Des maladies rénales rares aux maladies fréquentes, remodelage et réparation

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Remodelling and repair of renal tissue

Under the supervision of the following institutions and research bodies:

Institut National de la Santé Et de la Recherche Médicale

Université Paris 6 - Pierre et Marie Curie

December 2012

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

Research Units Department

President of AERES

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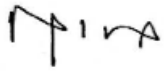
Department Head



Pierre Glaudes

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

Grading

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

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

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

- Grading table of the unit: Remodelling and repair of renal tissue

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

- Grading table of the team: Molecular bases of rare and inherited kidney diseases: From insult to repair

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

- Grading table of the team: Novel biomarkers and molecular targets to evaluate and treat chronic kidney diseases

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

Grading table of the team: Mouse models of renal cancer

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

Evaluation report

Unit name:	Remodelling and repair of renal tissue
Unit acronym:	
Label requested:	UMR_S
Present no.:	UMR_S702
Name of Director (2012-2013):	Mr Pierre RONCO
Name of Project Leader (2014-2018):	Mr Pierre RONCO

Expert committee members

Chair:	Mr Jan J. WEENING, University of Amsterdam, The Netherlands
Experts:	Mr Christian COMBE, University Bordeaux Segalen (CNU representative)
	Mr Mohamed DAHA, University of Leiden, The Netherlands
	Mr Kai-Uwe ECKARDT, University of Erlangen, Germany
	Mr Dominique ELADARI, University Paris Diderot (INSERM representative)
	Mr Dontscho KERJASCHKI, University of Vienna, Austria

Scientific delegate representing the AERES:

Mr Bernard DASTUGUE

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

Ms Chantal LASSERRE, INSERM

Mr Vincent MOULY, UPMC

1 • Introduction

History and geographical location of the unit

This unit has been created as a translational research unit from bench to bedside in the field of kidney research at Tenon hospital by Mr. G. RICHET in the 1960's. The unit is the only research laboratory in Hospital Tenon in the North East of Paris, in a new building built in 2007.

Management team

Three teams compose the Unit:

Team-1 under the guidance of the director of the unit has focused on rare and inherited diseases of the kidney and the role of metalloproteases.

Team-2 has devoted considerable efforts to identify new players of kidney disease progression and repair which could be used as "druggable" targets.

Team-3 joined the unit in 2010 and has developed unique genetically engineered mice for studies on kidney cancer and the molecular mechanisms of fibrosis through collaborative projects.

AERES nomenclature

SVE1_LS4

Unit workforce

Unit workforce	**Number as at 30/06/2012**	**Number as at 01/01/2014**	2014-2018 **Number of project producers**
N1: Permanent professors and similar positions	10[3.75]	10[3.75]	10
N2: Permanent researchers from Institutions and similar positions	5	5	5
N3: Other permanent staff (without research duties)	8[5.9]	8[3.8]	
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	5	4	1
N6: Other contractual staff (without research duties)	3[1.5]	3[1.5]	
TOTAL N1 to N6	**32**	**31**	**17**

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	11	
Theses defended	12	
Postdoctoral students having spent at least 12 months in the unit*	6	
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	12	14

2 • Assessment of the unit

Strengths and opportunities

- Very strong and internationally recognised leadership by the Director of the Unit.
- World-leading expertise in several areas of kidney diseases mechanisms.
- Highly relevant translational research at the best level of publication possible.
- Excellent balance between diversity of project and consistency of the overall program.
- Complementarity between the different teams and projects.
- Success in getting outside funding and obtaining tenure positions.
- Strong support from the University and School of Medicine, and INSERM.
- All recommendations made during the previous evaluation have been fully implemented.
- Very high level of productivity, including valorisation through patents.
- Attraction and support of young and talented investigators from France and abroad who will be leaders in research in the near future.
- Development of a new promising team in the field of kidney cancer research.
- Very transparent leadership and clear views on the future of research and of the Unit.
- Equal opportunities regardless of gender and nationality.

Weaknesses and threats

Weaknesses

- None identified

Threats

- Increased pressure on time of physician-scientists for research due to time constraints caused by ever-increasing clinical, administrative and search for grant applications tasks.
- Decreasing number of PhD students granted in PhD programs.
- Increasing dependence on extra-mural grant programs for research.
- Non-permanent position for the leader of Team-3.
- Loss of technical expertise through departure of research engineers because of lack of opportunities to have permanent positions in the Unit.

Recommendations

- Strongly consider the opportunity to expand the Unit into a Kidney Research Centre in order to take full advantage of the excellence and complementarity of research teams, leaders and technological tools and cores. In particular, a kidney research center which would be able to attract new groups and therefore to increase the manpower dedicated to cancer and basic cell biology.
- Stabilize and expand the kidney cancer research program through increased interactions with local and regional environment, and allowing a permanent position to its leader.
- Maintain current funding resources from INSERM and UPMC to enable the Unit to continue to generate extra-mural grants.
- Allow more flexibility in the utilisation of grant money for PhD students support.

3 • Detailed assessments

Assessment of scientific quality and outputs

- The research performed in this Unit is original, innovative, of excellent quality, highly coherent and strongly translational, directly relevant to the pathophysiology and treatment of renal diseases, particularly auto-immune diseases and chronic kidney disease. This translational research is directly beneficial to patients and society.
- By using GWAS and other innovative technologies, the Unit has been crucial in the unravelling of the mechanisms of one of the major auto-immune kidney diseases (membranous nephropathy) and of inherited basement membrane diseases.
- This has had a major impact as reflected by world-class publications (4 articles in the New England Journal of Medicine) and an advanced European Research Council grant, several awards and invitations to present lectures at major international scientific congresses (e.g. International Society of Nephrology Jean Hamburger Award).
- Over the last 4 years, the number of publications has increased by about 100%, the mean Impact Factor has risen from 5.3 to 6.7, and the number of citations from 887 to 2011.

The Unit has emerged as one of the leading kidney research centres in Europe and worldwide.

Assessment of the unit's academic reputation and appeal

This Unit has been awarded:

- 8 ANR research projects.
- 3 PHRC (National Hospital Clinical Research Programs).
- 3 FP6 or FP7 European programs.
- FRM (Medical research Foundation) labellisation for 2 teams.
- Numerous grants from Foundations, Patients' Associations, Ministries, Regional funds.

The Unit has been able to recruit:

- Two high standard researchers from foreign European countries (Greece and Germany), one of whom is leader of Team 3.
- Nine foreign post-docs and seven French post-docs.

Several awards have been gained by members of the Unit:

- Very prestigious international awards to the Unit Director (member of the Académie Nationale de Médecine) and to Team leaders.
- Other members of the Unit, including younger investigators, have been recognized personnally.

Members of the Unit belong to high-quality scientific journals Editorial Boards.

Invited reviews in high-rank journals have been written by the institution's members (Nature Reviews Nephrology, Current Opinion in Nephrology and Hypertension, Clinical Journal of the American Society of Nephrology).

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

The unit has produced eight patents; four patents are pending. These patents concern diagnostic tools, biomarkers, and therapeutic targets.

Five contracts with Industry (total of 500 000 €) are underway to exploit these patents.

Assessment of the unit's organisation and life

The working atmosphere is collegial, friendly, open, and constructive.

There is an excellent balance between directing the general objectives of the Unit, and allowing intellectual independence to all members.

All categories of professionals in the Unit are involved in the life of the structure. Most people we met do not consider working in any other place.

Lab meetings are held regularly on a weekly basis, and researchers from outside the Unit are frequently invited for seminars and lectures, providing an excellent milieu for scientific maturation.

Assessment of the unit's involvement in training through research

Training through research is a priority of the Unit as documented by:

- The interviews conducted with students during the visit (M2, doctoral, and post-doctoral students) who all gave a positive feed-back on their education, supervision and mentoring in the Unit.
- They all mentioned that direct contact with their supervisors were scheduled at least on a weekly basis, and whenever needed.
- Clear guidelines for authorship of students who had no doubts on the fact that they would be first authors of their own work.
- The number of students from all stages of training through research in the Unit (numbers detailed elsewhere).
- The impressive number of theses accomplished in the Unit during the last contract.
- The grant support of all students in the Unit.
- The positive professional outcome of doctoral and post-doctoral fellows of the Unit, with recruitment as senior researchers in the Unit granted for foreign students.
- The committee wants to emphasize that the training of all technicians into engineers is an accomplishment of this Unit, with some drawbacks, since some engineers have been recruited elsewhere because of their high-level of competence.
- The involvement of Senior Researchers of the Unit in the UPMC Doctorate School steering committee.
- The weekly seminar given every Thursday in the Unit by local or external researchers.

Assessment of the five-year plan and strategy

The overall consistency of the project is well-maintained, and it includes highly innovative approaches, such as HLA-peptidomics, epigenetic modifications of renal genes, new-generation sequencing, random mutagenesis.

The continuation of established research programs (e.g. membranous nephropathy, chronic kidney disease models) guarantees a high degree of success.

On top of this, some high-risk projects (epigenetics and peptidomics) have been intentionnally included, that may lead to major breakthroughs.

Although research projects remain focused on kidney diseases, broader concepts are addressed in the fields of autoimmunity, genetic diseases, inflammation and fibrosis, and cancer.

Notwithstanding the multiple components of the projected research programs, synergy is maintained by sharing experimental models and technology, and formal and informal exchanges between members of the different research groups.

A major strength of the Unit, namely translational research, will be solidified through:

- Continued involvement of MD PhD scientists in research projects.
- Use of patients materials from established biological collections with deeply phenotyped patients.
- The continuous establisment of animal models to test hypotheses derived from clinical experience (e.g. basement membrane research), or to develop new hypotheses.

Major sources of external funding have been already for the years to come, including a 2.5 million € from the EC, and 0.5 M€ through collaborations with industry.

The SWOT analysis of the unit is comprehensive and realistic. It reflects thorough self-assessment, and clear and self-critical vision of present and future challenges.

Despite being highly ambitious, the five-year plan is feasible and exciting.

4 • Team-by-team analysis

Team 1 : Molecular bases of rare and inherited kidney diseases: From insult to repair

Name of team leader: Mr Pierre RONCO

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3[1.6]	3[1.6]	3
N2: Permanent EPST or EPIC researchers and similar positions	3	3	3
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	
N6: Other contractual staff (without research duties)	1	1	
TOTAL N1 to N6	**11**	**11**	**6**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	4	5

• Detailed assessments

Assessment of scientific quality and outputs

Research held by Team-1 has led to major advances in the field of kidney diseases, with a continuous connection between basic science and clinical research. The PI of Team No. 1 is an internationally acclaimed and established scientist who has contributed several important results in nephrology. In particular, in recent years his work on the pathogenesis of membranous nephropathy that was published in several papers of highest impact, has won him international admiration. In addition to being a brilliant scientist with clear and realistic visions he has proved high talents for organizing complex collaborations and joint projects. He provides a highly impressive list of publications and invited lectures, and also of funding that was recently crowned by an ERC advanced grant. There is no doubt that the unique gifts of Mr Pierre RONCO are of invaluable importance for the success of this entire program. Overall, these has published 74 original publications (including 4 papers in the N Engl J Med), and 46 reviews with a mean impact factor of 8 and a mean citation index of 11.1.

Membranous nephropathy

Membranous nephropathy (MN) is one of the commonest types of glomerulonephritides in man. This team has contributed to the discovery of two different pathophysiological mechanisms which can lead to MN, one from a rare genetic defect in homozygous mothers leading to immunisation of heterozygous foetus leading to MN, the other because of immunisation against a foreign protein from food. They have also identified genetic loci associated to the development of MN, through a GWAS analysis linked to previous discoveries in the field of MN. Based on the excellent previous work of this group and their substantial funding, the ambitious projects proposed in this application have a very good chance to be accomplished in the proposed time and to substantially further our knowledge on the pathogenesis, diagnostic and specific treatment for MN.

Hereditary basement membrane diseases

The expertise of this team in the field of rare disease and glomerular basement membrane biology has led them to describe a new disease in humans that they have called **HANAC**: this multi-systemic inherited syndrome is due to a mutation in collagen type IV gene COL4A1. This description of several families with this new disease has been published in the New Engl J Med.

Role of matrix metalloproteases in renal diseases

This team has identified new roles of matrix metalloproteases such as MMP9 in nephron formation, in kidney cyst formation, and as an anti-apoptotic factor. They have characterized the effects of the splice variant MMP9-DEx2 and suggested a potential role of the LG3 fragment of endorepellin (a fragment of perlecan) in the progression of IgA nephropathy. The general hypothesis is that alterations of basement membrane composition (as observed in HANAC syndrome) or remodeling are important triggers of cyst formation, of alterations of vascular reactivity, and of fibrosis which is a prominent, but neglected lesion in many inherited kidney diseases. Part of the studies on matrix remodeling have been performed in close collaboration with Team 2.

Assessment of the unit's academic reputation and appeal

This team is one of the best in the world for research in kidney disease, both in basic and clinical science. Numerous awards have been given to its leader and to members of the group, including the 2007 Jean Hamburger Prize of the International Society of Nephrology, the 2011 Jean Dausset Prize of the French Society of Immunology, the 2010 Prize of the French Kidney Foundation, and others. Fellows from several countries have been involved in the lab, and researchers from outside France have spent sabbatical time in the unit.

The Team Leader has been President of the French-speaking Society of Nephrology, and has been instrumental in the organisation of several major international nephrology congresses. Invitations for plenary lectures are a sign of recognition of the reputation of the work done by this team.

The former President of the International Society of Nephrology has spent a sabbatical year in the lab, working on MN.

The founding in 2010 of the ***European MN consortium*** for the study of membranous nephropathy with Dutch and British partners has led to major articles, and to invitations in prestigious congresses. This illustrates the charisma of the Team leader, and his ability to federate scientists on research projects.

Members of the Team are in several scientific and editorial boards and committees, both international and national, the recognition of their expertise is obvious.

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

Several research projects are conducted in connection with European labs, with funding by EU FP7 program. Other funds have been raised from public and private sources, with a clear interaction between the team and industry.

Actions targeted to a broad audience such as the World Kidney Day and TV appearances are elements of interaction far beyond academic communication. The Team leader is vice-president of the Fondation du Rein, the Francophone Kidney Foundation, which aim is to provide funds for kidney research, in connection with patients associations.

The Team leader has initiated the making of Archives of interviews of Francophone and European pioneers of Nephrology. He is the only nephrologist member of the prestigious Institut Universitaire de France, whose main mission is to promote the development of high quality university research, and to strengthen interdisciplinary projects between scientific and medical disciplines on the one hand, and arts, humanities and social sciences on the other.

A diagnostic test for idiopathic MN has been commercialized from the work of Team-1, with the collaboration of a private company. One patent has been obtained, another one is pending.

The Team is also the French reference centre for the genetic diagnosis of COL4A1-related diseases, and a member of the national reference centre MARHEA (Hereditary Diseases of Children and Adults) whose missions are the diagnosis, care, and information of patients and families with inherited kidney diseases.

Assessment of the unit's organisation and life

As mentioned above, there are 4 differents areas of research in Team-1, all of them are being supervised by the Team leader. There are good and collegial interactions between members of the Team, with a governance which gives all researchers, including post-docs, the possibility to have an impact on research developments. This was very apparent from the meetings with doctoral and post-doctoral fellows during the visit.

Assessment of the unit's involvement in training through research

All members of the Team are actively involved in the curriculum of the Graduate School of UPMC, Paris 6 University « Physiologie et Physiopathologie » (ED394), and in teaching Physiology, Cardiology and Nephrology to the Medical students (1st, 2nd and 3rd cycle and Biological and Medical Masters) of the Faculty of Medicine UPMC, Paris 6.

The number of master, doctoral, and post-doctoral students trained by the team are coming from several countries, including non-European ones. Many of the students and post-docs met during the visit expressed their desire to pursue an academic career, even though this will not be an easy task in some countries which lack research infrastructures.

Since 2007, Team 1 has trained 4 Master 1, 12 Master 2, and 7 PhD students and 6 post-doctoral investigators. Four PhD dissertations have been presented between January 2007 and June 2012 of whom 1 pursues post-doctoral training, 1 has an academic Faculty position, 2 have permanent contracts in the private sector.

One professor of team 1 has received a “Doctoral management prime” (Prime d’Encadrement).

Assessment of the five-year plan and strategy

Membranous nephropathy

Based on their extensive experience in detailed characterization of major nephritogenic antigens in human MN, the applicants propose a search for further target molecules and for relevant epitopes by a systematic approach based on **HLA class II peptidomics** in co-operation with a renowned lab in Switzerland. They will also use a random peptide library to search further antigens recognized by antibodies in the sera of MN patients. Both approaches use leading-edge technology and are based on a large collection of well-defined human samples. The questions addressed are of high relevance for taking the experimental insights on the molecular pathogenesis of MN to the bedside.

The identification of immune response triggers deals with the follow-up on the initial finding of an association with HLA-DQA1 in recurrent MN after renal transplantation. The hypothesis is that variants of the HLA-D gene are associated with recurrence of the disease. **Deep-sequencing of the entire HLA-D region** and of additional genes is expected to reveal insights into this situation. This part of the project is a potentially important aspect of the pathogenesis and treatment of relapsing MGN (and possibly also of primary MGN). The analysis is based on solid methodology which is being set up in the laboratory of the PI.

The applicants propose to detect **mutations and polymorphisms in complement regulatory proteins**. They plan to sequence several genes that code for different complement activation pathways. This is a timely approach to reveal a molecular cause for complement activation in the glomeruli in iMN that is arguably the major damaging system for podocytes in this disease. In a more direct approach, the applicants plan to examine the scavenging properties of complement factor H in models of MN *in vivo*. These experiments are straight-forward and could add on to the known list of complement protection systems in podocytes that, however, are overrun in MN. It is proposed that also the scavenging activity of the serum S-protein (vitronectin) is examined in the same context. The experiments may yield a **druggable target** to ameliorate the glomerular damage in MN.

Novel hereditary basement membrane diseases

As in some patients with syndromes close to HANAC COL4A1 genes and proteins were normal, the plan is to identify the underlying lesions in detail by deep-sequencing of exomes of these patients. The general scientific information to be expected from these experiments is a deeper understanding of the structure and stabilization of the glomerular basement membrane.

In a logical extension of their description of HANAC in humans, the authors have generated several mutant mice similar to those found in patients. These animals will be used to study the mechanisms of the renal damage observed in HANAC, using *in vitro* metanephric kidneys to study nephron development. On the other hand, they plan a focussed research on the $\alpha_3\beta_1$ integrin pathway, because this integrin interacts with COL4A1. It is planned to also follow up on the observation that glomerular parietal epithelial cells are phenotypically altered in HANAC.

New players in Polycystic Kidney Disease (PKD)

The applicants plan to use mice with a mutation in the SAM domain of Anks6 - a protein in primary cillia - that develop different subforms of PKD depending on the genetic lesion. They plan to identify interaction partners with Anks6 that may be involved in the pathological phenotype, with the idea that Anks6 interacts with polycystins functions in the kidney. They will also try to identify binding partners to Anks6, using two hybrid systems, tandem affinity purification, and GST pull-down methodologies, followed by mass spectrometry. They further will go on to examine *in vitro* the function of Anks6 in its potency to form cysts of MDCK cells grown in 3D-culture and also in organotypic culture of embryonic kidneys. *In vivo*, they plan to use siRNA technology to target Anks6 in the kidney.

The reversal of polycystic phenotype in mice will be studied, based on the chance observation that PKD was reversed in mice substrains by mutations on chromosome 10. Here, they plan to identify the precise modifier gene responsible for this regression.

Repair of renal fibrosis and epigenetic regulation of tissue repair

In this project, overlaps of the transcriptomes of circulating leukocytes and of renal tissue of several forms of renal fibrosis models will be studied. This will be done by genomic analysis and be confirmed by immunohistochemistry, should some consistent markers be revealed by this approach. In collaboration with Team No. 2, an epigenetic analysis of the animal models created in this part of the program will be performed. Eventually, these results will be exploited by developing experimental therapies to prevent or intervene in fibrotic disease.

Overall Assessment of the Program of Team 1

The five-year plan will focus on three research themes which prolong and extend the work done so far: the first will be in the field of MN and auto-immune diseases with new techniques based on high-risk technologies which are thought to be necessary to make significant new discoveries in pathogenesis and treatment. The other fields of interest will be on diseases linked to abnormalities of the basement membrane, and the identification of new mechanisms of progression of polycystic kidney disease. The strategies described are based on a strong scientific background, with collaborations and innovative technologies as needed.

Overall, there is no doubt that the quality of research by this team ranks it amongst the best in the field, at the highest international level. Very few teams have such records of publications in high-rank journals, including 4 papers in the NEJM during the last 5-year period. The aims are focussed, although diverse experimental approaches are proposed that, given the proven strength and cohesion of the groups, will be achieved with great certainty. Attention has to be paid to the fact that the entire program depends on novel technologies, such as deep-sequencing, which requires not only good instrumentation, but also dedicated personnel and especially a good bioinformatics set-up. Thus, with the proposed staffing and adequate financial resources on the one hand, and enough freedom of time from clinical and administrative work on the other hand, there is a high probability that the entire program can be successfully accomplished within the proposed time limits.

Conclusion

- Strengths and opportunities:
  - Very experienced and distinguished leader and associates.
  - Research projects are at the best international level, with constant interactions between bench and bedside, a hallmark of the Team Leader.
  - Very strong foundation for the planned research by preliminary work and established protocols and knowledge.
  - Focused projects, based on relevant scientific and clinical research questions.
  - Innovative strategies, with some high-risk projects, which may lead to major discoveries.
  - Expertise in rare diseases, with established partnerships in France and other European countries, based on common research projects funded by the EU, and on databases with biological collections which give the possibility to test pathophysiological hypotheses with a very short delay.
  - Planned transition towards more involvement in the role of genetics in the diseases studied, including auto-immune diseases.
  - Strong coordination between research themes within the team and with Team 2 and 3.
  - Support for research programs obtained from several sources of public and private funding, including the EU and French sources.

- Weaknesses and threats:
  - Watch out for overload by excessive clinical and administrative duties.
  - Protect key positions in the Team (scientists, engineers and admininIstrators).

- Recommendations:

The excellence of this team is quite obvious from its achievements, with a very high level of publications and scientific discoveries. We recommend to maintain connections between clinical and scientific questioning in research programs. The forthcoming contract period will have the priority to strengthen leaders for future research programs, as a safeguard to maintain such high standards.

4 • Team-by-team analysis

Team 2 : Novel biomarkers and molecular targets to evaluate and treat chronic kidney diseases

Name of team leader: Mr Christos CHATZIANTONIOU

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	7 (2.15)	7 (2.15)	7
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)	5 (3.2)	5 (3.1)	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	2	1
N6: Other contractual staff (without research duties)	2 (1.5)	2 (1.5)	
TOTAL N1 to N6	**19**	**18**	**10**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	8	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	7	8

• Detailed assessments

Assessment of scientific quality and outputs

During the last contract period, members of team 2 have been involved in a large number of complementary studies. All these studies were based on the pioneering observation made by investigators of this group that the progression of renal fibrosis, the main lesion that accounts for the progressive decline of renal function and ultimately terminal renal failure, can be at least in animal models stopped and sometimes even reversed and cured.

Therefore, the group has logically invested major efforts to dissect critical potential mechanisms that account for either the triggering and diffusion of potentially harmful events like inflammation, apoptosis, and fibrosis; or for potentially protective events like repair, stabilization and regression of renal fibrosis.

The approaches used for these studies were innovative, original, and focused on specific mediators or signaling pathways, and in line with the overall topic of the unit but also with the clinical investigation driven in parallel to the basic research by the many physicians involved in the research of team 2.

Particularly, Team 2 has been very successful in using animal models or therapy driven approaches to demonstrate:

- The role of several specific factors (Connexins, Calpains, DDR1, vitronectin) in the progression of renal fibrosis.
- The importance of endothelial dysfunction in the progression of renal damage, and the critical role of other signaling pathways in this process (Notch 3, Ang II-BMP/TGF/EGFR).
- The group has also contributed strongly to the search for biomarkers that might be useful tools in clinical practice. These efforts were focused on the detection and follow up of the development of harmful renal fibrosis which is considered as a main target for specific therapy of renal injury.
- In parallel, to these basic research activities physicians of the unit, involved in the team, have established very important and complete cohorts of patients with chronic renal failure, renal transplants and rejection, renal stone disease and sickle cell disease. These cohorts are an important resource and will be a major strength when it will be necessary to translate the basic findings into clinical research and reciprocally. Moreover, the physicians already exploited these cohorts with a regular production of very high quality and high impact clinical investigation articles.

During the last 4 years, members of the group have proven to be very productive with the production of 117 original publications and 34 reviews with a mean IF of 5.5, and a mean citation index of 9. Scientific production is regular and is in the best and high impact journals of biology and kidney research: Circulation, Circ Res, J Am Soc Nephrol (1st journal in the field), Kidney Int, Hypertension, Faseb J, Nat Medicine (as collaborators), and importantly also in other biological or medical fields (e.g., hematology and biochemistry) which attest from the broad and general interest for the results issued from the team's research.

Assessment of the unit's academic reputation and appeal

This team is one of the best in the world for research in kidney disease, both in basic and clinical science. Members of the group have been invited to give lectures in the annual meetings of the International, American, European or French Societies of Nephrology, Physiology, Transplantation or Pharmacology. Fellows from several countries have been involved in the lab, and researchers from outside France have spent sabbatical time in the unit. Members of the team are members of Faculty 1000, recipients of Contract Research-Hospital or of the "prime d'encadrement doctoral" or of the "prime d'investissement recherche", corresponding members of the Academy of Medicine, Academic Editors (PLoS One), members of editorial boards (Am J Physiol, Kidney Int).

Senior members of the team have been instrumental in the organisation of several major international and national nephrology or physiology congresses. Invitations for plenary lectures are recognition of the reputation of the work done by this team.

During the preceding evaluation the AERES committee noticed that there was not enough valorization given the very high clinical relevance of team 2 research. In reaction to this critique, Team 2 has made a huge effort to address this concern. As a consequence, Team 2 has now registered 7 patents and has 3 other pending which is a major strength.

Furthermore, Team 2 is part of the FP7 network RISET.

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

The achievement of Team 2 in termes of valorisation and relation with the civil society is excellent indeed:

- We have mentioned above the valorisation policy of the team.
- Team 2 has also obtained contracts with pharmaceutical companies (Merck, Sanofi, Wyeth, Genfit, Novartis, Hoffman-Laroche) for a total amount of 500 000 euros and 200 000 US §.
- Members of team 2 have been also actively involved in the organisation of international meetings among which : Faseb summer conference, European Society of Clinical investigation.
- Two members of team 2 are Heads of Hospital Poles.

Assessment of the unit's organisation and life

Organization of the life of the team is excellent. Practically, the leader of team 2 is supervisor of all themes. However, practically all different themes or "projects" of team 2 are led by a tenured researcher or professor, assisted by post doctoral fellows, students and technical staff. Lab meetings are organized on a weekly basis to monitor the progress of all projects and to maintain a cohesion between the different themes and investigators. It is worth to note that all themes are supported by the whole team and all investigators are helped by the others when necessary.

There is an important place dedicated to the technical staff which can participate to the direction and planning of the experiments and who is actively involved in the publication process. A great care is also taken to ensure that the technical staff can regularly benefits from dedicated training and can evoluate in terms of knowledge and career.

Assessment of the unit's involvement in training through research

As detailed below Team 2 is actively involved in training and academic teaching:

- Members of team 2 are actively involved as lecturers in the PhD program of UPMC, Paris 6 University « Physiologie et Physiopathologie ».
- Members who are professors of Medicine are also teaching Physiology, Cardiology and Nephrology medical students (1st, 2nd and 3rd cycle and Biological and Medical Masters) in the Faculty of Medicine UPMC, Paris 6.
- Team 2 has also created an inter-university diploma of renal intensive care and a university diploma of renal physiology.
- Members of team 2 serve in the Direction Committee of the "Ecole Doctorale Physiologie Physiopathologie" ED 394 and in the Committee of Thesis and HDR of UPMC.
- Since 2007, Team 2 has trained 6 Master 1, 24 Master 2, and 15 PhD students and 8 post-doctoral investigators. Nine PhD dissertations have been presented between January 2007 and June 2012, 3 were presented during September 2012, and 2 more are scheduled for February 2013. Among the 12 PhDs, 3 pursue post-doctoral training, 5 have an academic Faculty position, 4 have permanent contracts in the private or public sector.
- Three professors of team 2 have received a "Doctoral management prime" (Prime d'Encadrement).

Assessment of the five-year plan and strategy

The results obtained during the preceding contract provide the group with a very solid ground upon which they will be able to build their new very ambitious project. As they indicate in their project proposal now is the time to move toward more global approach or analyses of the signaling networks participating in the progression of renal damages, and also that they have acquired enough new results to be able to launch their ambitious, innovative, but also high risk programs in parallel to their more « classical studies ».

Identification of new targets of renal inflammation and disease

This topic is in line with the previous studies from the group and hence, is the logical extension of the preceding contract. The group has however, chosen to focus on the three most promising factors identified previously: Calpains (as a mediator of inflammation/aging); DDR1 a non-integrin collagen receptor with tyrosine kinase activity. And interendothelial junction's molecules (connexin 43 and CD146).

These projects, as stated above, will use the same « classical » strategies, i.e., modulation of these factors expression and activity with specific drugs or antisense in animal models of renal injury and test of the potential beneficial effects of this modulation. The original part of this project is that it brings together basic research in animal models with clinical research studies, in which the potential involvement of these molecules, and their putative use as biomarkers will be systematically assessed.

Discovering of new mediators

During the preceding contract, the group has made important observations supporting the critical role of endothelial dysfunction in the progression of renal fibrosis. They also observed a critical role of Notch 3 in the myogenic response of kidney vessels. They now propose to link both observations and will study the involvement of the notch pathway in renal failure. To achieve this goal, they will benefit strongly from the tools developed by Team 3 to modulate specifically Notch 3 in vivo in transgenic mouse models. The justification of this research is that it will provide evidence to explain some apparent discrepancies observed from one patient to another. Indeed, hypertension is a well-known factor that promotes the progression of renal lesions. However, there is no good correlation between the level of blood pressure and the intensity of progression of renal fibrosis. A difference in local modulation of Notch signaling is proposed by the investigators to explain at least part of these differences and discrepancies.

Using a transcriptomic approach in animals with chronic renal failure and fibrosis, team 2 has identified new biomarkers like periostin. They want now to solidify their observations by demonstrating that beyond their role of « markers » many biomarkers (including periostin) are actually active players in the progression of renal injury. If this hypothesis proves to be right then it will be a major breakthrough contributing even more to the search of biomarkers as putative druggable targets.

Several researchers of the team are clinicians who are specialized in renal transplantation. Logically, these investigators will develop very stimulating projects to understand acute and chronic transplant rejection as an important paradigm of renal fibrosis. Their driving hypothesis is that renal epithelial (tubular) cells are the target of injury during rejection and that this promotes the development of phenotypic alterations of these cells that in turn favors pro-fibrotic events. This topic is evidence-based and will benefit strongly from the large cohorts of patients followed at Tenon hospital and from a very large historic collection of renal tissue obtained from these patients.

Epigenetic regulation of renal fibrosis

This project is probably the most ambitious but also the most risky from this group. However, it comes from a very true statement from the investigators that the research that they have developed until recently (identification of specific markers and characterization in a pathogenic process) is useful and highly productive. On the other hand it is far too limited to obtain a global overview on the pathophysiological mechanisms involved in renal fibrosis or repair. Thus since the team has obtained significant success in the preceding period, they logically decided to develop a more ambitious strategy even though they admit that the completion of this project will be more uncertain.

Since the team is not fully dedicated to this task, and since other « more conventional » projects are still developed, the committee thinks that the risk is limited and the possibility to force a major breakthrough in renal disease research is more than reasonable.

This project is based on the hypothesis that all kidney injury can trigger the modification of a large number of genes either potentially harmful or useful. And that this occurs because any injury can modify the epigenetic control of the different renal cells. Particularly, the group suspects a critical role of histone acetylation in the modulation of gene networks that can lead either to the progression of fibrotic lesions or to the reparation of renal tissue. To test their hypothesis, they propose to generate a description of the histone acetylation events in the setting of renal disease. They also plan to use cutting edge sequencing technologies to determine which genes undergo epigenetic modifications after renal injury. Then they want to transfer the knowledge obtained from animal models into humans by applying in parallel the same approaches in human tissue material from their bio-banks.

Conclusion

- Strengths and opportunities:

  - The project is coherent, logically developed from previous evidence generated for the major part by the group itself, supported by an absolute requirement for the understanding of the pathophysiology of renal injury/repair. The group benefits from the leader who is internationally recognized and is a charismatic figure in the field. The insertion of the team in the local and international environment is excellent. All major tools required for the proposed plan are in place or were developed previously.
  - The project is an excellent and innovative combination of classical studies with more ambitious but risky projects.
  - Extensive experience with basic research of the established PI and team members.
  - Strong experimental models and tools.
  - There is an excellent translation of basic research in clinical research and reciprocally.
  - The group members have very diverse and complementary educational backgrounds.
  - The involvement of the group members in teaching, knowledge diffusion, and valorization is excellent.

- Weaknesses and threats:

  - Like for any other group in France there are less and less young fellow/investigators who are motivated by research and seek research as a career track.
  - The new task proposed by the team (epigenetics of renal injury) is, as underlined by the applicant, a risky project.
  - The number of research sub-projects is high, requiring close monitoring of details and essentials.

- Recommendations:

The group is excellent and has major chances to be successful. The committee has no real reservations. However, the team is rather large and involves researchers and physicians, some efforts should be made to make sure that the basic research and the clinical investigations are coordinated in a practical sense.

Probably, for the next contract, the emergence of new leaders will become evident. The unit or the team has to anticipate what they will propose to help emerging scientists to obtain their independence. Particularly, the unit has now the size and international recognition that is sufficient to propose the creation of a research center dedicated to kidney research in which each team will be built around one or two investigators.

The team should build a strong strategy, which will require a strong support from the university and medical school, to encourage the identification and recruitement of young investigators that will access to a tenure-track position in order to ensure the renewal of the team forces.

4 • Team-by-team analysis

Team 3 : Mouse models of renal cancer

Name of team leader Mr Robert KOESTERS

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent EPST or EPIC researchers and similar positions			
N3: Other permanent staff (without research duties)	1[0.7]	1[0.7]	
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**2**	**2**	**1**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

This team does exist since two years only and the team leader just arrived in France. **Therefore his achievements cannot be evaluated as part of the unit evaluation; i.e. this section is not relevant**. During the past years, the PI of this group has proven to be a very successful scientist as attested by:

- The production of the first mouse model allowing kidney specific and tetracycline-dependent gene targeting in the whole tubular system. This model has initially been published in a top journal (Nat Med.) and has subsequently been used by many groups worldwide, as attested by the many ongoing collaborations that use this model.

- The fact that the team leader received funding from the DFG in Germany, and then from the UPMC and from Association pour la Recherche sur le Cancer.

- The team leader was also laureate from an international call for proposal from UPMC, INSERM and AP-HP and obtained a position as Professor of Genetics.

In summary, even though it is impossible to evaluate this team yet as a part of the unit, the team leader is a talented researcher with a good productivity and international recognition as a specialist of mouse engineering. Moreover, he has integrated rapidly into the unit and the excellent perspectives arising from this are very obvious.

Assessment of the unit's academic reputation and appeal

This team does exist since two years only and the team leader just arrived in France. **Therefore this section is not relevant (see above)**.

However, the team leader is recognized worldwide as a leader in mouse genetic engineering and is regularly invited to international meetings.

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

This team does exist since two years only and the team leader just arrived in France. **Therefore this section is not relevant (see above)**.

Assessment of the unit's organisation and life

This team does exist since two years only and the team leader just arrived in France. Moreover, the team right now consists in only two persons. **Therefore this section is not relevant (see above)**.

Assessment of the unit's involvement in training through research

This team does exist since two years only and the team leader just arrived in France. **Therefore this section is not relevant (see above)**.

Assessment of the five-year plan and strategy

Team 3 is a small group restricted to a PI, and one engineer ± post-docs and students. The PI was recruited through an international call with the main objective to develop a research dedicated to renal cancer, that would create the bridge with the highly performing renal unit already existing in Tenon Hospital. Logically, thus, the PI of team 3 is dedicated to develop renal cancer research. However, he is also taking care of developing new tools that are expected to be critical for projects of team 1 and 2, and hence to participate to the other topics of the Unit. The unit deserves credit for complementing its expertise in this way rather than recruiting a scientist with more similar research focus. Eventually the novel approach and technologies provided by the new team leader (mouse genetics, tubular function, cancer) in combination with the existing expertise (autoimmunity, matrix biology and remodelling) will lead to very innovative strategies and findings.

Identification of renal cancer genes in transgenic mice (sleeping beauty)

This first ambitious task aims at identifying genes involved in renal cancer by a genome wide screening strategy. This strategy is based on an elegant method of random insertional mutagenesis in transgenic mice. Preliminary results are very encouraging, and indicate that the strategy is very effective. There is also a high likelyhood that it will lead to identification of genes that rare relevant for kideny cancer in humans.

Development of mouse models of renal cancer

Research of pathophysiological mechanisms involved in renal cancer apparition and development has been hampered until now by the lack of good mouse models of renal tumors. Therefore, one of the first goal of the team is to develop different mouse models leading to the development of renal cancer that mimic the classical tumors observed in human patients (clear cell carcinoma, papillary cell carcinoma, translocation type carcinoma.) To develop these models, the researcher uses his expertise in transgenesis.

Collaborative studies

The researcher as stated above has developed unique tools that allow kidney – and time-specific gene targeting. These tools are highly valuable for many other group studies and have led to many different collaborations that are expected to produce significant results soon.

Translational research

This project is a direct extension of the first (sleeping beauty one). The researcher plans to analyze samples obtained from human patients suffering renal cancers in order to verify that genes identified in the mouse are also involved in human cancers.

Conclusion

- Strengths and opportunities:
  - The project is very original.
  - There is almost no group specifically dedicated to the study of the pathogenesis of renal cancer, particularly in France.
  - The topic is of significant clinical relevance and adrresses an area of unmet medical need.
  - The group benefits from the expertise of the leader in cutting-edge technology of gene targeting.
  - The project is highly ambitious and yet feasible.
  - The research plan is logic and appropriate with the plan to: map the list of putative candidate genes involved in renal carcinogenesis; develop the mouse models that are lacking in the field; verify in human patients that the observation made in mice can be directly applied to human pathology.
  - The researcher has developed a nice network of collaboration in the unit and outside with other groups.

- Weaknesses and threats:
  - The PI is not tenured yet
  - The team is very small, and the success of the project might eventually be limited by the inability to characterise the biology of all interesting candidate genes identified.
  - While the researcher will benefit from the knowledge of the other researchers of the unit in the field of renal pathology, the environment in term of researchers involved in cancer biology would ideally be stronger and allow a better interaction with researcher from « cancer research units ».

● Recommendations:

The project is overall very important and ambitious. It would be important that the position of the PI be secured as soon as possible.

Given the expertise of the researcher, this initial phase of the project has great chances to be successful. However, it will be difficult for the researcher to start a second phase more dedicated to the exploitation of the models generated and to the characterization of the biological function and pathophysiological role of the candidate genes identified, if the team does not recruit new researchers and if there is not a good integration of the applicant with a solid network of other groups involved in cancer biology.

Team 3 should also be involved in a tight collaboration with urologists from the hospital who are in charge of the treatment of renal cancer, possibly through an INSERM interface contract.

5 • Conduct of the visit

Visit date:

Start: December 17, 2012 at 8:00 am

End: December 17, 2012 at 05:00 pm

Visit site: Hopital Tenon, Paris

Institution: UPMC

Address: 4, Rue de la Chine, Paris 75020

Specific premises visited:

Research building Tenon

Conduct or programme of visit:

Four weeks before the committee performed its official site visit, the members had received the comprehensive report of the Unit's performance over the past 4 years and its programme envisioned for the next period. These documents had been studied in depth by the committee members and summaries had circulated among the committee members before the visit. At the day of the site visit, the AERES evaluation process and the site visit committee were introduced by Mr Bernard DASTUGUE. Then the Unit presented the research programme as being executed by the different Teams. Plans for the future were presented. The presentations were impressive and highlighted the excellent quality of research. There was ample time for discussion. After the scientific exchange, the committee had discussions with the representatives of INSERM, UPMC, The Medical School of UPMC, and Tenon Hospital. During coffee and lunch breaks, the committee members used the opportunity to discuss scientific, social and educational aspects with all members of the Unit. The committee split up to discuss more formally with the various groups of collaborators (researchers; postdocs & PhD students; research engineers and technicians) on the organization and functioning of the Unit. Thereafter, the committee withdrew for the writing of the report.

Specific points to be mentioned:

The committee was genuinely impressed by the scientific quality of the Unit and its leadership as well as by the collegiality and open atmosphere among the collaborators. The scientific and social exchange experienced by the committee was inspiring.

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

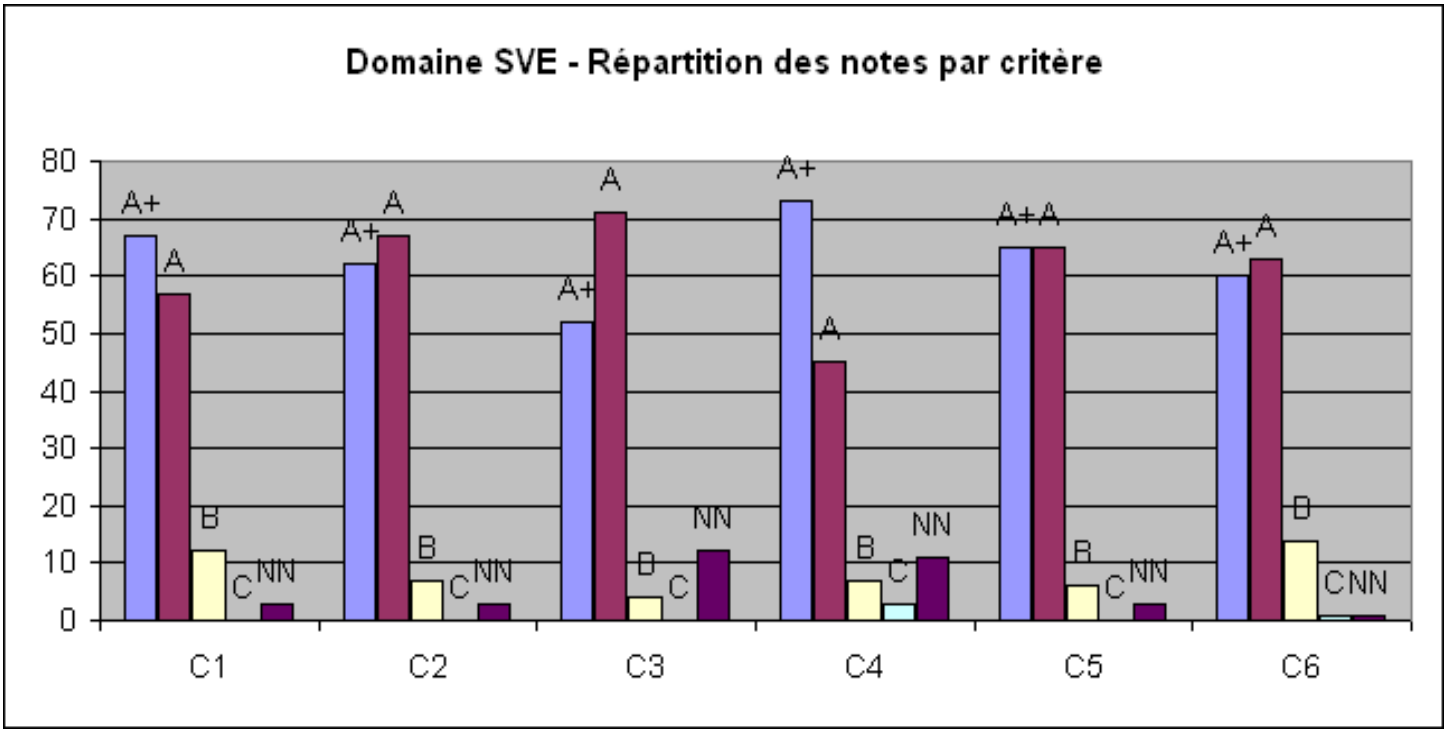
Grades

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

Percentages

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

Histogram



7 • Supervising bodies' general comments

Paris le 10 04 2013

Le Président
Didier Houssin
Agence d'évaluation de la recherche
et de l'enseignement supérieur
20 rue Vivienne - 75002 PARIS

M. le Président,

Nous avons pris connaissance avec le plus grand intérêt de votre rapport concernant le projet du laboratoire Remodelage et réparation du tissu rénal, porté par M. Ronco. Nous tenons à remercier l'AERES et le comité pour l'efficacité et la qualité du travail d'analyse qui a été conduit.

Ce rapport a été transmis au directeur du laboratoire qui nous a fait part en retour de ses commentaires que vous trouverez ci-joint. Nous espérons que ces informations vous permettront de bien finaliser l'évaluation du laboratoire.

Restant à votre disposition pour de plus amples informations, je vous prie de croire, M. le Président, à l'expression de mes salutations respectueuses.

Le Vice -Président Recherche et Innovation

Paul Indelicato

Vice-présidence Recherche et Innovation
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www.upmc.fr

Inserm
Institut national
de la santé et de la recherche médicale

UPMC PARISUNIVERSITAS

Unité INSERM UMR S 702
Remodelage et réparation du tissu rénal
Pr Pierre RONCO

Ref D2014-EV-0751722P-S2PUR140005591-001895-RT

Replies to AERES report

First of all, we would like to thank AERES and his representative for having selected a panel of renowned experts. These experts are among the most prominent nephrologists and nephropathologists in Europe and Worldwide. Overall, the interaction with the visiting committee was very constructive and helpful, the best that our Unit had ever had in the last years.
We would also like to thank the experts for their very positive appreciation regarding our scientific work, innovative efforts, coherence and complementarities of the teams, training activities and feasibility of the different projects. Their appreciation and the overall comments such as: "**The committee was genuinely impressed by the scientific quality of the Unit and its leadership as well as by the collegiality and open atmosphere among the collaborators. The scientific and social exchange experienced by the committee was inspiring**" encourage us to pursue with determination our objectives for the coming period.

Concerning specific comments and recommendations, following are the corrective actions that are taking place:

- Assessment of the Unit:

We are very pleased to see that the committee identified **13 Strengths** and **no Weakness**.

Regarding the identified "**Threats**", four of them are depending directly on the general policy of our institutions, the Ministry for Research, the *Assistance Publique-Hôpitaux de Paris* or the Government. These are:
- Increasing pressure on time of physician-scientists caused by increasing clinical, administrative and search for grants tasks;
- Decreasing number of PhD students granted in PhD programs;
- Increasing dependence on extra-mural grants;
- Loss of technical expertise through departure of engineers because of lack of opportunities to have permanent positions in the Unit.

We will take every opportunity to participate in decision bodies, steering and consulting committees of our institutions (Inserm, UPMC, AP-HP) to explain these general threats for the French science and to help promote the best solutions.
Members of our unit are, or will, participate in the coming period in several institutional committees such as CCS4-Inserm, CNU-UPMC, Scientific Council of Medical Faculty Pierre et Marie Curie (UPMC) and of Fondation Maladies Rares, Steering committee of CORDDIM (Domaine d'Intérêt Majeur, Région Ile-de-France), Direction of the Doctoral School-UPMC, Direction of Hospital Poles-AP-HP.

For the last threat 'Non-permanent position for the leader of Team 3', see below the answer of the assessment for Team 3.

Recommendations:

• Strongly consider the opportunity to expand the Unit into a Kidney Research Centre
We fully agree with the recommendation of the visiting committee for a long term-policy that will lead to the creation of a research center, locally at Tenon Hospital and we will support any effort of the University, Inserm and AP-HP to this direction. We are eager to increase the manpower dedicated to cancer and basic cell biology thus taking the opportunity for feeding kidney research with new expertise, and to host new, high-calibre small research teams on the available surface in the research building at Tenon hospital.

• Stabilize and expand the kidney cancer research program through increased interactions with local and regional environment, and allowing a permanent position to its leader
See below assessment of Team 3.

• Maintain current funding resources from INSERM and UPMC to enable the Unit to continue to generate extra-mural grants
We believe that our previous and current records and the evaluation of the Aeres committee are convincing elements for at least maintaining the current funding resources from our institutions. Regarding extra-mural funding, we are currently negotiating three contracts with private partners and we are PIs in two calls of the EU including ERC advanced grant and EUREnOmics.

• Allow more flexibility in the utilisation of grant money for PhD students' support.
Again this is an institutional decision, and we are combining our efforts with other colleagues towards this direction

- **Assessment of the Team 1**:

Weaknesses and Threats:

• Watch out for overload by excessive clinical and administrative duties
• Protect key positions in the Team (scientists, engineers and administrators)
See our answers above regarding the Threats of the Unit

Recommendations:

We recommend maintaining connections between clinical and scientific questioning in research programs. The forthcoming contract period will have the priority to strengthen leaders for future research programs, as a safeguard to maintain such high standards.

The leader of Team 1 has an established record of more than 30 years of 'bench to the bedside' research. All the junior members of his team (and the unit) have been 'bred' with this philosophy and almost all the proposed projects carried on by the younger investigators are translational. Two talented MD-PhDs have established an independent research group and will be able to take over by the end of the next contract.

- **Assessment of the Team 2**:

Weaknesses and Threats:

• Like for any other group in France there are less and less young fellow/investigators who are motivated by research and seek research as a career track.
We agree with the committee that this is a general problem in France (and in the European space in general). We will continue our efforts to convince bright young fellows to pursue a researcher and/or professor career. Please note that a CR1 has been recruited in 2010 and a MCU will be recruited in 2013.

• The new task proposed by the team (epigenetics of renal injury) is, as underlined by the applicant, a risky project.
We are fully aware of the risks of this project. However we felt, that since all the other projects which are based on very solid previous results and experience, are likely to be successful, we can capitalize on these projects and add risky, but very promising directions. The committee agreed with this concept, concluding that'Since the team is not fully dedicated to this task, and since other «more conventional» projects are still developed, the committee thinks that the risk is limited and the possibility to force a major breakthrough in renal disease research is more than reasonable'.

• The number of research sub-projects is high, requiring close monitoring of details and essentials.
The number of sub-projects (7) may appear high, but it should be compared to the number of senior investigators and project producers (10). In addition, some of these sub-projects are well advanced and probably will be finished before the end of the next period. Of note, since the creation of Team 2 (2004 by the fusion of 3 pre-existing teams with 16 sub-projects), a considerable effort has been undertaken to coordinate means, models and personnel and to progressively decrease the number of projects and increase efficiency and quality by focusing on the most promising ones. As a result, the number of publications and almost all the bibliometric indices of the team have been increased by 2-fold during the last period.

Recommendations:

• The group is excellent and has major chances to be successful. The committee has no real reservations. However, the team is rather large and involves researchers and physicians, some efforts should be made to make sure that the basic research and the clinical investigations are coordinated in a practical sense.

As noted above, Team 2 was successful in integrating basic research and clinical investigators during the last period. Since the team leader remains the same and the senior investigators have a proven record of collaborating and integrative projects, we think that we will not encounter particular practical problems.

• Probably, for the next contract, the emergence of new leaders will become evident. The unit or the team has to anticipate what they will propose to help emerging scientists to obtain their independence. Particularly, the unit has now the size and international recognition that is sufficient to propose the creation of a research center dedicated to kidney research in which each team will be built around one or two investigators.
This comment refers more to the whole unit than to Team 2. As mentioned above, we fully agree with the recommendation to create a research center, locally at Tenon Hospital and we will support any effort of the University, Inserm and AP-HP to this direction. The unit is a "nursery" of young talents: there are 2 such candidates aged 40 to 50 in Teams 1 and 2, respectively, who will be able to take over at the end of the next contract.

• The team should build a strong strategy, which will require a strong support from the university and medical school, to encourage the identification and recruitment of young investigators that will access to a tenure-track position in order to ensure the renewal of the team forces.
Despite the existing environment of budget reduction in France, our team was successful in recruiting one tenured CR1 researcher (Inserm 2010), two full professors (UPMC 2011, 2012) and one MCU (UPMC 2010). For the coming period, we already anticipate the promotion of the MCU to PU-PH (2014) and the recruitment as MCU (UPMC 2014) of a fellow who performed his PhD in Team 2 and who is now in post-doctoral training overseas. Of course we will continue our effort to recruit additional bright and young fellows through Inserm or the University.

- **Assessment of the Team 3**:

Weaknesses and threats

• The PI is not tenured yet

The PI is currently under a 4-years contract which ends in april 2014. Meetings and discussions about a possible prolongation will be held in the first half of 2013. A tenure position for the PI will be the major goal of these negotiations.

• The team is very small, and the success of the project might eventually be limited by the inability to characterise the biology of all interesting candidate genes identified

The team has been very small in the past (in Germany) as well, but the PI conducted his scientific work successfully thanks to technological leadership and a broad local and international network. The international network is still running well and leads to important scientific publications on a regular basis. In Paris, however, implementation of a new local network has only just begun. It will be expanded in the next years. Despite that, we will seek every opportunity to attract more funding and to increase the size of the team by hiring pre-doctoral students and post-doctoral scientists. Gain in visibility as an internationally leading renal cancer research group will help us to achieve these goals. Characterization of the

biology of interesting candidate genes to be identified will be performed by establishing appropriate collaborations in due course.

• While the researcher will benefit from the knowledge of the other researchers of the unit in the field of renal pathology, the environment in term of researchers involved in cancer biology would ideally be stronger and allow a better interaction with researcher from « cancer research units »

The success of our group is based on a strong background in nephrology because our mouse models are not limited to renal cancer research per se. However, cancer mouse models take usually longer to get established than mouse models of other acquired diseases. Hence, the interaction with non-cancer research groups was stronger in the past than with other cancer research groups. Having accomplished the difficult to achieve but important step of developing renal cancer models in transgenic mice, we are now in a position to focus on cancer research only. The recent launch of a university cancer centre (IUC) provides an excellent framework for better integration into the Parisian cancer research network.

Recommendations

The project is overall very important and ambitious. It would be important that the position of the PI be secured as soon as possible.

See above.

• Given the expertise of the researcher, this initial phase of the project has great chances to be successful. However, it will be difficult for the researcher to start a second phase more dedicated to the exploitation of the models generated and to the characterization of the biological function and pathophysiological role of the candidate genes identified, if the team does not recruit new researchers and if there is not a good integration of the applicant with a solid network of other groups involved in cancer biology.

See above.

Team 3 should also be involved in a tight collaboration with urologists from the hospital who are in charge of the treatment of renal cancer, possibly through an INSERM interface contract

The urology department is currently being restructured; new recruitments with an emphasis on oncology are expected.

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