Néphropathies héréditaires et rein en développement

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit:

Néphropathies héréditaires et rein en développement

University Paris 5

February 2009

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Research unit :

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University Paris 5

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

February 2009

Evaluation report

The research unit :

Name of the research unit : Néphropathies Héréditaires et Rein en Développement

Requested label : UMR_S

N° in case of renewal : U 574

Head of the research unit : Mme Corinne ANTIGNAC

University or school :

University Paris 5

Other institutions and research organization :

INSERM

Date of the visit :

February, 3rd 2009

Members of the visiting committee

Chairman of the committee :

M. Jean-Pierre GIROLAMI, Université Toulouse 3

Other committee members :

M. Christos CHATZIANTONIOU, Université Paris 6

M. Xavier JEUNEMAITRE, Université Paris 5

M. Robert UNWIN, University College London, UK

Ms. Roser TORRA, Fundacio Puigvert, Spain

CNU, CoNRS, CSS INSERM, représentant INRA, INRIA, IRD.... representatives :

Ms. Nicole PHILIP, CNU représentative

M. Marc BENHAMOU, INSERM CSS representative

Observers

AERES scientific representative :

M. Pierre BEDOSSA

University or school representative :

M. Paul KELLY, Université Paris 5

M. Bruno VARET, Université Paris 5

Research organiztion representatives :

M. Raymond BAZIN, INSERM

Mme Annick BERTAULT, INSERM

Evaluation report

1 • Short presentation of the research unit

- Numbers of lab members, 26 including
  - 3 researchers with teaching duties
  - 2 full time researchers, including 1 INSERM and 1 CNRS
  - 1 other researcher
  - 6 postdoctoral fellows
  - 4 PhD students, all with a fellowship
  - 10 engineers, technicians and administrative assistants

- Number of HDR : 6
- Number of PEDR : 1
- Numbers of students who have obtained their PhD from Jan 2004 to Jan 2008 : 4
- Average length of a PhD during the past 4 years : 3.5 years
- Number of « publishing » lab members : 5 out of 5

2 • Preparation and execution of the visit

The paper form of the quadrennial report was distributed to Committee members as soon as early October 2008 and the visit took place on February 3, 2009. A very comprehensive program including all the documents used during the sessions was given to all participants before the presentation. The first presentation given by the director summarized the background history, organization, scientific objectives, doctoral policy, budget and major achievements of the unit and its two teams. This was followed by two presentations by senior scientists involved in the two teams. All presentations were of very high quality, and they generated an extensive discussion. Two speakers were involved in the presentation of each team. The afternoon session was devoted to two roundtables, the first one, with technicians, engineers and secretaries, the second one with students. The visit was very informative and interactive pointing out an overall very good atmosphere. This unit includes a majority of young members and the committee had good opportunities to exchange with them. A short talk with the director allowed new questions to be considered from the previous meetings. Then, the committee members deliberated during one and half hour to reach to a final agreement on the evaluation of the two teams. The visit ended at around 6 pm.

3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

As a whole the Unit is likely one of major leader groups in the world in the field of renal genetic diseases.

Although the Unit has undergone important restructuring following the departure of the previous team 3 leader who left for a clinical position, the new organization of the group is highly coherent.

While keeping on with their original and efficient strategy of genetic studies, the investigators are now developing an important cell biology approach to investigate the role of the proteins derived from the candidate genes they have identified. To achieve this new orientation, the Unit has already developed a large panel of new in vivo and in vitro models and found the appropriate collaborations. This new strategy has already produced clear and fascinating data published in major journals.

The Avenir team is associated with team 1. It is very promising and already shows very good published results. However this team should be strengthened to reach a larger size suitable to compete efficiently in a highly competitive field.

The local, regional and national position is also excellent as the group has a leader position in several national projects. This group is also one of the leader groups of the IMAGINE project in Necker Hospital. The group and the director has been much involved in the development of local platforms and DNA bank.

The funding resources are very secure, the two teams appear to contribute quite equally and shared resources are clearly discussed. Finally, this unit has a large group of young investigators (5 doc and 7 post doc) most of them having an MD degree and strongly motivated. The weaker point is the partnership with industry but, considering that this is borderline with the field of investigation of the Unit, the committee has evaluated positively the efforts that the Unit has demonstrated in this direction. Altogether this Unit has the real potential to successfully develop the proposed programs.

4 • Specific appreciation team by team and/or project by project

Team 1 :

The work is focussing on two major topics : (1) Cystinosis and (2) Hereditary Nephrotic Syndrome with special attention to the Steroid Resistant Nephrotic Syndrom (SRNS). During the period of evaluation several important findings have emerged among which :

- Identification of a new protein interaction network between cystinosin (Ctns) and the proton-pumping vacuolar-ATPase and between cystinosin and galectin-3. This is a really new direction for the team besides their internationally recognized expertise in genetic studies. This new area includes the development of *in vivo* models (Ctns -/- mice) and *in vitro* models (various transfected cells). New *in vivo* and *in vitro* models will be developed : Ctns -/-, Gal 3-/- double knockout mice and cells derived from Ctns-/- mice and cell lines collected from patients urines. The expected results could account for deregulation in cell junction , cell polarity and provide new directions to explain proximal tubulopathy in cystinosis.

- Identification of the SRNS genes in 2 loci and identification of a novel gene (GMS1) mutated in Galloway-Movat Syndrome (a rare genetic disorder including nephrotic syndrome). The projects include characterization of the GMS1 protein by various approaches (Western blot, in situ hybridization, immuno-histochemistry) and generation of animal models (podocyte-specific Cre transgenic mice to knock-out the floxed GMS1 gene and Zebra fish).

The increasing understanding of the mechanisms of Nephrotic syndrome caused by genetically determined defect in podocytes allows the proposal for new therapeutic strategies (inhibitors of cyclin, antagonists of the renin-angiotensin system. This team has also participated in the characterization of a novel hereditary renal disease in collaboration with Inserm U 702. This team welcomes an Inserm Avenir team directed. Although this group develops his own independent project concerning glomerular pathology, given that, several natural interactions have been established with the other teams. The overall objective is to define the role of miRNA in Kidney development and function, and in renal diseases. To that aim, the miRNA profilings of normal kidney during development and in the various experimental model of chronic renal diseases will be compared. As well, the impact of podocyte-specific DICER, or miR-30, knocking-out on kidney development will be examined. The concept of miRNA deregulation is a new approach to investigate novel pathophysiological pathways.The funding of team I is excellent (Several grants) in spite of the uneasiness to obtain financial support from industry in this field. The team is involved in a european program.

Nom de l'équipe : Pathophysiologie de la cystinose et des maladies glomérulaires héréditaires

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+

Team 2 :

This team results from the restructuring of former teams 2 and 3 of U574 from 2004-2008 due to the new professional situation of one of its members. He left Inserm and is now at the Assistance Publique-Hopitaux de Paris to coordinate the Reference Center of Hereditary Renal Diseases of Children and Adults (MARHEA) and thereby maintains a part-time research activity. So the research project of team 2 combines the projects and includes three aspects of kidney developmental pathology.

1-Pathophysiology of nephronophthisis. This team was the first to identify a candidate gene for familial juvenile nephronophthisis. During the period of evaluation, they significantly extended the knowledge of the role of nephrocystins in this pathology by : (1) Identification of a novel mutated gene (RPGRIL1L also termed NPHP-8): the RPGRIP1L protein colocalizes with other nephrocystin genes products (NPHP-4 and –6; (2) Generation of a Rpgrip1L -/- mice: these mutants show renal microcystic dilatations of the proximal tubules (3) Identification of mutations in Meckel syndrome which can be responsible for liver fibrosis and cystic kidney disease; (4)Characterization of nephrocystin 1/4 complex using transfected epithelial cells and animal models (mice and Zebra fish). The *in vitro* data suggest that NPHP-1 and 4 may serve as docking proteins. They make the hypothesis that NPH-1 and -4 are involved in tight junction formation and that apico-basolateral and planar cell polarity. The *in vivo* data confirm a crucial role in the maintenance of kidney functions and provide a new model (Nphp4 -/- mice) to investigate new treatments. This part of the project already relies on very strong data.

2-Molecular mechanisms involved in diffuse mesangial sclerosis and Wilms' tumor(WT). This project results from the merging with former Team 3 previously headed by L Heidet who left INSERM for a position at Assistance Publique-Hôpitaux de Paris. This program, now headed by R Salomon (MD, PU-PH) is investigating the oncogenic mechanisms of different WT tumor classes reaching to the following recent results : (1) A significant association was found between a WTX mutation (a new Wilms tumor gene on the X chromosome) and the tumor aggressiveness. (2) A cellular model is under development to characterize the role of WTX in tumorigenesis.

3-Genetic bases of renal hypodysplasia as common developmental defects of the kidney. This project was initiated in former team 3 and will be developed with at least 2 objectives : (1) Characterize the genetics of RHD (Cohorts of Children through MARHEA (Centre de référence des maladies rénales héréditaires de l'enfant et de l'adulte). The collection of DNA is partly organized and supported by PHRC and ANR grants. (2) Analyse the consequences of mutations and other identified genetic alterations on kidney development.

All projects of team 2 are supported by grants. Since this team is showing a new organization, it needs time to reach an optimal efficiency. However it is important to underline that this team is already very succesfully headed by a 36 year-old investigator who has already proven her capacity to reach an excellent scientific production. The committee noted the complementarity between the different projects in terms of expertise, models and methodology necessary to cover the different aspects that are addressed.

Nom de l'équipe : Pathophysiologie de la nephronophtise et des hypodysplasies rénales

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

5 • Appreciation of resources and of life of the research unit

— Management :

We noted a clear organization regarding both the administrative and scientific. The various tasks of the laboratory are clearly assigned to one or several persons (biohazard management, purchasing orders, supervision of animal experiments etc…). The internal communication is organized around weekly scientific meetings of the whole Unit, on informal discussions and on the search for general agreement to major decisions which result in a very good general atmosphere and a great homogeneity of the two teams.

— Human resources :

This unit has a large number of talented young investigators thereby showing a huge human potential. The technicians are well "distributed" between both teams allowing a good balance in human resources within the Unit.

One important point appears the managements of short-term programs, the director is very much concerned by the future of the persons involved in such programs at the end of their contract. In every situation an extension period of the contract with a salary has been secured until stabilization of the position.

— Communication :

The director has a very high international visibility. This point should be improved for the team leader 2 who is still very young. Of note, the Unit is involved in education of patients through its participation to patient associations and family support groups. One web site is currently under development.

— Funding :

As noted before, the research Unit has an excellent level of funding obtained through numerous grants that are witness to the great impact of the research carried on by the group.

6 • Conclusions

— Strong points :

The original background of the unit relying on the genetic expertise, which obviously should be continued. The bedside–to-bench strategy followed has proven fertile since it has allowed to make significant progresses both in the understanding of genetic diseases and in fundamental biology.

The excellent collaboration with former members of the Unit ensuring the knowledge transmission in the field of renal diseases.

The excellent scientific level that has been achieved reflected by the excellent output in term of publications and grants.

Very strong links with the clinic ensuring sample availability.

The presence of two already established very young investigators showing also excellent international output.

The presence of several other promising young investigators who have already the level to apply for an established investigator position.

The active participation to doctoral formation and the presence of several MD in that cursus.

A very good team of technicians.

The project of developing in vivo and in vitro models to investigate the functions of the protein encoded by genes identified.

New areas of investigations and adequate collaborations (i.e.: roles for miRNA in kidney development and functions, roles of proteins in vesicular trafficking, cellular polarity and cilia function).

— Points to be strengthened :

The group acknowledges a weakness in bioinformatics which could be transiently overcome by funding a post doctoral position.

Although rare diseases are not a major concern of private industry, finding collaboration with industrial partners could be improved.

The new development towards cell biology should be strengthened by welcoming investigators that specialize in cell biology. As well, the Avenir group needs more support in order to face the high competition in its field.

The Team 2 should increase its international visibility mostly in term of invited conferences.

— Recommendations :

This group should be fully supported and reinforced by new young investigators to optimize the development of the very promising area covered by its research.

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+

UNIVERSITÉ
PARIS DESCARTES

Le Président
Axel KAHN

Paris, le 31 mars 2009

DRED 09/n°123

Monsieur Pierre GLORIEUX
Directeur de la section des unités de l'AERES
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Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'unité «**UMR-S 574 Néphropathies héréditaires et rein en développement** » rattachée à mon établissement.

Ce rapport n'appelle pas de commentaire particulier de la part de l'Université.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma meilleure considération.

Le Président de l'Université

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Néphropathies Héréditaires
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Corinne Antignac, Directeur

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Institut national
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Professeur Corinne Antignac

Paris, March 26, 2008

Remarks concerning the AERES committee report

We identified several inaccuracies in section 4 detailing our results and proposed research projects that we think should be clarified. Our main concern deals with point 2 in team 2. This aspect of the project has, in fact, almost been completed and will it not be pursued further. Moreover, the work was not performed by the persons indicated and I thought all names should be omitted in the report.
In addition, it should be mentioned that the *Rpgrip1l-/-* mice have been generated by our collaborators and that the work of our group has been to characterize the renal phenotype.

Corinne Antignac

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