclusions:

The committee felt this is a very good team if one considers the scientific production.

– Weaknesses and threats, Recommendations:

The rationale in building up the teams was clear and comprehensible in most cases, but some of its ‘subgroups’ having independent projects could be restructured to gain strength and effectiveness and to allow even better management within the team. In general it might be more adequate to first evaluate individually the proposed projects and subsequently, based on these project-specific evaluations, produce an evaluation of the whole team, especially because the topics appeared somewhat heterogeneous even though they were all dealing with virology.

4.9. Team 9 - Title of the team: Viral infection: Pathogenesis of viral infections of the central nervous system

Name of the team leader: Mr Daniel GONZALES DUNIA

- Staff members (on the basis of the application file submitted to the AERES):

	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 of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	2
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results:

The members of this new group have performed highly relevant research on altered neuronal functions due to BDV-infections since 2005. The experimental approaches also prove the originality of the research which was both well focussed and also covering different complementing scientific topics. The research was performed using an high, adequate and up to date methodological standard and combined technologies from different specialities, namely virology, molecular biology, electro-physiology, immunology and biochemistry. The quality and impact of the results obtained are very good, especially when taking in consideration the size of the group.

The number and quality of the publications is very good. The number of publications is absolutely adequate to the number of researchers and practically all results have been published in top journals of the respective fields. One Master-student and 3 PhD-students (1 PhD-student before 2005) have been supervised since 2005 by the team leader, which is a very convincing number.

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

National and international partnerships do exist and especially the cooperation with a leading virologist from Freiburg University has enabled the team to generate virus mutants by reverse genetics. All mentioned national and international partnerships are documented by common publications.

A few young scientists have been successfully gathered to build this new team (January 2011). This will also guarantee the availability of a multitude of methodologies including behavioral experiments in animals. Ability to recruit high levels scientists, post-docs and students, and more particularly from abroad has been appreciated.

- Appreciation on the strategy, governance and life of the research unit:

The team is not yet complete and therefore relatively small. It is too early to evaluate the management of the team.

- Appreciation on the project:

Based on its published results and thereby documented expertise, this newly established team proposes a focussed research program composed of 4 projects investigating 4 different but very nicely complementing aspects of the pathogenesis of bornavirus infection and disease as a model for chronic neurological disease. The 4 projects (BDV transport in neurons, viral interference with neuronal PKC-signaling and neurodegeneration, Impact of BDV phosphoprotein on neuronal function and behavior, mechanisms of neuronal damage caused by cytotoxic T-lymphocytes) are all innovative and cover the fields from molecular pathogenesis and functional analysis in neuronal cells (electrophysiology) to functional (behavioral) analyses in an established rat model and T-cell immunology. The latter project lies a bit more distant from the others but should remain included due to the long standing cooperation with the team 5. The projects are well written including a comprehensible workplan. The projects are excellently suited for a long term fruitful scientific work. As already mentioned above the combination of different approaches in the proposed focussed projects from molecular biology to cell biology and animal experiments provide excellent oportunities for very good or even excellent scientific results.

- Conclusions:

The committee felt this is a very good team if one considers the scientific production.

– Strengths and opportunities:

The implementation of this small, new and promising teams headed by a young scientist with an already clearly visible scientific record and reputation is seen as a very positive initiative which reinforces the structure and scientific strength of the CPTP.

4.10.Title of the team: Monocytes/macrophages polarization, nuclear receptors and pharmacological approaches in control of infections

Name of the team leader: Mr Alexis VALENTIN

- Staff members (on the basis of the application file submitted to the AERES):

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		3
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)		4
N7: Number of staff members with a HDR or a similar grade		5

- Appreciation on the results:

This group has been working in diverse areas of parasitology and pharmacology. For the pharmacological part of the team, patents on novel antimalarial drugs including a hybrid of arthemisine coupled to chloroquinone emerged from this team; the latter patent is a breakthrough for the drug resistant malaria, licensed to Sanofi and is now in phase II of clinical trial. Further, the team is pioneering natural medicines discovery, where several exciting,

potential drug candidates are in the pipeline. However, the pharmaceutical discovery is not well structured and the parasite targets are poorly discussed.

For the parasitology part of the team, several significant publications have been done in relation to macrophage polarization in the context of IL-13 response. The role of PPAR gamma in the activation of macrophage and in the pathophysiology of infectious diseases (Candida albicans, Hepatitis C) has been illustrated by pertinent publications. The role of PPAR gamma was also investigated in the field of toxicology (carbon nanotubes).

The scientific output of this group is related to the size of the group and includes many state of the art research papers published in scientific journals appropriate for the field.

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

This team has many national and international collaborations and activities. The antimalarial discovery research is recognized at the national and international levels, with four patents and an excellent publication record. The recently recruited young scientists in the team certainly will further enhance the impact of the scientific production. The team is clearly attractive for young scientists and overall the local network is well developed.

- Appreciation on the strategy, governance and life of the research unit:

The overall management plans are well designed, but not yet fully implemented. In fact the different drug discovery groups have highly diverse activities. The team made a real effort to integrate different groups working on Pharmacology, Parasitology and Immunology and an Avenir project in the future. The team is not yet fully integrated in the CPTP and dispersed over different geographical locations, but the integration is planned for 2010. Clearly, the team will benefit from the physical integration into CPTP and the gain in critical mass.

The implementation of a unifying macrophage research project of high quality and state of the art will aid to the integration with the drug discovery teams. The process of drug discovery to the development of active antimalarial is more refined streamlining, which may enhance the success. There is however a great promise for success.

- Appreciation on the project:

The proposed project on M2 macrophage differentiation and the effect of PPARgamma differentiation is an excellent effort to increase investigations on host defense mechanisms. The proposed study on macrophage specific mannose receptor and Dectin-1 inactivation is not sufficiently developed, the relevance especially the role of mannose receptor in host response to Candida infection is not convincing. This group has a good potential to allow the emergence of young scientist in the field. One next member of the team who just received an Avenir project, and will start begin of 2010 on Toxoplasma infection, is outstanding, and his arrival will have a major impact on the research of apicomplexa and the immune response to intestinal infection. But improving the structure of the team will be critical for the successful integration of the Avenir project. The drug discovery process, which is a typical pharmaceutical R&D program, is very promising, but not sufficiently structured and described.

A major problem is the fact that the group of the team leader in not yet on the campus. However with the physical integration, there is high chance that the team will adopt a more structured and integrate approach in the CPTP.

The presented projects are all state of the art and feasible for the expertise of the team. Nevertheless, it is necessary to limit the number of ‘mini-project’ and to strengthen the major projects. The scientific output of this group is in relation to the size of the group and includes many state of the art research papers published in scientific journals appropriate for the field and in top journals.

- Conclusions:

The committee felt that overall this team, in its present configuration, did not meet the standard of other components of the CPTP.

– Weaknesses and threats, Recommendations:

Better integration within the CPTP is recommended by the committee as well as a more careful prioritisation of the projects.

4.11. Title of the team: Molecular and cellular pathogenesis of E. Coli infections

Name of the team leader: Mr Eric OSWALD

- Staff members (on the basis of the application file submitted to the AERES):

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	5	7
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	2
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results:

The team aims to increase the understanding of bacterial interactions with the human host and the focus is on the different variants of Escherichia coli, a bacterium that both appears as the main facultative anaerobic/aerobic species in the normal intestinal microbiome and as pathogen either in the intestine or in extra-intestinal locations such as the urinary tract. Using a multidisciplinary approach, including e.g. methodology from microbiology, molecular biology, immunology and cell biology, the research efforts by the team have led to several discoveries regarding bacterial factors that cause effects on the host cell cycle events. They have highlighted how certain bacterial products, the cyclomodulins, may modulate the cell cycle at different stages and contributed in particular to original findings about the toxic factors CNF, CDT, Cif and Colibactin that all may be produced by variants of E. coli. The partnerships within the team seem highly relevant and aimed at high quality research. The team has shown very good publications output during the last four years and is continuously publishing their results in well reputed international research journals and also have contributed in top level general science journals. The work has also been presented at several international research symposia and congresses.

- 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 has a clear international profile and has established stable and very fruitful collaborations with a network of scientific partners in France and in different countries worldwide. Their research has attracted strong support through competitive funding including both individual grants for the projects and network grants for exchanges and collaborative efforts nationally and internationally. Results from the team have also provided the basis for inventions and international patent applications. The team leader has acted as chair person and organizer of scientific workshops at international congresses and symposia on several occasions. Furthermore, he has been serving on grant review panels and is regularly honored by editorial tasks, and other team members also act as reviewers, for several international scientific journals. The team has a proven ability to recruit scientists at different levels (e.g. visiting senior scientists, postdocs, PhD students) both from abroad and nationally.

- Appreciation on the strategy, governance and life of the research unit:

The composition of the team, its management, and the plan for future research seems to ensure that they will be a very strong and productive part of the research unit. The research of the team is hypothesis-driven and their link

to the diagnostic bacteriology laboratory of the medical teaching hospitals will enable the team to address the scientific questions with relevant clinical specimens in the best possible manner. And they will both be contributing to, and benefiting from, the other teams with complementary research disciplines of the unit as planned.

- Appreciation on the project:

The planned scientific project is both extremely timely with respect to newly emerging serious medical implications of E. coli infections currently when antibiotic resistance problems are acute and with respect to the newly acquired knowledge about the evolution of pathogenic variants through gene transfer and changes in expression of newly discovered virulence traits. The team has a very strong competence profile in this research area and, with hypothesis-driven research; their work is characterized by the aim to elucidate the molecular mechanisms involved in the bacteria-host interactions. It is expected to result in original, cutting edge, findings useful both for better understanding of, and for development of new means to prevent, the effects of these infections.

- Conclusion :

The committee felt this is an *excellent* team.

4.12. Title of the team: Molecular signalling in rare diseases of growth and osteogenesis

Name of the team leader: Mr Jean-Pierre SALLES

- Staff members (on the basis of the application file submitted to the AERES):

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	3	3
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	3
N7: Number of staff members with a HDR or a similar grade	5	4

- Appreciation on the results:

This group has been working on the biology of Prader-Willi syndrome (PWS), Noonan and LEOPARD syndromes and achondroplasia. One team member is coordinator of the PWS network in France and has a vast clinical expertise in this syndrome and access to clinical data and samples. This group studied the regulation of ghrelin secretion and its relation to hypothalamic function in PWS and the cellular sensitivity to growth hormones in fibroblasts from patients with PWS.

This team is also involved in research directed towards the growth plate. They investigated the importance of LPA-LPA1 interaction and of Gαi and adenylate signalling in the growth plate. They further investigated the effect of the specific achondroplasia *FGFR3* mutation on RAS-MAPK signalling in the growth plate and they are working on a preclinical treatment model for achondroplasia in the mice using soluble wild type FGFR3 injections.

A third research topic which is related to the previous topic concerns the cellular and biochemical effects on RAS-MAPK signalling resulting from mutations in *PTPN11* previously reported in Noonan and LEOPARD syndrome. They

discovered a specific activation of the PI3K pathway in fibroblasts of LEOPARD patients and suggest that this might be responsible for the higher frequency of hypertrophic cardiomyopathy in this syndrome as compared to its frequency in *PTPN11* associated Noonan syndrome.

The scientific output of this group is in relation to the size of the group and includes many state of the art research papers published in scientific journals appropriate for the field.

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

This team has many national and international collaborations and activities. They are coordinating the PWS clinical care and research in France and regarding the other research topics they are also at the top level in France. This group operates in the mainstream of the international research landscape. They are not the international opinion leaders in their field.

- Appreciation on the strategy, governance and life of the research unit:

The evaluation panel had the impression that this team was not yet fully imbedded in the CPTP and was dispersed over different locations and research themes. They would benefit from an increase in the critical mass of human genetics research in CPTP. Some of the research seems to be more related to metabolic disorders, a topic of the other campus in Toulouse.

The choice of topics was guided by opportunities (PWS research is only distantly related to the other topics but the National Coordination Centre for PWS is in Toulouse) and was less thematic.

The panel feels that the different research topics of this team in the past did not always integrate well. The expertise gained in some projects was often of insufficient benefit for their other projects. The panel expressed concerns that some of their research avenues were not pushed to their limit. This could be due to their thematic dispersion. This team performs good research but if they want to further improve the quality of their research output, the panel would advice to continue to further increase the focus, critical mass and to further reduce the projects to a smaller number of closely related projects as was suggested in the future project of this team. At the moment the research efforts are spread quite thin and this does not always allow an in depth analysis. A concentration of their efforts on fewer projects would allow them to be more inquisitive and competitive and thus to make a more significant dent into our knowledge of the corresponding disease processes. This could also be limiting in highly competitive fields such as their therapeutic trials.

- Appreciation on the project:

The new team will change in the future and focus more on specific aspects of PWS, Noonan syndrome and achondroplasia.

The team wants to investigate the effects of ghrelin on dopaminergic cells in culture and plans to use iPS cells derived from PWS fibroblasts. They will stimulate these cells to differentiate into dopamine producing cells. The potential effect of snoRNAs from the PWS minimal critical deletion region on dopaminergic cell biology will be studied. They will continue their research on growth hormone sensitivity in PWS using a number of cell types derived from PWS patients (lymphocytes, fibroblasts, adipocytes, adipose MSC, osteoblasts). They plan further preclinical studies in the mouse model of achondroplasia and Noonan syndrome using soluble FGFR3 as a decoy receptor. The future project also includes preclinical studies using siRNA to normalize growth plate biology in Noonan syndrome.

The presented projects were all state of the art and feasible for the expertise of the team. The projects benefit from the national PWS and Noonan syndrome networks.

- Conclusion :

The committee felt this is a very good team.

4.13. Title of the team: System genetics applied to iron metabolism and other complex traits

Name of the team leaders: Ms Marie-Paule ROTH and Ms Hélène COPPIN

- Staff members (on the basis of the application file submitted to the AERES:

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	3
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results:

Team 13 focuses most of their scientific efforts onto one integrated query, namely the regulation of iron content in the blood. Complex regulatory mechanisms are needed to maintain iron concentrations delicately tuned, as too much or too little can be pathogenic. It is also known that not all carriers of pathogenic mutations in the genes known to be involved in maintaining this balance are equally affected: in other words, incomplete penetrance is indicative of the presence of modifier loci.

Hence, two major questions are addressed by this team: the identification of modifier loci acting in hemochromatosis, and the mechanisms of hepcidin-mediated regulation of iron. The basic approach is genetic, though the team is also applying additional techniques as needed, including the state-of-the-art -omics technologies.

Their productive, high quality research has led them to uncover the specific role of BMP6, through its activation of the Smad signaling pathway, on regulation of iron content. Lack of BMP6 in mice results – via the reduction both in phosphorylation of Smad1/5/8 and in expression of hepcidin–, to stabilization of ferroportin, leading to massive iron overload. These results were recently published in a series of high tier scientific publications such as Blood and Nature Genetics.

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

These spectacular achievements have been internationally recognized as witnessed by the added News and Views coverage given by Nature Genetics. Additional indicators of this recognition are (1) the attribution in 2009 of the Marcel Simon Award for excellence by the International Bioron Society and (2) several invited lectures on this topic, since the publication of these results.

- Appreciation on the strategy, governance and life of the research unit:

This is a solid, coherent and well-integrated team, reflecting the high quality of its management. They synergize well with the CPTP and have a few collaborations with other teams of this Center. MP Roth is also involved in various management activities in the CPTP, where she is also Deputy-Director. Of note, the team will also recruit next year, a young scientist returning from his post-doc, with a solid expertise in the cellular biology aspects of iron regulation and a good publication records in this field.

- Appreciation on the project:

Just like for the description of their past activities, the presentation of their future plans was clear and based on sound logical premises. The experimental plan for the positional cloning of the modifier loci was convincing: F2 mapping in mice, supplemented by transcription profiling, construction of expression modules, eQTL mapping. These procedures are state-of-the-art, combining the power of linkage analyses with endo-phenotypes and molecular sub-phenotypes. This is the right way to go in order to increase the resolution power and likelihood to land onto the genes/polymorphisms involved in the studied trait. It falls short of becoming systems biology, though they could well venture into it, by applying various perturbations (eg mutations, siRNA, etc) and modeling. Any lead thus discovered will eventually be tested for its involvement in iron content regulation in humans.

In addition they also presented plans for the identification, using proteomics, of Hfe partners, as well as the hunting for suspected miRNAs involved in regulating iron availability.

As of next year, a new member will join this team. He will focus on specific lipid raft domains of macrophages. While the panel was impressed by his scientific plans and knowledge, it nevertheless recommended that more focus be paid on the merging of his interests with the existing skills and competences of this team, i.e. their powerful genetic approach.

- Conclusion :

The committee felt this is an *excellent* team.

– Strengths and opportunities, Recommendations:

An expert in statistical genetics who collaborates already on some aspects of this project as well as with projects led by other teams (e.g. team 5) was said to emerge, according to their plans, as an independent statistical genetics team in 2015. There are great needs in highly qualified statistical geneticists worldwide. It is thus recommended that these plans be accelerated if possible.

4.14. Team 14 - Title of the team: Genetics of refractive and developmental defects of the eye

Name of the team leaders: Mr Patrick CALVAS and Mr François MALECAZE

- Staff members (on the basis of the application file submitted to the AERES):

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	3
N7: Number of staff members with a HDR or a similar grade	2	

- Appreciation on the results:

The project of this team is devoted to decipher the genetics and the pathophysiology of vision threatening diseases. The project revolved around three main topics: the genetics of refractive disorders (keratoconus and high myopia), the corneal wound healing and the molecular embryology of congenital ocular malformations. For both refractive disorders a common approach is proposed, genome wide association studies (GWA) based on the analysis of a cohort of patients. In parallel a quantitative analysis of the transcriptome and a comparative analysis of the proteome has been undertaken to study keratoconus. Posterior capsule opacification (PCO) is the main common complication of cataract surgery. Using adenovirus-mediated gene transfer, the team reported that it was feasible to prevent PCO by overexpressing pro-apoptotic molecules capable of inducing therapeutic programmed cell death in vitro and in vivo in residual lens cells post-cataract surgery. The pitfalls of this approach, target of the gene transfer and vectorisation, have been properly raised by the team. The ongoing project on corneal wound healing aims at restoring the corneal transparency by injecting MMP14-expressing vector or by modulating the early inflammatory response. The third topic aims at deciphering the molecular basis of micro/anophtalmia, by identifying targets of some transcription factors involved in eye morphogenesis.

- 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 has a limited international recognition.

- Appreciation on the strategy, governance and life of the research unit:

Two Professors at the University and the Hospital (PU/PH), one geneticist and one ophthalmologist, head jointly the team, each of them at 25% of working time. The team is composed of 2 scientific staff (joining the team in 2011), 2 assistant professors (University or University/Hospital), 3 post-doc, 2 technical staff and 3 PhD students. Both professors have teaching responsibilities as well as strong clinical involvement, leaving them too little time for managing their scientific activities.

- Appreciation on the project:

  - Strengths and opportunities:

A good recruitment of patients suffering from high myopia and from keratoconus (Centre National de Référence pour le kératocône) as well as of patients with micro/anophtalmia in each case a nationwide or even ECwide collection of patients has been built up.

The topic of the research on the development of therapeutic strategies for the prevention of secondary cataract by gene transfer has an important clinical impact. Two patents have been obtained on this project which has also the best publication record and the team has an expertise in the field. The clinical links of the team should facilitate the transfer of potential therapeutic strategies for these disorders.

High levels of funding from Institution as well as industry partner are collected by the team leaders.

  - Weaknesses and threats:

Although the proposed work on the genetics of refractive disorders is of interest and could bring new and important data, the relevance of the proposed program is more of an open question.

The genome wide association studies proposed may not prove a suitable approach with the small cohorts of patients even with the multi-centric recruitment expected by the investigators given the underlying genetic heterogeneity. In addition the experimental plans of the proposed GWAS, subsequent haplotype analyses and targeted resequencing are also not convincing.

The project searching for target genes regulated by selected transcription factors in microphthalmia appears coherent, but preliminary the data are not convincing, the experimental feasibility appears uncertain, and the sample sizes used for the transcriptomic and proteomic analyses are largely underpowered. The outcome of the complicated research strategy on the gene identification in rare monogenetic cases of micro-/anophthalmia is highly uncertain and no alternative strategy is proposed in case the approach did not provide the expected findings.

A concern of the committee is the limited scientific productivity in terms of quality which is not entirely satisfactory in relation to the size of the research group, only 12 publications on the work described in the present proposal, 4 of them in relation to the project on micro/anophtalmia which is a collaborative project, other publications arise from clinical activities, and too few publication in journals with high impact factors.

Two permanent researchers (CR1 INSERM) planned to join the team in 2011, the first one with expertise in the field of cell proliferation to strengthen the corneal wound healing topic and the second with expertise in genetics will reinforce the group. However, their integration in the team was not clearly presented.

- Conclusion :

For the various reasons detailed above the committee scored this team as fair.

  - Recommendations:

Whereas the productivity appears globally satisfactory in quantity, the level of publication is medium/low and an effort should be made to increase their impact. More importantly we have noticed a certain lack of justification in the current projects. Although we agree that deciphering the genetics and the pathophysiology of vision threatening diseases is a relevant issue, the proposed program mainly involves the repetition of previous analyses and the alternative approaches (transcriptomics and proteomics) are poorly constructed. The feasibility of the corneal wound healing project appears better given preliminary results. However, a convincing demonstration of the originality and of the pertinence of the choices made has not been provided. On this basis, despite high level of funding, the committee was concerned about the limited competitiveness of this team's scientific program.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A+	A+

Nom de l'équipe : VIRAL INFECTIONS: PERSISTENCE, HOST RESPONSE AND PATHOPHYSIOLOGY

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	B	A

Nom de l'équipe : PATHOGENESIS OF VIRAL INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	Non noté	A+

Nom de l'équipe : T CELL DIFFERENTIATION AND AUTOIMMUNITY

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	B	B	A	A+

Nom de l'équipe : ESTROGENS AND CALCIUM CHANNELS IN THE PHYSIOPATHOLOGY OF ALLERGIC AND AUTOIMMUNE DISEASES

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A+

Nom de l'équipe : IMMUNITY, PREGNANCY AND THERAPEUTICS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Nom de l'équipe : INFLAMMATORY DISEASES OF THE CENTRAL NERVOUS SYSTEM: MECHANISMS AND THERAPY

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A+	A+

Nom de l'équipe : MOLECULAR AND CELLULAR PATHOGENESIS OF E. COLI INFECTIONS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A	A	A+	A+

Nom de l'équipe : SYSTEMS GENETICS APPLIED TO IRON METABOLISM AND OTHER COMPLEX TRAITS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A+	A+

Nom de l'équipe : MOLECULAR SIGNALLING IN RARE DISEASES OF GROWTH AND OSTEOGENESIS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	B	A

Nom de l'équipe : MONOCYTES/MACROPHAGES POLARIZATION, NUCLEAR RECEPTORS AND PARMACOLOGICAL APPROACHES IN CONTROL OF INFECTIONS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	B	B

Nom de l'équipe : MOLECULAR DYNAMICS OF LYMPHOCYTES INTERACTIONS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A+	A+

Nom de l'équipe : TOLERANCE AND AUTO-IMMUNITY

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A	A+	A+

Nom de l'équipe : MEDIATORS OF INFLAMMATION, INFECTION AND INFLAMMATORY PAIN

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A+	A	A

Nom de l'équipe : GÉNÉTIQUE TROUBLES RÉFRACTION ET DÉVELOPPEMENT DE L'ŒIL

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	A	B	B

Direction de la Recherche

Toulouse, le 11 mars 2010

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Le Président

au

Président du comité d'experts de l'AERES

Objet : Observations de portée générale sur le rapport d'évaluation
de l'unité **« Centre de Physiopathologie de Toulouse Purpan (CPTP)» - UMR 563 INSERM/UNIVERSITE Paul-Sabatier…**
portée par **…Roland LIBLAU**

Gilles FOURTANIER

Unité de Recherche UMR563
Centre de Physiopathologie
de Toulouse Purpan (CPTP)

Project 2011-14
Director: Roland Liblau
Deputy Directors:
Marie-Paule Roth
Nathalie Vergnolle

Reply to the AERES comments

1) Concerning the Committee's assessment of the Research Centre:

On behalf of the Centre's staff, I would like to thank the evaluation committee for their in-depth and overall very fair evaluation of our organization, scientific achievements and projects. We are indeed collectively proud that the Centre was deemed very productive, attractive, and very efficiently managed.

Twelve of the 14 teams are ranked as "excellent or very good". Nevertheless, two teams do not yet "meet the standards of the other components of the CPTP".

One of these teams results from the recent merge of 3 distinct groups, and has not yet as a whole physically relocated in the Centre, which was identified as a weakness. Since the visit of the committee, part of that team, specifically the ATIP-AVENIR laureate Nicolas Blanchard, has now integrated physically the Centre (as of March 2010). Moreover, space has been identified to welcome the other members of that team. Consequently, the whole team will be integrated fully as of January 1st, 2011 in the Centre. Each of the 3 groups from that team has a very good track record (please refer to the reply from team 10 below), and we believe that once unified, they will be even more successful. This team has made a major structuring effort to bring together the forces of immuno-parasitology, a quite neglected field in France. We believe that the team proposed here, with its 2 different components: clinical and basic pharmacology of parasitic infection, and basic research in host immune response to parasitic infection, gathers quite uniquely parasitology forces and has great potential.

The second team (team 14) is the French leading research team in diseases of the anterior segment of the eye and in the genetics of myopia. They publish in the most visible journals in the field and are involved in several national and international networks (please refer to the reply from team 14 below). They collaborate productively with other teams of the Centre (teams 6 & 7) and are key players in our effort to strengthen the human genetics component of the Centre.

The Committee has pinpointed 3 weaknesses and threats, and on this basis has made specific recommendations.

1- As we discussed extensively during the visit, the fact that our animal facility has insufficient space to cover our needs is a major concern to us. A real and 'definitive' solution (a brand new animal facility) is foreseen by mid-2012 thanks to the financial commitment of the University, the hospital and Inserm. In the meantime we are, hand in hand with the director of IFR150, organizing temporary solutions.

2- Our choice of having a strong component in Genetics in the Centre has been endorsed by the Committee. We will follow the suggestion of the Committee to 'brain-storm' in order to identify the best way to reorient the programs devoted to Genetics to achieve better competitiveness and

critical mass. Recent publications from the Centre indicate that good seeds are already in place (see publications by M-P. Roth in *Nature Genetics* 2009 and by G. Fournié and A. Saoudi in *Science Translational Medicine 2009)*. As pointed out by the Committee, the Centre has attracted in 2006 Dr. Maria Martinez, an internationally recognized expert in statistical genetics, and we will make all possible efforts to accelerate the emergence of an independent team around this expert. There are indeed great needs for highly qualified statistical geneticists worldwide, and we feel that this know-how present in the Centre will be attractive for young or more senior geneticists. Efforts will also be devoted to the recruitment of one or two leading scientists who could rapidly head independent genetic teams on topics of relevance for the Research Centre, such as genetics of immune response or genetics of host-pathogen interactions. A currently vacant University-Hospital Professor position in Genetics may be used for that purpose.

3- The way we have incorporated some young AVENIR laureates in the Centre was felt not totally adequate. The (ATIP-) AVENIR program has been set up to enable young scientists to develop independently their own scientific project within an existing structure. Ultimately, this program aims at promoting the creation of new independent teams. The head of the Centre is fully aware of this mission and the recent past speaks for us on that matter. Indeed, the previous AVENIR laureates from the CPTP have all succeeded in building their independent research and are now proposed as head of independent teams (teams 7 & 9). Since its creation, the Centre has tried to find the best way to allow gifted young scientists to blossom. We feel that our policy to allow them to interact closely with an established structured team working on a related topic has several advantages. First, it allows rapid installation of their group, benefiting from reagents, protocols, know-how and experience of a running team. Second, it prevents any risks of isolation, promoting exchanges with the existing teams. Finally, it shields the young scientists from excessive administrative burden, allowing them to focus specifically in building up their own group. In all cases, the association of the young AVENIR laureate and the welcoming team is made on mutual agreement and, above all, is based on obvious and strong scientific interactions. We are fully aware that the scientific and financial independence of the (ATIP-) AVENIR laureates has to be preserved and we take this opportunity to stress that we have committed to that and will continue to do so.

2) Concerning the Committee's assessment of the individual teams:

E1: Tolerance and Auto-Immunity (Prof. Joost van Meerwijk)

1-Update since submission
None

2- Reply to the AERES comments
None

E2: Molecular dynamics of lymphocyte Interactions (Dr Salvatore Valitutti)

1-Update since submission

PUBLICATIONS
Gaudenzio N, Espagnolle N, Mars LT, Liblau R, Valitutti S, Espinosa E. Cell-cell cooperation at the T helper cell/mast cell immunological synapse. Blood, 2009, 114:4979.

Trifari S, Scaramuzza S, Catucci M, Ponzoni M, Mollica L, Chiesa R, Cattaneo F, Lafouresse F, Calvez R, Vermi W, Medicina D, Castiello M-C, Marangoni F, Bosticardo M, Doglioni C, Caniglia M, Aiuti A, Villa A, Roncarolo M-G and Dupré L. Revertant T lymphocytes in a Wiskott-Aldrich syndrome patient: analysis of function and distribution in lymphoid organs. J Allergy Clin Immunol, 2010, 125:439.

Carreño L, Riquelme E.M., González PA, Espagnolle N., Riedel CA, Valitutti S. and Kalergis AM. T cell antagonism by short half-life pMHC ligands can be mediated by an efficient trapping of T cell polarization towards the APC. PNAS, 2010, 107:210

2- Reply to the AERES comments
None

E3: Estrogens and calcium channels in the physiopathology of allergic and autoimmune diseases (Dr Jean-Charles Guery and Dr Lucette Pelletier)

1-Update since submission

- Publication Prior to AERES visit:
Pelletier L, Guéry, JC . nov 2009, "Inhibitors and antagonists of calcium channels in the treatment of asthma ", European patent (EP09306160.4)

- Publication Post AERES visit:
Djata Cabral M, Paulet PE, Robert V, Gomes B, Renoud ML, Savignac M, Leclerc C, Moreau M, Lair D, Langelot M, Magnan A, Yssel H, Mariame B, Guery JC, Pelletier L. Knocking-down Ca_v1 calcium channels implicated in Th2-cell activation prevents experimental asthma. Am J Respir Crit Care Med. 2010 Feb 18. [Epub ahead of print] (press release by INSEREM and coverage in several daily and weekly French newspapers as well as local TV coverage)

2- Reply to the AERES comments
None

E4: T cell differentiation and autoimmunity (Sylvie Guerder)
Avenir Team: Nicolas Fazilleau

1-Update since submission

Publications:

Prior to AERES visit:
C. Viret, Lamare, C., M. Guiraud, B. Malissen, A . Carrier & S. Guerder. 2009. The protease TSSP contributes to the diversification of the functional CD4 T cell repertoire. (Submitted)

Post AERES visit:
C. Viret, Lamare, C., M. Guiraud, N. Fazilleau, A. Bour, B. Malissen, A . Carrier & S. Guerder. 2009. The protease TSSP contributes to the diversification of the functional CD4 T cell repertoire. (Under revision).

Henri S., L.F. Poulin, S. Tamoutounour, L. Ardouin, M. Guilliams, B. de Bovis, E. Devilard, C. Viret, H. Azukizawa, A. Kissenpfennig, & B. Malissen. CD207+ CD103+ dermal dendritic cells cross-present keratinocyte-derived antigens irrespective of the presence of Langerhans cells. J. Exp. Med. 2010 ; 207:189-206.

C. Laurent, N. Fazilleau & P. Brousset. 2010. A Novel subset of T-helper cells: Follicular T-helper cells and their markers. Haematologica. 95:356-358.

N. Pelletier, L. J. McHeyzer-Williams, K. A. Wong, E. Urich, N. Fazilleau & M. G. McHeyzer-Williams. 2010. Plasma cells negatively regulate the follicular helper T cell program. (Under revision).

J. Milner, N. Fazilleau, M. G. McHeyzer-Williams & W. E. Paul. 2010. Lack of High Affinity Competition for Peptide in Polyclonal CD4+ Responses Unmasks IL-4 Production. (Under revision).

New Grants:

To SG:

- 2010-2011: EFSD/Lilly European Diabetes Research Program. (100k€). Study of the function of the protease TSSP, a protease that controls diabetogenic CD4 T cell development and autoimmune diabetes in the NOD mouse.
- 2010-2012: FRM. Post-doctoral Fellowship to Nathalie Joncker.

To NF:

- 2010-2013: Marie Curie International Re-integration Grant (100k€). 'In vivo characterisation of Follicular Helper T cells'
- 2010-2011: ARC- Subvention fixe (50k€). 'Biology of Follicular Helper T Cells and Lymphomas'
- 2010-2011: La Ligue contre le Cancer Midi-Pyrénées (50k€). 'Follicular Helper T Cells and Cutaneous Lymphomas'
- 2010: FRM "Aide à l'implantation d'une nouvelle équipe" (68k€)

Diploma:

Feb. 2010: Nicolas Fazilleau. Habilitation à Diriger des Recherches, Université Paul Sabatier Toulouse III (France).

2- Reply to the AERES comments

The team leader has shown her ability to manage small yet productive team in the past. Hence for the period of 2001-2004, the team of 4 people (2PhD students, 1 ITA and the team leader) published 6 articles as senior authors in highly recognized journals (1 J. Exp. Med., 3 J. Immunol., 1 Int. Immunol. and 1 Genesis). For the period under evaluation, the number of published articles was more limited with, beside several collaborative studies, 2 primary articles as senior authors (J.

Immunol and Cell Death Diff.) and 2 visible review articles (J. Immunol. and Trends Immunol.) despite the small size of the team (1 CR1, 1 post-doctorate, 1 technician and 1 CDD). Importantly the scientific production was delayed due to the recruitment of an entirely new team and, more importantly, to development of new projects. These developments are now productive since 2 important articles are presently under revision in the best journals of the specialty.
One of the major objective of the team leader since its establishment in the CPTP (end of 2005) was to build a team of optimal size. The team leader has a long-lasting interest in understanding the regulation of CD4 T cell responses and one of the team's project addresses the molecular events controlling Th1 cell differentiation. To implement and reinforce this research line the team leader has tried over the years to recruit new team members. Due to obvious scientific complementarities the team leader attracted a young investigator with strong expertise in the study of a new effector CD4 T cell population, TFH cells. This allowed the successful recruitment at a CR1 position of the young investigator, who was awarded, subsequently an Avenir Grant. The young investigator has now succeeded in raising substantial fundings to develop his ambitious project as well as the HDR that allows him to directly supervise PhD students. The scientific complementarities and strong interactions between the young investigator and team leader have already translated into a joint publication (under revision, see above) and should permit optimal development of young investigator's group.
The team leader also succeeded in attracting a new post-doctoral fellow with strong expertise in the field of NK cells and anti-tumoral CD4 T cell responses. This strategic recruitment should permit the revival and development, through consolidation of a small group headed by the new fellow, of a quiescent project aiming at understanding the role and regulation of CD4 T cells in anti-tumor responses.

In conclusion, the team leader has now established in the CPTP an optimal size team with talented junior scientists and strong complementary scientific projects. In addition, new productive and challenging projects are now well established in the laboratory.

E5: Inflammatory diseases of the nervous system: mechanisms and therapy (Roland Liblau and Abdelhadi Saoudi)

1-Update since submission

Update of the Publications since October 2009

M. Jagodic* , C. Colacios* , R. Nohra , A.S. Dejean , A.D. Beyeen , M. Khademi , A. Casemayou , L. Lamouroux , C. Duthoit , O. Papapietro , L. Sjöholm , I. Bernard , D. Lagrange , I. Dahlman , F. Lundmark , A.B. Oturai , H.B. Soendergaard , A. Kemppinen , J. Saarela , P.J. Tienari , H.F. Harbo , A. Spurkland , S.V. Ramagopalan, D.A. Sadovnick , G.C. Ebers, M. Seddighzadeh , L. Klareskog , L. Alfredsson , L. Padyukov , J. Hillert , M. Clanet , G. Edan , B. Fontaine , G.J. Fournié# , I.Kockum# , A. Saoudi# , T. Olsson#. A role for *VAV1* in experimental autoimmune encephalomyelitis and multiple sclerosis.
Science Translational Medicine. 2009. 1, 10ra21
*and # these authors contributed equally to the work
This article was highlighted by a press release by INSERM and covered in several daily and weekly French newspapers as well as by local TV).

Gaudenzio N, Espagnolle N, Mars LT, Liblau R, Valitutti S, Espinosa E. Cell-cell cooperation at the T helper cell/mast cell immunological synapse. ***Blood.*** 2009 Dec 3;114(24):4979-88.

Liblau R. Glatiramer acetate for the treatment of multiple sclerosis: evidence for a dual anti-inflammatory and neuroprotective role. ***J Neurol Sci***. 2009 Dec;287 Suppl 1:S17-23.

Hyun E, Ramachandran R, Cenac N, Houle S, Rousset P, Saxena A, Liblau RS, Hollenberg MD, Vergnolle N. Insulin modulates protease-activated receptor 2 signaling: implications for the innate immune response. ***J Immunol***. 2010 Mar 1;184(5):2702-9.

Chappert P, Leboeuf M, Rameau P, Lalfer M, Desbois S, Liblau RS, Danos O, Davoust JM, Gross DA. Antigen-specific Treg impair CD8(+) T-cell priming by blocking early T-cell expansion. ***Eur J Immunol.*** 2010 Feb;40(2):339-50.

Bernard I, Fournié GJ, Saoudi A. Genomics studies of immune-mediated diseases using the BN-LEW rat model. ***Methods Mol Biol.*** 2010;597:389-402.

Lagrange D, Fournié GJ. Generation of congenic and consomic rat strains. ***Methods Mol Biol.*** 2010;597:243-66.

Venken K, Hellings N, Liblau R, Stinissen P. Disturbed regulatory T cell homeostasis in multiple sclerosis. ***Trends Mol Med***. 2010 16(2):58-68.

S. Hunot and R. Liblau. Neuroimmunologie. in Priorité Cerveau. **O. Lyon-Caen, E. Hirsch Ed. Odile Jacob**. 2010. In press.

New grants since October 2009

Arthritis Curtin, 40 K€ The VAV1 signaling hub in immune homeostasis and diseases 2010 – 2012
Yakult, 90 K€ Probiotics and CNS inflammation in rats 2010 – 2011**.**

2- Reply to the AERES comments

None

E6: Immunity, Pregnancy and Therapeutics (Philippe Le Bouteiller)

1-Update since submission

- March 2010: Collaborative contract to be signed between P. Le Bouteiller's team and "Laboratoire Français du fractionnement et des Biotechnologies (LFB)" which took over the license dealing with CL1-R2 anti-CD160 antibody.

2- Reply to the AERES comments

The committee has expressed some concerns about the future maintenance of the international visibility in reproductive immunology. I would like to emphasize the true involvement in this field of both Nabila Jabrane-Ferrat, CR1 CNRS and Julie Tabiasco, CR2 Inserm (~50% of their time) as well as of Maryse Aguerre, IE Inserm (80%). This is assessed by 3 major publications in this field in which J. Tabiasco is 1st author (Placenta 2006, RBMOnline 2009) or last author (J. Immunol. 2008) and 10 reviews in which she is co-author. N. Jabrane-Ferrat is presently the supervisor of 1 post-doctoral fellow (Ysabel Casart, Professor of Human Reproduction, University of Caracas, on sabbatical leave) and 2 Master students (one of them, Johan Siewiera, is likely to start his PhD training in our team starting September 2010). The post-doctoral fellow and under graduate student are working full-time on the effector functions of uterine NK cells in response to pathogens. A manuscript dealing with theme with N. Jabrane-Ferrat as last author is in preparation.
We already followed the committee's encouragement to establish intra-CPTP collaborations including with the C. Davrinche (cytomegalovirus) and, more recently, A. Valentin (Plasmodium falciparum) teams. Our team is also strongly associated with one local obstetrician, Dr Alain Berrebi (PH, HDR) and one recently recruited biologist of Reproduction, Roger Léandri (MCU-PH) who was just granted by the Scientific Council of the Medical Toulouse University as a new teacher ("accueil de nouveaux enseignants") to perform research on "HLA-G and oocytes" as a predictive marker of embryo implantation potential.

E7: "Mediators of Inflammation, Infection and Inflammatory Pain" (Nathalie Vergnolle)

1-Update since submission

- Changes in team composition:
Another investigator: Dr. Claire Racaud, will join the team as of January 2011. She is a "Chargé de Recherche" CNRS who has worked on intracellular signaling pathways, and she will join the themes already defined and reviewed by the committee.

Publication Prior to AERES visit:
- Cenac, N., Altier, C., Motta, J.P., Galeano, S., Zamponi, G.W., Vergnolle, N. *Potentiation of TRPV4 signalling by histamine and serotonin: a central mechanism for visceral hypersensitivity.* **Gut** (In Press)

- Vergnolle, N., Cenac, N., Altier, C., Cellars, L., Chapman, K., Zamponi, G. W., Trevisani, M., Liedtke, W., Geppetti, P., Bunnett, N.W. *Transcient Receptor Potential Vanilloid 4 activation provokes Neurogenic Inflammation: A Mechanism of Tonicity-Induced Inflammation.* **Br. J. Pharmacol.** (In Press)

- Benard, A., Cavaillès, P., J. Boue, Chapey, E., Bayry, J., Blanpied, C., Meyer, N., Lamant, L., Kaveri, S.V., Brousset, P., Dietrich, G. *Mu-opioid receptor is induced by IL-13 within lymph nodes from patients with Sézary syndrome*. **J. Invest. Dermatol**. (In Press)

Publications Post AERES visit:
- Vergnolle, N., Cenac, N., Altier, C., Cellars, L., Chapman, K., Zamponi, G. W., Trevisani, M., Liedtke, W., Geppetti, P., Bunnett, N.W. *Transcient Receptor Potential Vanilloid 4 activation provokes Neurogenic Inflammation: A Mechanism of Tonicity-Induced Inflammation.* **Br. J. Pharmacol.** (In Press)

- Hyun, E., Ramachandran, R., Cenac, N., Houle, S., Saxena, A., Liblau, R.S., Hollenberg, M.D., Vergnolle, N. *Insulin modulates Protease-Activated Receptor-2 (PAR_2) signalling: implications for the innate immune response.* **J. Immunol.** (In Press)

- Hyun, E., Andrade-Gordon, P., Steinhoff, M., Beck, P., Vergnolle, N. *Contribution of bone marrow-derived cells to the pro-inflammatory effects of Protease-Activated Receptor-2 in colitis* **Inflamm. Res.** (In Press)

Patents Post AERES visit:

- **European patent**: "*Recombinant probiotics bacteria for the prevention and treatment of Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS)*"
Application number: EP10305045.6, submitted 14th January 2010
Inventors: Nathalie Vergnolle, Philippe Langella, Jean-Michel Sallenave

- Additional grants obtained since the written document was submitted:
After the visit of the committee:
- Pierre Fabre (private contract): 25 000 €

2- Reply to the AERES comments
None

E8: "Viral infections : persistence, host response and pathophysiology" (Christian Davrinche and Jacques Izopet)

1-Update since submission

Publications *(after the visit of the AERES committee)*

B. Rauwel, B. Mariamé, H. Martin, R. Nielsen, S. Allart, B. Pipy, S. Mandrup, MD. Devignes, D. Evain-Brion, T. Fournier, C. Davrinche. Activation of the nuclear receptor PPARγ by human Cytomegalovirus (HCMV) for de novo replication impairs migration and invasiveness of cytotrophoblast from early placenta. **J. Virol** 2010 ; 84: 2946-54.

M. Mavigner, P. Delobel, M. Cazabat, M. Dubois, FE. L'Faqihi, S. Raymond, C. Pasquier, B. Marchou, P. Massip, J. Izopet. HIV-1 residual viremia correlated with persistent T-cell activation in poor immunological responders to combination antiretroviral therapy. **PLoS ONE** 2009 ; 4 : e7658.

P. Delobel, S. Raymond, M. Mavigner, M. Cazabat, B. Marchou, P. Massip, J. Izopet. Shift in phenotypic susceptibility suggests a competition mechanism in a case of acquired resistance to maraviroc. **AIDS** (sous presse).

S. Raymond, P. Delobel, M. Mavigner, L. Ferradini, M. Cazabat, C. Souyris, K. Sandres-Sauné, C. Pasquier, B. Marchou, P. Massip, J. Izopet. Prediction of human immunodeficiency virus type 1 subtype C trospism by genotypic algorithms built from subtype B viruses. **J AIDS** (sous presse).

N. Kamar, L. Rostaing, F. Abravanel, C. Garrouste, L. Esposito, I. Cardeau-Desangles, JM. Mansuy, J. Selves, JM. Peron, P. Otal, F. Muscari, J. Izopet. Pegylated alpha-interferon for treating chronic hepatitis E virus infection after liver transplantation. **Clinical Infectious Diseases** 2010 ; 50 : e30-3.

N. Kamar, F. Abravanel, J. Selves, C. Garrouste, L. Esposito, L. Lavayssière, O. Cointault, D. Ribes, I. Cardeau, MB. Nogier, JM. Mansuy, F. Muscari, JM. Peron, J. Izopet, L. Rostaing. Influence of immunosuppressive therapy on the natural history of genotype 3 hepatitis-E virus infection after organ transplantation. **Transplantation** (sous presse).

F. Legrand-Abravanel, N. Kamar, K. Sandres-Saune, C. Garrouste, M. Dubois, JM. Mansuy, F. Muscari, F. Sallusto, L. Rostaing, J. Izopet. Characteristics of autochthonous hepatitis E virus infection in French solid-organ transplant recipients. **Journal of Infectious Diseases** (sous presse).

N. Kamar, J. Izopet, P. Cintas, C. Garrouste, E. Uro-Coste, O. Cointault, L. Rostaing. Hepatitis E virus-induced neurological symptoms in a kidney-transplant patient with chronic hepatitis. **American Journal of Transplantation** (sous presse).

L. Alric, N. Kamar, D. Bonnet, M. Danjoux, F. Abravanel, V. Lauwers-Cances, L. Rostaing. Comparison of liver stiffness, fibrotest and liver biopsy for assessment of liver fibrosis in kidney-transplant patients with chronic viral hepatitis. **Transplant International** (sous presse).

***Grants** (after the visit of the AERES committee)*

- Recherche clinique translationnelle INSERM/DHOS (Responsables :B. Wacogne, A. Coaquette, 150000€) : équipe participante au projet «Application d'un microsystème de détection optique de matériel viral par technique d'immunofluorescence pour rendre possible le dépistage du cytomégalovirus à la naissance au berceau du nouveau-né: étude de validation en situation clinique »
- Bonus qualité recherche Université P. Sabatier, (S. Chavannas, 13000€) : «Infection des cellules souches neurales par le cytomégalovirus humain : physiopathologie moléculaire et cellulaire et criblage automatisé d'actifs »

2- Reply to the AERES comments

We appreciate the committee's comments on the quality of our past work and future projects.
We understand that criticisms come from the appreciation on the strategy, governance and life of the team. The team raised in 2007 from the shared will of Jacques Izopet and Christian Davrinche to strengthen forces in fundamental and clinical virology in Toulouse including expertise in HCMV and EBV (INSERM team in CPTP) on the one hand and in HIV, HCV and HEV infections (University team) on the other hand. During the last three years we benefited from our weekly scientific meetings, and new projects with clinicians were initiated thanks to the fact that they are members of the team (for instance monitoring of anti-HCMV T cell responses in transplanted patients). We decided to focus our projects on HCMV, HIV and HEV as reported in the present application to strengthen our visibility and to improve our efficacy.
We acknowledge and are aware that connections between the two groups were not enough highlighted in the work plan and this is due to the fact that during the last year we had the opportunity to welcome new scientists but the challenge in this short period of time to propose new

projects with respect to their own expertise. We started to establish connections between Stéphane Chavanas, a young scientist interested in epigenetics of neural stem cells infections and people interested in HCMV and HEV, between Eric Champagne an expert in $\gamma\delta$ T cell responses and people interested in T cell response against HCMV and HEV with special care on the role of these cells in transplanted patients with members of the team who have in charge the kidney transplantation unit in Rangueil hospital, and between Elmostapha Bahraoui who is working for a long time on HIV infection and those already involved in this field.
We are convinced that the present format of the team will allow us to catch opportunities to develop new initiatives and we expect to benefit from this period of time to identify the more promising projects in order to be in an optimal position to apply with new flowcharts.

E9: Pathogenesis of viral infections of the central nervous system (Daniel Gonzalez Dunia)

1-Update since submission

Publication Post AERES visit:

Schmid S., Metz, P. Prat C.M.A., Gonzalez-Dunia D. and Schwemmle M. Protein kinase C dependent phosphorylation of Borna disease virus P protein is required for efficient viral spread. *Arch. Virol.* In press, **2010.**

2- Reply to the AERES comments

None

E10: Monocytes/macrophages polarization, nuclear receptors and pharmacological approaches in control of infections (Alexis Valentin)

1-Update since submission

Publications Post AERES visit:

In collaboration with members of the CPTP Centre

- Legrand-Abravanel F, Colson P, Leguillou-Guillemette H, Alric L, Ravaux I, Lunel-Fabiani F, Bouviers-Alias M, Trimoulet P, Chaix ML, Hézode C, Foucher J, Fontaine H, Roque-Afonso AM, Gassin M, Schvoerer E, Gaudy C, Roche B, Doffoël M, D'Alteroche L, Vallet S, Baazia Y, Pozzetto B, Thibault V, Nousbaum JB, Roulot D, Coppere H, Poinard T, Payan C, Izopet J. Influence of the HCV subtype on the virological response to pegylated interferon and ribavirin therapy. 2009. *J Med Virol*; 81:2029-35

- Mavigner M, Delobel P, Cazabat M, Dubois M, L'faqihi-Olive FE, Raymond S, Pasquier C, Marchou B, Massip P, Izopet J. HIV-1 residual viremia correlates with persistent T-cell activation in poor immunological responders to combination antiretroviral therapy. 2009. *PLoS One* .4:e7658.

- Bouldouyre MA, Charreau I, Marchou B, Tangre P, Katlama C, Morlat P, Meiffredy V, Vittecoq D, Bierling P, Aboulker JP, Molina JM; ANRS 106 Study Group. Incidence and risk factors of thrombocytopenia in patients receiving intermittent antiretroviral therapy: a substudy of the ANRS 106-window trial. 2009. *J Acquir Immune Defic Syndr*. 52:531-7.

- Martin-Blondel G, Cuzin L, Delobel P, Cuvinciuc V, Dumas H, Alvarez M, Massip P, Marchou B. Is maraviroc beneficial in paradoxical progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome management? 2009. *AIDS*. 23:2545-6.

- Raymond S, Delobel P, Mavigner M, Cazabat M, Souyris C, Encinas S, Bruel P, Sandres-Sauné K, Marchou B, Massip P, Izopet J. Development and performance of a new recombinant virus phenotypic entry assay to determine HIV-1 coreceptor usage. 2010. *J Clin Virol*. 47:126-130.

From the members of team 10

- Chevalley S, Coste A, Lopez A, Pipy B, Valentin A. Methodology: Flow cytometry for the evaluation of antiplasmodial activity of drugs on Plasmodium falciparum gametocytes. 2010. *Malaria Journal*, 9:49.

- Nepveu F, Kim S, Boyer J, Chatriant O, Ibrahim H, Reybier K, Monje MC, Chevalley S, Perio P, Lajoie BH, Bouajila J, Deharo E, Sauvain M, Tahar R, Basco L, Pantaleo A, Turini F, Arese P, Valentin A, Thompson E, Vivas L, Petit S, Nallet JP Synthesis and Antiplasmodial Activity of New Indolone *N*-Oxide Derivatives. *J. Med. Chem.* 2010. **53**:699-714

- Galès A, Conduché A, Bernad J, Lefevre L, Olagnier D, Béraud M, Martin-Blondel G, Linas MD, Auwerx J, Coste A*, Pipy B*. *Co senior authors. PPARgamma controls dectin-1 expression required for host antifungal defense against Candida albicans. 2010. *PLoS Pathog*. Jan;6(1)

- Raymond S, Delobel P, Mavigner M, Ferradini L, Cazabat M, Souyris C, Sandres-Sauné K, Pasquier C, Marchou B, Massip P, Izopet J. Prediction of HIV type 1 subtype C tropism by genotypic algorithms built from subtype B viruses. 2010. *J Acquir Immune Defic Syndr*. 53:167-75.

- Witkowski B, Lelièvre J, López Barragán MJ, Laurent V, Su XZ, Berry A, Benoit-Vical F.
Increased tolerance to artemisinin in Plasmodium falciparum is mediated by a quiescence mechanism. 2010. *Antimicrob Agents Chemother.* Feb 16. [Epub ahead of print]

Grants since submission

- Integration, as co-investigator of A. Berry and B. Marchou in a National PHRC (clinical research project) intitled "MALA-RIA : essai multicentrique d'efficacité et de tolérance du traitement de l'accès palustre simple d'importation par Riamet® versus Malarone ®" headed by S. Houzé (Hopital Bichat - Cl Bernard) et O. Bouchaud (Avicenne).

- N. Blanchard : Marie Curie International Reintegration Grant

2- Reply to the AERES comments

We agree with the content of the report which clearly highlights some of our essential strengths. For example, team 10 was seen as “very attractive for young scientists" and the committee wrote that "the scientific output … includes many state of the art research papers published in scientific journals appropriate for the field and in top journals".

We acknowledge the 2 weaknesses noted by the committee and agree with their recommendations for improvement. Our major weakness is linked to our present configuration. Team 10 is to be created from 3 existing groups plus an ATIP-AVENIR group for the next period (2011-2014). Our willingness to work together as a single team within the Centre is based on solid and relevant scientific grounds and is fully supported by the Centre direction. Our integration within the Centre (planned for January 2011) will i) facilitate the further development of collaborative projects which are already initiated with other teams of the Centre (e.g. J. Van Meerwijk or P. Le Bouteiller); ii) strengthen our management as early as 2011 beginning by working in the same place and exchanging with the Centre members.

The second recommendation is to better prioritize the projects. We agree that it is an important objective towards which we have already worked. We are progressively integrating and reducing the number of our research topics through common applications to grants (one ANR "blanche" application and one ANR-MI2 application since the visit by the committee) and refocusing certain projects by reinforcing our strength on the role of nuclear receptors on the M2 polarization of the macrophages and on their anti-infectious efficiency (one MCF to be recruited in 2010 in the team). The global aim of our team is to address the two complementary arms of the fight against pathogens: the host (macrophage polarisation and nuclear receptors, inflammation, antigen processing) and the pathogen (pharmacological approaches and drug discovery). We have signed and co-signed, as pointed out by the committee some high level papers on these subjects (for example see: Benoit-Vical F. *et al.* 2007. *Antimicrob. Agents Chemother.* 51: 1463-1472 ; Coste A. *et al.* 2008. *J. Immunol.* 180:4939-47 ; Blanchard, N et al. 2008. *Nature Immunology* 9:937-944 ; Cachet N *et al.* 2009. *Antimicrob Agents Chemother*. 53:4303-4398. Witkowski B. *et al.* 2009. *Drug Resistance update.* 12:42-50), and more recently a paper in *PLoS Pathogens*, a leader journal in infectious diseases (Galès A et al. 2010. *PLoS Pathog*. 6:1).

We are confident that, in the rich scientific environment of the Center, our newly created team 10 in association with the ATIP-AVENIR team leaded by N. Blanchard will reach an even higher level of scientific output and we hope to meet the standard of the best components of the Center in less than 4 years.

E11: Molecular and cellular pathogenesis of E. coli infections (Eric Oswald)

1-Update since submission

None

2- Reply to the AERES comments

None

E12: Molecular signalling in rare diseases of growth and osteogenesis (JP Salles)

1-Update since submission

Publications Post AERES visit:

Alvarez F, Kottler ML, Paul C, Gennero I, Salles JP, Mazereeuw-Hautier J. Albright hereditary osteodystrophy: report of a particular clinical phenotype caused by a novel GNAS mutation. ***J Eur Acad Dermatol Venereol.*** 2009 Dec 15.

Eva Feigerlová, Gwenaëlle Diene, Isabelle Oliver, Isabelle Gennero, Jean-Pierre Salles, Catherine Arnaud, Maïthé Tauber. Elevated IGF-1 values in children with PWS compared with GHD children during two years of GH treatment. ***J Clin Endocrinol Metab***

Thomas Edouard, Jean-Philippe Combier, Audrey Nédélec, Sophie Bel-Vialar, Mélanie Métrich, Françoise Conte-Auriol, Stanislas Lyonnet, Béatrice Parfait, Maithé Tauber, Jean-Pierre Salles, Armelle Yart, Patrick Raynal. Functional effects of PTPN11 (Shp2) mutations causing LEOPARD syndromeon EGF-induced PI3K/Akt/GSK-3β signalling. ***Mol Biol Cell***

2- Reply to the AERES comments

The members of the team have carefully read the comments of the AERES committee and will take them into account for the future.

E13: Genetics and functional genomics of complex traits (Marie-Paule Roth and H. Coppin)

1-Update since submission

Publication Prior to AERES visit:

Kautz L, Meynard D, Besson-Fournier C, Darnaud V, Al Saati T, Coppin H, Roth MP. BMP/Smad signaling is not enhanced in Hfe-deficient mice despite increased Bmp6 expression. Blood 2009, 114: 2515-2520.

Publications Post AERES visit:

Auriac A, Willemetz A, Canonne-Hergaux F. Lipid rafts-dependent endocytosis: a new route for hepcidin-mediated regulation of ferroportin in macrophages. Haematologica (accepted 22/02/2010)

Camberlein E, Abgueguen E, Fatih N, Canonne-Hergaux F, Leroyer P, Turlin B, Ropert M, Brissot P, Loréal O. Hepcidin induction limits mobilisation of splenic iron in a mouse model of secondary iron overload. Biochim Biophys Acta 2010, 1802:339-346.

Min-Oo G, Willemetz A, Tam M, Canonne-Hergaux F, Stevenson MM, Gros P. Mapping of Char10, a novel malaria susceptibility locus on mouse chromosome 9. Genes Immun 2010, 11:113-23.

Ramey G, Deschemin JC, Durel B, Canonne-Hergaux F, Nicolas G, Vaulont S. Hepcidin targets ferroportin for degradation in hepatocytes. Haematologica 2010, 95:501-504.

Aguilar-Martinez P, Bismuth M, Blanc F, Blanc P, Cunat S, Dereure O, Dujols P, Giansily-Blaizot M, Jorgensen C, Konate A, Larrey D, Le Quellec A, Mura T, Raingeard I, Ramos J, Renard E, Rousseau F, Schved JF, Picot MC. The Southern French registry of genetic hemochromatosis: a tool for determination of clinical prevalence of the disorder and genotype penetrance. Haematologica, in press.

Aguilar-Martinez P, Giansily-Blaizot M, Bismuth M, Cunat S, Igual H, Schved JF. HAMP promoter mutation nc.-153C>T in non p.C282Y homozygous patients with iron overload. Haematologica, in press.

Saint Pierre A, Vitezica Z, Martinez M. A comparative study of three methods for detecting association of quantitative traits in samples of related subjects. BMC Proc 2009, 3 Suppl 7:S122.

2- Reply to the AERES comments

None

E14: Genetics of refractive disorders and developmental defects of the eye (Patrick Calvas and François Malecaze)

1-Update since submission

Publications

Chaabouni, M., Etchevers, H., De Blois, M. C., Calvas, P., Waill-Perrier, M. C., Vekemans, M., and Romana, S. P. Identification of the IRX B genes cluster as candidate genes in severe dysgenesis of the ocular anterior segment. Invest Ophthalmol Vis Sci 2010 Feb. 17 (Epub ahead of print)

Costrop, L. M., Vanakker, O. O., Van Laer, L., Le Saux, O., Martin, L., Chassaing, N., Guerra, D., Ronchetti, I. P., Coucke, P. J., and De Paepe, A. Novel deletions causing pseudoxanthoma elasticum underscore the genomic instability of the ABCC6 region. J Hum Genet 2010 55, 112-117

Khau Van Kien, P., Baux, D., Pallares-Ruiz, N., Baudoin, C., Plancke, A., Chassaing, N., Collignon, P., Drouin-Garraud, V., Hovnanian, A., Martin-Coignard, D., Collod-Beroud, G., Beroud, C., Roux, A. F., and Claustres, M. Missense mutations of conserved glycine residues in fibrillin-1 highlight a potential subtype of cb-EGF-like domains. Hum Mutat 2010 31, E1021-1042

Le Boulanger, G., Labreze, C., Croue, A., Schurgers, L. J., Chassaing, N., Wittkampf, T., Rutsch, F., and Martin, L. An unusual severe vascular case of pseudoxanthoma elasticum presenting as generalized arterial calcification of infancy. Am J Med Genet A 2010 152A, 118-123

Meng, W., Butterworth, J., Malecaze, F., and Calvas, P. Axial length: an underestimated endophenotype of myopia. Med Hypotheses 2010 74, 252-253

Simon, D., Laloo, B., Barillot, M., Barnetche, T., Blanchard, C., Rooryck, C., Marche, M., Burgelin, I., Coupry, I., Chassaing, N., Gilbert-Dussardier, B., Lacombe, D., Grosset, C., and Arveiler, B. A mutation in the 3'UTR of the HDAC6 gene abolishing the post-transcriptional regulation mediated by hsa-miR-433 is linked to a new form of dominant X-linked chondrodysplasia. Hum Mol Genet, 2010 Feb 24 (Epub ahed of print)

Spataro, G., Malecaze, F., Turrin, C. O., Soler V., Duhayon, C., Elena, P. P., Majoral, J. P., and Caminade, A. M. Designing dendrimers for ocular drug delivery. Eur J Med Chem 2010 45, 326-334

Naouri M, Boisseau C, Bonicel P, Daudon P, Bonneau D, Chassaing N, Martin L. Manifestations of pseudoxanthoma elasticum in childhood. Br J Dermatol. 2009 Sep;161(3):635-9.

Fournié P, Gordon G, Dawson D, Malecaze F, Edelhauser H, Fini ME. Correlation between Epithelial Ingrowth and Basement Membrane Remodeling in Human Corneas after Laser-Assisted in Situ Keratomileusis, Arch Ophtalmology, In press.

David, Chassaing N, Raynaud M, Jonard L, Feldmann D, Loudon N, Denoyelle F, Toutain A. Marlin S, Moizard M-P,. Phenotype and genotype in females with POU3F4 mutations. Clin Genet, In press.

Chassaing N, Cluzeau C, Bal E, Guigue P, Vincent M-C, Viot G, Ginisty D, Munnich A, Smahi A, Calvas P; Mutations in EDARADD account for a small proportion of hypohidrotic ectodermal dysplasia; Br J Dermatol, In Press.

Clauss F, Chassaing N, Smahi A, Vincent M-C, Calvas P, Moll M, Lesot H, Alembik Y, Hadj-Rabiah S, Bodemerh C, Manière M-C, Schmittbuhl M, C X-linked and autosomal recessive Hypohidrotic Ectodermal Dysplasia: genotypic- dental phenotypic findings from a retrospective study of 26 families, Clin Genet. In Press.

Patent

The patent “Novel nucleic acid molecules and their therapeutic use in ophthalmology” Inventors : Malecaze F, Couderc B was accepted December 3 2009 by the European Patent Commission

Publications of members joining the Team as of January 2011

Pendaries V, Gasc G, Titeux M, Leroux C, Vitezica ZG, Mejía JE, Décha A., Loiseau P, Bodemer C, Prost-Squarcioni C, Hovnanian A Immune reactivity to type VII collagen: implications for gene therapy of recessive dystrophic epidermolysis bullosa -Squarcioni. GeneTherapy, In press.

Titeux M, Mendonça V, Décha A, Moreira E, Magina S, Maia A, Lacaze-Buzy L, Mejía JE, Torrão L, Carvalho F, Eça-Guimarães J, Hovnanian A. Keratitis-ichthyosis-deafness syndrome caused by GJB2 maternal mosaicism. J Invest Dermatol 2009 129: 776-779

Miura N, Sato R, Tsukamoto T, Shimizu M, Kabashima H, Takeda M, Takahashi S, Harada T, West JE, Drabkin H, Mejia JE, Shiota G, Murawaki Y, Virmani A, Gazdar AF, Oshimura M, Hasegawa J. A noncoding RNA gene on chromosome 10p15.3 may function upstream of hTERT. BMC Mol Biol 2009 10:5.

Allouche M, ALK (anaplastic lymphoma kinase) Atlas Genet Cytogenet Oncol Haematol In Press.

2- Reply to the AERES comments

Appreciation on the impact, the attractiveness of the research unit and of the quality of its link with international, national and local partners.

We feel that the lack of a specialist in the field of ophthalmology and ophthalmic genetics led to an under-evaluation of our international recognition level. Our group is the only French team involved in an European network on myopia

We participate in a world consortium on myopia genetics. This network is currently headed by Prof. T Young in Duke University (Durham,NC, USA) and this active collaboration has led to the recent publication of 2 articles in *Investigative Ophthalmology and Visual Sciences* the top journal in the field of eye research.

For our work on research on “keratoconus”, F. Malecaze has received two prestigious awards in 2006 from the “Institut de France” and the major European Society for eye diseases”(ESCRS).

We are reviewers for the major journals in the field of Ophthalmology and Ophthalmic genetics (*Invest Ophtahlmol Vis Sci ; Ophthalmology, Exp Eye Res, Br J Ophtahlmol*…) and in human genetics (*Hum Mutat, Eur J Hum Genet, Eur J Med Genet, Clin Genet*…).

As was mentioned in our written report, we have delivered **ten invited** conferences in our research field of interest during the last 4 years and we have also organized two international meetings on keratoconus and myopia.

We are co-organizers of the forthcoming world conference in myopia which will be held in Tübingen (Germany) in July 2010 (http://www.imc-2010.org/)

We currently have grants from Europe (MyEuropia network) and ANR.

Appreciation on the strategy, governance and the life of the research unit :
Many INSERM Research teams are headed by one University/Hospital professor (PU-PH), whereas our team is directed by two professors, each one competent in one field i.e. Ophthalmology and Genetics respectively, allowing us to be complementary. Our clinical and teaching activities are the bases on which we built our research.

Appreciation on the project :
Strength and opportunities

We are disappointed that the fact that we have two new full-time permanent researchers (CR1 INSERM and CR1 CNRS) joining the team was not seen as a Strength despite their individual productivity (see above). Moreover no opportunity was given to these researchers to present their role in the future team as the committee denied them any speaking time or slide presentation, as we had proposed. Consequently it seems unfair to state that "their integration in the team was not clearly presented".

Weakness and threats
Genome Wide Association Studies are proposed to overcome the limits we reached with previously conducted linkage analyses. They have been conceived with proper consideration to statistical significance bearing in mind that a compromise has to be found between a large number of subjects (that we are able to collect) and a cost-effective study. We thus decided to design multi-step studies during which each step will allow us to review the ongoing strategy (for example affording the possibility to switch to QTL analysis) for high myopia.
As keratoconus is a rare disorder, the number of available patients is necessarily limited. Nevertheless the patient cohort we have gathered is, as far as we know, the most important ever studied. It is because of this limitation that we have proposed to also perform transcriptomic and proteomic analyses.
The search for micro-anophthalmias genes has been designed to circumvent the lack of families presenting such major defects. Our chromatin immunoprecipitation (Chip) approaches have been highly approved by previous scientific evaluators (i.e. INSERM). We constituted a human embryo collection allowing a repeated access to embryonic eyes, allowing the repetition of Chip experiments. Moreover we presented alternative strategies consisting in the use of embryonic cell lines engaged in ocular differentiation, expressing the targeted transcription factors, whose transcriptome will be modified by over-expression (transfection) or knock-down (siRNA) of the major transcription factors involved in early eye development. In addition we have previously demonstrated our ability to use classical linkage analysis or homozygosity mapping techniques to localize genes. Such techniques will implicitly be used if a family (or families) can be collected. This project is obviously led by our team, while the collaborative part of the work is devoted to the enrollment of patients.
We agree that a large amount of our publication record derives from clinical work. This clinical involvement however, has been essential for constructing the research team, and is at the heart of all modern-day translational research. We point out that original publications resulting from the team's activity have been published in journals devoted to ophthalmological research (Invest Ophth Vis Sci, Exp Eye Res, Mol Vis) or human genetics (Hum Mutat, Gene Ther, J. Med Genet, Am J Med Genet) that are considered among the best in the field. Furthermore, the submission of a second patent application has necessarily delayed the publication of relevant papers, one of which has just been submitted.

Conclusion : Recommendations
We do not agree with the idea that our proposal "mainly involves the repetition of previous analyses". To date, no large European cohorts have been constituted to study refractive disorders genetics and we began the first familial study in Europe. After we submitted a grant application on the design of a GWA study in French population, a similar analysis has been recently published in a Japanese cohort of patients with high myopia (Nakanishi at al. PloS genetics 2009;5:e1000660). This highly similar design with the experiment we conceived validated the strategy we developed to build the experiment.

Concerning the alternative approaches (transcriptomics and proteomics) , we would like to say that these two techniques were only very briefly presented during the oral presentation. A poster was specifically dedicated to these techniques but unfortunately the board had no time to look at and to discuss this poster. They therefore had only a very limited view of the methodology. The transcriptomic study has been performed on a cohort large enough (20 human corneas despite the difficulty of collection in this rare disease) to get statistically significant and biologically relevant data. As was presented in the poster, we have already identified several differences between keratoconus and control transcriptomes. These candidate mRNAs have now been validated by real time PCR on another sample cohort and a paper is actually being submitted.
The Board's questioning of the originality and pertinence of the wound healing study appears rather surprising since the results we presented during the oral presentation constitute a "proof of concept" and support the rationale of targeting molecules involved in collagen metabolism.

In conclusion
As previously stated, the arrival of two new full-time researchers in our group will undoubtedly reinforce our competitiveness.
We would like to emphasize, once again, that the absence of a specialist in the field of ophthalmology deprives the review board of expert advice on the context and challenges of our field of study. Moreover, it is our considered opinion that this lack of appropriate familiarity led the board to greatly undervalue the international standing of our research group.