Institut Necker - enfants malades - un centre de médecine moléculaire

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Institut Necker Enfants Malades

INEM

Under the supervision of the following institutions and research bodies:

Université Paris Descartes

Institut National de la Santé et de la Recherche Médicale

Centre National de la Recherche Scientifique

January 2013

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

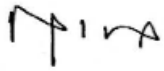
Research Units Department

President of AERES

Didier Houssin

Research Units Department

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 its in-house teams received the following grades:

- Grading table of the unit: Institut Necker Enfants Malades - INEM

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

- Grading table of the team 1: Cellular homeostasis and signaling in liver and kidney pathophysiology

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

- Grading table of the team 2: Epithelial channelopathies : Cystic Fibrosis and others diseases

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

- Grading table of the team 3: Inhibition of ribosome biogenesis: effects on cellular homeostasis and pathological implications

C1	C2	C3	C4	C5	C6
NN	NN	NN	NN	NN	B

- Grading table of the team 4: PRL/GH Pathophysiology: translational approaches

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

- Grading table of the team 5: Cell growth control by nutrients

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

- Grading table of the team 6: Mechanisms and therapeutic strategies of chronic kidney diseases

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

- Grading table of the team 7: Immunoregulation and Immunopathology

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

- Grading table of the team 8: Regulatory T cell biology and biotherapy applications

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

- Grading table of the team 9: Antigen presentation by MHC molecules : mechanisms and impact of Toll-like receptors

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

- Grading table of the team 10: Normal and pathological lymphoid differentiation

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

- Grading table of the team 11: Pathogenesis of systemic infections

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

- Grading table of the team 12: Development of the immune system

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

- Grading table of the team 13: Differentiation and physiology of T lymphocytes

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

Evaluation report

Unit name:	Institut Necker Enfants Malades
Unit acronym:	INEM
Label requested:	UMR, UMR_S
Present no.:	
Name of Directors (2012-2013):	UMR_S 783 – Ms Claude-Agnès REYNAUD, UMR_S 845 – Mr Gérard FRIEDLANDER, UMR_S 1002 – Mr Xavier NASSIF, UMR_S 1013 – Mr Peter VAN ENDERT, UMR_S 1020 – Ms Benedita ROCHA, UMR8147 – Mr Michel DY
Name of Project Leader (2014-2018):	Mr Xavier NASSIF

Expert committee members

Chair:	Mr Marc BONNEVILLE, Nantes University (CoNRS representative)
Experts:	Mr Renaud BEAUWENS, Free University Brussels, Belgium
	Ms Ariela BENIGNI, Mario Negri Institute, Bergamo, Italy
	Mr Gabriel CHOUKROUN, Amiens University (CNU representative)
	Mr Julian DAVIS, Manchester University, United Kingdom
	Ms Claudia MAURI, University College, London, United Kingdom
	Mr Richard MORIGGL, Ludwig Boltzmann Institute for Cancer Research, Vienna, Austria
	Mr Jean-Marc REICHHART, Strasbourg University (INSERM representative)
	Mr Jean-Christophe RENAULD, Ludwig Institute for Cancer Research, Brussels, Belgium
	Ms Federica SALLUSTO, Insitute for Biomedicine, Bellinzona, Switzerland
	Mr Alberto SANCHEZ-FUEYO, King's College, London, United Kingdom
	Ms Marina SANTIC, Rijeka University, Croatia
	Mr Tom TAGHON, Ghent University, Belgium

Scientific delegate representing the AERES:

Mr David DOMBROWICZ

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

Mr Stefano MARULLO, Paris Descartes University, Paris

Ms Stephanie POMMIER, INSERM

1 • Introduction

History and geographical location of the unit

The Necker campus currently encompasses 16 INSERM/CNRS/University research units located within the Hospital and in the Medical Faculty building. As of 2013, these units will be reorganized into 33 teams within two research institutes, Imagine (20 teams) and Institut Necker Enfants Malades (INEM) (13 teams). The Imagine Institute will be located in a new building, the construction of which is almost completed. Most INEM teams will be located in the Faculty of Medicine after its extensive refurbishment, which should be achieved within 2 to 3 years. In the meantime, several teams from INEM located in the old Medical Faculty building will move to a new location within the Broussais Hospital, at an approximately 30 min walk distance from the Necker campus. This move actually occurred few weeks before the site visit, so that currently INEM teams are in two distinct locations that are several km apart. This peculiar situation, which should last at least until the end of 2015, raises some organizational issues that will be detailed and discussed in the report. Strong links between the Imagine and INEM teams will be maintained through the "Structure Federative de Recherche" SFR Necker, primarily in charge of running the 13 core facilities of the campus.

INEM corresponds to the merging of five INSERM units: UMR_S783, UMR_S845, UMR_S1002, UMR_S1013, UMR_S1020 and two teams from the CNRS unit UMR_8147. This institute will gather 13 teams and around 250 people (including 60 senior scientists, 60 research assistants (technicians and engineers), 70 postdoctoral fellows and 60 PhD students). It will be structured around two departments : (i) the "Cell Biology" department, gathering 6 teams from the UMR_S845 that work on the pathophysiology of kidney and liver diseases, cystic fibrosis, metabolism and nutrition ; and (ii) the "Immunology, Infectiology and Hematology" department, gathering 7 teams derived from the five other units, currently scattered all over the Necker and Broussais campus. Within the new institute, some of these teams will undergo significant remolding, with merging or splitting of existing groups.

Management team

The INEM director will be Mr Xavier NASSIF.

There is no deputy director. However the director will be helped by a general secretary, and a management team that will include the department heads, an administrative head, four principal investigators, the "Hygiene et Securité" officer and a technology transfer officer.

AERES nomenclature

SVE1-LS4 and SVE1-LS6

Unit workforce

Unit workforce	**Number as at 30/06/2012** UMR_S 783 / UMR_S 845 E1, E2, E3, E5, E7, E8 / UMR_S 1002 UMR_S 1013 UMR_S 1020 UMR8147 E2, E4	**Number as at 01/01/2014**	2014-2018 **Number of project producers**
N1: Permanent professors and similar positions	22	24	24
N2: Permanent researchers from Institutions and similar positions	31	32	34
N3: Other permanent staff (without research duties)	35	36	
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	12	11	11
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	31	33	33
N6: Other contractual staff (without research duties)	23	16	
TOTAL N1 to N6	**154**	**152**	**102**

Percentage of producers	***100 %***

Unit workforce	**Number as at 30/06/2012** UMR_S 783 / UMR_S 845 E1, E2, E3, E5, E7, E8 / UMR_S 1002 UMR_S 1013 UMR_S 1020 UMR8147 E2, E4	**Number as at 01/01/2014**
Doctoral students	38	
Theses defended	55	
Postdoctoral students having spent at least 12 months in the unit*	23	
Number of Research Supervisor Qualifications (HDR) taken	9	
Qualified research supervisors (with an HDR) or similar positions	46	44

2 • Assessment of the unit

Strengths and opportunities

Strengths

- This institute gathers many outstanding teams in the field of immunology, metabolism, microbiology, hematology and nephrology. This is attested by an impressive number of publications in high profile journals (such as *Science, Cell, Nat Immunol, N Engl J Med, Cancer Cell, Cell Metab, Nat Med...*) and the presence of four ERC awardees.

- Several team leaders have a very strong international reputation, are actively involved in several international networks and regularly invited to write comments and reviews in prestigious journals.

- Several INEM founding teams have established strong and fruitful links with clinical departments, which have allowed significant diagnostic and therapeutic breakthroughs.

Opportunities

- Creation of a center into a single building should (i) improve the overall visibility and attractiveness of the participating teams and the Institute as a whole, (ii) foster new synergies, and (iii) lead to the structuration of a new institute with complementary expertise with the Imagine institute. It could also facilitate emergence of new "small" teams and team turn over.

- Funding from the IDEX "Sorbonne Paris-Cité" could help attract young researchers.

- A joint venture between the Imagine institute and INEM should facilitate access to new platforms and cutting edge techniques.

- The planned creation of a new animal facility, much larger than the existing one, offers new opportunities for implementing physiopathological projects.

- The move of several teams from Broussais hospital to Imagine will liberate space available for new teams. In this regard contacts have been already established with several candidates and a call for creation of new teams is planned this year.

Weaknesses and threats

Weaknesses

- The participating teams are currently scattered all over the Necker campus, which could hamper collaborations between the INEM teams and implementation of joint actions.

- There is a lack of concrete plans and budget for future organization of the Center (dedicated staff, new groups, career development, core facilities....).

- There is a lack of concrete budget for implementation of common policies and actions regarding : (i) PhD programs, (ii) internal seminars among immunology, hematology, microbiology teams, (iii) administrative support (e.g. informatics...), (iv) attendance and presentation at meetings and (v) organization of retreats involving the whole institute.

- There are no real interactions among PhDs and post doctoral fellows from different teams of INEM.

Threats

- The move from Necker to Broussais hospital (and vice versa when the Medical Faculty building is refurbished) could hamper attraction of new scientists.

- Several founding principal investigators are close to retirement: the outcome of their team when they retire remains unclear.

- There is a risk of creating a two-headed center with two independent departments.

Recommendations

- INEM should promote attraction of young researchers eligible for competitive starting grants.

- The management team should implement as soon as possible common policies for internal organization of the Center in order to create a campus spirit. In this regard, organisation of an annual retreat for the whole center could help establish internal collaborations and strengthen the overall coherence of the institute.

- The applicants should exploit the flexibility offered by the creation of the center to promote emergence of small teams led by young principal investigators.

- The institute should propose as soon as possible shared actions involving teams from the two departments to avoid splitting of the center into two distinct entities: eg common administrative support, etc...

- The managing team should prioritize actions that will foster interactions between PhDs and postdoctoral fellows: seminar series, PhD retreats, organization of seminars...

- Plans to ensure balanced allocations of permanent research assistants to the teams from INEM are strongly recommended.

- There is a need to create an external scientific advisory board able to perform a proper and objective SWOT analysis of the center and take when necessary tough decisions.

3 • Detailed assessments

Assessment of scientific quality and outputs

The committee has been impressed by the outstanding quality of many founding teams, who made since 2007 several major breakthroughs in basic and clinical research in diverse fields, such as antigen presentation, autoimmunity, T and B cell development, oncohaematology, chronic kidney diseases, epithelial channelopathies, prolactin receptor biology, metabolic diseases, or systemic infections (see team-by-team reports).

In this regard, the overall publication output since 2007 is quite remarkable, with more than 900 publications, including 122 with IF>10 and 35 with IF>20. The most salient findings have been published in several high profile journals such as: *NEJM* (4), *Science* (2), *Cell*, *Nat Med* (2), *Nat Immunol* (4), *Cell Metab*, *Cancer Cell*, *Sci Transl Med* (2), *J Clin Invest* (5), *PNAS* (8), *J Exp Med* (6), *PLoS Pathog*...

Importantly this excellent output is rather well balanced within the founding teams, since 11/13 teams have published several papers in high profile journals (IF>15).

Assessment of the unit's academic reputation and appeal

The excellent reputation of many INEM founding teams is supported by the following indicators :

- Four teams have been awarded an ERC grant (3 senior, 1 junior).

- Most INEM teams have been involved during the last 6 years in EU-supported networks (n = 17).

- More than 120 grants have been obtained since 2007 from national public agencies (eg ANR, PHRC,...) or charities (eg FRM, Ligue...), 13 grants from charities from US (eg Gates Foundation, JDRF...) or other foreign countries.

- Several team leaders have been invited to write comments and reviews in prestigious journals (*eg N Engl J Med for team* #1, Nat Rev Immunol, Nat Rev Endocrinol, N Engl J Med, J Clin Invest for team #7; *Immunity, Curr Opin Immunol* for team #9; *Annu Rev Immunol, Nat Rev Immunol, Curr Opin Immunol* for team #12; *Nat Immunol, Immunol Rev* for team #13...).

- Several principal investigators are in the editorial boards of major nephrology (eg team #1), immunology (eg team #9) or infectiology (eg team #11) journals.

- Principal investigators from the founding teams have been awarded by the Académie de Médecine (team #6), the Académie des Sciences (team #7 and #11), and the Société Française d'Immunologie (team #9). One principal investigator was appointed senior professor at the IUF (team #7), one has become a member of the French Academy of Science (team #12), and another one was recently awarded the CNRS silver medal (team #13).

- Principal investigators from the majority of INEM founding teams have organized, co-organized or have been invited at major international conferences (eg Gordon, FASEB : team #4 ; Keystone, Int Congress Immunol : team #7 ; Gordon, Eur Congress Immunol : team #9, Gordon, CSH.. : team #11 ; Keystone, Gordon, Eur Congress Immunol : team #12 ; Keystone, Int Congress Immunol : team #13...).

The founding teams have been able to attract on a regular basis a large number of postdoctoral fellows (currently 70, i.e. around 30 % of INEM staff), including many foreign ones from european and non-european countries. Nevertheless, although a young principal investigator that joined several years ago the UMR_S845 was recently awarded an ERC junior grant, the number of high profile junior researchers eligible for competitive starting grants (ERC junior, ATIP-AVENIR...) that have been attracted by the founding teams during the last six years has remained limited. This is probably due in part to the long standing uncertainties regarding the outcome of several teams located in the old Medical Faculty building, but also to the lack of a clear strategy to promote attraction of such researchers. Hopefully the creation of INEM could help address this key concern.

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

The links established by the INEM founding teams with the socio-economical environment are quite significant in several respects.

From an economical standpoint, the INEM teams have issued >20 patents (11 of which have been licensed), have created 3 start-up companies, and raised about 20 industrial contracts (eg with Cellectis (#2), Ipsen and Pfizer (#4), Roche (#6), GSK (#7), Servier and Medesis Pharma (#9), BioMerieux (#12)...). This is a fairly good output, but owing to the strong translational component of many topics addressed by the founding teams, it could be even better. Industrial links and tech transfer activities will certainly benefit from the creation of the Institute (which has planned to hire a dedicated tech transfer officer), and from the future move of INEM teams into the refurbished building, where a whole floor will be allocated to emerging companies.

From a biomedical standpoint, several translational and clinical studies (in many cases supported by the PHRC call) have been undertaken, thanks to the medical appointments of close to half of INEM senior scientists and location of several INEM teams close to the relevant clinical departments. Several principal investigators are directly heading clinical research reference centers (eg on cystic fibrosis), and take an active part in biobanking (eg on lymphoid malignancies). Several observations have resulted in new therapeutic approaches (assessed in phase I, II and even phase III trials) or new diagnostic tools, e.g. in metabolic, chronic kidney or autoimmune diseases. In summary, the overall biomedical output of the founding teams has been perceived as excellent by the committee.

Assessment of the unit's organisation and life

Since the decision to create an Institute gathering all the founding teams has been taken quite recently, it is too early to assess the overall coherence and internal life of the INEM as a whole during the last 5 years (see further comments in "Assessment of the five-year plan"). With respect to the founding units, their organisation and management policies have been quite heterogeneous during the last five years, mainly due to size disparities. The merging five years ago of several teams within the UMR_S845 unit has been quite successful, as attested by new internal collaborations and joint publications in high profile journals such as *NEJM, J Clin Invest, EMBO Mol Med*..., and by implementation of common policies regarding in particular administrative support or organization of internal seminars. Accordingly organisation and life in this very large unit have been perceived very positively by the UMR_S845 staff during the interviews with the evaluation committee. This successful joint venture has certainly helped convince the other INEM founding teams to merge within a single institute.

Regarding the other founding teams, the committee does not have particular concerns regarding their internal organization during the last five years, since they performed quite well even under a presumably suboptimal setting. However some small teams have suffered from a deficient or insufficient administrative and/or technical support, which has possibly affected their overall efficacy, attractiveness for PhD and postdoc fellows, and implementation of new programs. Creation of INEM could help solve these problems, provided that the founding teams are truly willing to establish and follow common policies within the new institute, in terms of administrative organization, PhD programs, organization of seminars and retreats, as well as research assistant allocations.

Assessment of the unit's involvement in training through research

Involvement of the founding teams in training through research has been fairly good, though heterogeneous from one team to another.

Above 50 PhD students have defended their thesis since 2007, > 50 master students and many clinicians (in particular hematologists) have been trained.

Most principal investigators have been involved in teaching in master courses, some of them have organized annual courses in proteomics, lipidomics and various DIU (eg on orphan diseases and endocrinology).

One principal investigator is chairing an international education program from the European Society of Organ Transplantation (Hesperis) with the aim of training high level transplant clinicians.

Despite this, the committee has been concerned by the lack of concrete and well scheduled plans to implement a PhD program, organization of internal student seminars and retreats, or any actions that could foster interactions between PhDs and postdoctoral fellows within or between the teams, and which could help create a real life within the Institute.

Assessment of the five-year plan and strategy

The rationale for creating a single institute gathering most Necker campus teams from the medical faculty is excellent. The founding teams have a real potential to create a center for molecular medicine with a strong international visibility in diverse fields, such as immunology, infectious and kidney disease, immune disorders, cystic fibrosis and endocrine disorders. Creation of INEM will most probably enhance the overall visibility and attractiveness of the founding teams, and help create a new research institute with complementary expertise with Imagine. It could also facilitate emergence of new "small" teams and team turn over. The move of most INEM to a single building should help establish new synergies and internal collaborations. Moreover since one floor of the refurbished building will be dedicated to start ups and other industrial partners, socioeconomical outputs will be probably boosted.

The two departments that will be created within the INEM will not have a dedicated budget, and thus will not have any specific means to implement their own strategy. While these departments could facilitate dissemination of information and enforcement of common policies within the Institute, there is a risk of creating two distinct entities with their own dynamics within the Institute, possibly aggravated by the scattering of several founding teams in the Necker and Broussais campus at least until 2015-2016.

Since the Cell Biology department is already well structured and has already established common organizational policies, it will be key to implement actions that will foster interactions between the two departments, and that all INEM teams comply to INEM policies and bylaws as soon as possible. Typically organization of annual retreats involving the whole institute rather than teams from a given department could help create an INEM "spirit", and avoid its eventual splitting into two distinct entities.

Several actions are planned in order to promote (i) attraction of young researchers through funding of starting grants, (ii) interactions between PhD students and postdoctoral fellows within the Institute (e.g. through organization of weekly or monthly seminar series), (iii) professional insertion of PhD students and postdoctoral fellows (e.g. through organization of courses to prepare job interviews or job searching and creation of an alumnus community and database), and (iv) communication and INEM advertisement (e.g. through creation of a website).

These are sound actions that will certainly strengthen the overall coherence of the Institute and its added value. In this regard, the possibility to fund starting packages for newly created teams through the IDEX "Sorbonne Paris-Cité" represents an excellent opportunity to attract young researchers to laboratory spaces that will be soon liberated in the Broussais campus, after the move of several teams to the Imagine building. Concrete plans to apply for such an IDEX call in the coming months were presented by the Institute and Department heads during the site visit, and several contacts with candidates have already been established.

However, the committee is concerned by the fact that no specific budget from the Institute has been planned yet for the other internal actions. Therefore how and when these will be implemented is at present unclear.

Another concern of the committee is that some teams from the "Immunology, Infectiology and Hematology" department do not seem to be really aware that their integration within the Institute implies significant changes in their current organization, management of their PhD students and postdoctoral fellows, and internal/external communication and exchanges with other INEM teams. As an example, the highly heterogeneous written scientific reports and oral presentations by the founding teams from the "Immunology, Infectiology and Hematology" department suggest a rather limited coordination of the preparation of the site visit by the department head, and presumably limited exchanges between the teams from this department before the visit.

The creation of INEM also represents an excellent opportunity to promote emergence of small teams lead by young principal investigators. Unfortunately most INEM teams turn out to be quite large, and in several cases correspond to the merging of several projects each run by a senior principal investigator who could have led a smaller independent yet highly competitive team. Moreover, while several team leaders are becoming quite old, whether their team will disappear when they retire, or will be taken over by younger researchers within or outside the institute remains unclear.

4 • Team-by-team analysis

Team 1 : Cellular homeostasis and signaling in liver and kidney pathophysiology

Name of team leader: Mr Patrice CODOGNO & Mr Gérard FRIEDLANDER

Workforce

Team workforce	Number as at 30/06/2012 U845 – E2	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	4	4
N2: Permanent EPST or EPIC researchers and similar positions	1	3	3
N3: Other permanent staff (without research duties)	5	7	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	4	4
N6: Other contractual staff (without research duties)	2	2	
TOTAL N1 to N6	**14**	**20**	**11**

Team workforce	Number as at 30/06/2012 U845 – E2	Number as at 01/01/2014
Doctoral students	1	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	4

Assessment of scientific quality and outputs

This team has been involved since many years in studies aimed at evaluating cellular and molecular mechanisms underlying the progression of renal lesions in chronic kidney disease with a particular perspective on phosphate homeostasis. Starting from the discovery of mutations of NPT2a and NHERF1 in patients with hyperphosphaturia, the determinants of Na-phosphate (Pi) leak have been dissected at hormonal level and Pi reabsorption focusing on the NaPO4 cotransporter type III, PiT1. The observation has been extended to the liver, and has led to the evidence that PiT1 has a role in liver development and pathophysiology. This team also described a new role of PiT1 in controlling cellular proliferation and apoptosis in the liver but also in other organs including the kidney. This team recently merged with another team showing much experience in autophagy, and will evaluate the role of autophagy in PiT1 function. The combination of these expertises could help find unexplored pathways of disease progression as well as broaden the observations on the kidney to liver diseases. The team would also provide the expertise on autophagy to other groups belonging to the Department and in the future to INEM. The availability of patient cohorts in Necker-Enfants Malades Hospital strengthens the value of this joint venture. The research activity of the team is well focused and the expected outcomes are clear. The methodology used is updated and involves the use of transgenic mice made by another team from INEM, confirming the interdisciplinary and intra-laboratory nature of the work. The availability of the experimental models will enhance the value of the results of the autophagy studies that so far did not provide significant data.

Both leaders have an excellent track record of publications with some papers as main investigators in Journals with IF>20 (eg *NEJM*) and many papers in the best specialty journals (eg 3 *Kidney Int*, 3 *JBC*, 3 *JBMR*...). They have also contributed to many collaborative articles published in *J Clin Invest, JASN (2), Cell Host Micr, EMBO Mol Med, JBC (5), Oncogene, Gastroenterol, JCEM (4)*...) as well as invited reviews and comments in high profile journals (eg *Nat Rev Drug Discov, Nat Rev Mol Cell Biol, Sci Signal, Nat Cell Biol, Mol Cell, Cell Metab*...). One of them has organized international meetings and both leaders were invited speakers to several international meetings. One principal investigator was part of the Editorial Boards of international nephrology journals.

Assessment of the team's academic reputation and appeal

Both leaders are internationally regarded and have a very good academic reputation, as attested by invitations to write reviews in prestigious journals such as *NEJM*. They closely collaborate with the groups of the Department and have international collaborations mainly based on projects dealing with phosphorus homeostasis. A high number of institutional and industry grants substantially contribute to the support of the research work on top of INSERM and University funds.

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

The project is of importance for the area of chronic kidney diseases, which are increasing worldwide at an alarming rate and will soon represent an unbearable economical burden even for developed countries. Both leaders have strong interactions within the Department, with Paris Descartes University and with national and international groups. The leaders organized international meetings and have been invited to national and international conferences. The team has issued one patent.

Assessment of the team's organisation and life

Although it is difficult to judge externally, the organization of the team seems to function well, although effective collaboration between the two senior scientists seems a bit artificial. The added value of this joint venture is not really attested by joint publications between the two sub-teams.

Assessment of the team's involvement in training through research

The team has trained several PhD students and post-doctoral staff over the past five years although the present number of post-doctoral staff and students is low with respect to people with permanent positions. One of the two leaders displayed teaching activity in Paris and abroad (Italy and Sweden).

Assessment of the five-year plan and strategy

The project is original and is a good example of translation research that fits with the mission of INEM. It is promising based on excellent past work with documented achievement records and productive research group with solid internal and external collaborations. Clear prospects with strong creative and cutting-edge research. The autophagy team should better integrate its work with the team involved in kidney and liver pathophysiology. The synergy of the two groups within the team will allow to define new pathways that should be targeted for therapeutic purposes. The team will need to recruit PhD students and young established researchers.

Conclusion

- Strengths and opportunities:

The combination of the expertise of the two leaders could help find unexplored pathways of disease progression as well as new targets for therapy in chronic kidney disease and liver cancer. The close links with the clinical departments and access to patient cohorts in Necker-Enfants Malades Hospital strengthens the value of this joint venture. The high reputation of the two groups together with the suitable research environment represents an opportunity to attract young investigators and possibly economic support.

- Weaknesses and threats:

The synergy of the two groups has great potential but seems to be a bit artificial yet. It should be actually strengthened. The team is composed by a high number of staff without research duties.

- Recommendations:

The two principal investigators should strengthen collaborations in order to enhance the added value of their merging within a single team. The recruitment of young scientists or PhD students is recommended.

Team 2 : Epithelial channelopathies : Cystic Fibrosis and others diseases

Name of team leader: Ms Isabelle SERMET-GAUDELUS & Mr Aleksander EDELMAN

Workforce

Team workforce	Number as at 30/06/2012 U845 – E1	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	2	2
N2: Permanent EPST or EPIC researchers and similar positions	4	1	1
N3: Other permanent staff (without research duties)	4	3	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	3	3
N6: Other contractual staff (without research duties)	2	2	
TOTAL N1 to N6	**14**	**11**	**6**

Team workforce	Number as at 30/06/2012 U845 – E1	Number as at 01/01/2014
Doctoral students	4	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	2

• Detailed assessments

Assessment of scientific quality and outputs

The team has a long experience and expertise in the field of cystic fibrosis and epithelial channelopathies both in clinical and basic research. Using original approach (proteomics, molecular modelling and experiments), the team identified new targets for functional correction of the main mutation of the CFTR gene; e.g. interaction sites with cytoskeletal protein, keratin 8. Two functional correctors interrupting this interaction were patented and will be further tested in animal models and possibly in humans.

The group is of high scientific quality in terms of number of publications and quality of journals in which these reports have been published (more than 100 publications including 5 papers with IF > 10 between 2007-2012, including 3 *AJRCC* as leading authors and *PNAS*, 2 *NEJM*, *Gastroenterology* and *AJRCC* as collaborators). The principal investigators have a good track record of competitive grant funding (from EU, ANR, INSERM, Paris Descartes University).

Assessment of the team's academic reputation and appeal

The lab is well recognized nationally and internationally in the field of cystic fibrosis, as attested by numerous invitations of the two PIs at international meetings (including several Gordon conferences). The team leaders have been quite active in organizing national and international conferences. They have a good network of international collaborators, in particular through EU-funded networks (one STREP, 2 Marie Curie projects and 1 TEAM). One PI is leading a clinical trial in cystic fibrosis. Moreover the team has attracted several foreign visiting researchers (eg from US and Germany). In brief, the principal investigators are clearly placed among the 3-4 world's most highly regarded research groups in their field.

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

Interactions with industry (collaboration with Cellectis supported by the Medicen pole), track of generating intellectual property (one patent issued regarding newly identified correctors for cystic fibrosis), plan to develop potentially useful clinical application are all excellent. A start-up company is being planned to foster transfer activities. From a biomedical standpoint, the team has been recognized as a reference centre of clinical research on cystic fibrosis within a European clinical trial network. Moreover it has raised a PHRC grant in 2010 on phenotypic of cystic fibrosis patients. One team leader has organized yearly meetings with cystic fibrosis families, has taken part in TV shows to present new cystic fibrosis treatments, has coordinated the establishment of international guidelines for cystic fibrosis, and has been involved in several review panels and evaluation committees at the national and international levels.

Assessment of the team's organisation and life

The structure is well organized within the Department of Cell Biology and a number of collaborations with the Department has been developed in the past. There are several ongoing collaborations with other groups within INEM, the Necker campus and international groups, and the team optimally interacts with the clinical service at Necker hospital. One of the two principal investigators is the head of the clinical Department dealing with children affected by cystic fibrosis.

Assessment of the team's involvement in training through research

The team shows a very good track of training at the postgraduate level. Between 2007 and 2012 the group has trained 12 PhD students, 7 post-doctoral fellows, and 16 Master 2 students.

Assessment of the five-year plan and strategy

The project focuses on mechanisms underlying the abnormal interaction between mutated CFTR and Keratin 8. It also aims to gain further insight in correctors interrupting this interaction at the molecular, cellular and animal levels. Importantly, the project includes a strong part of translational research linking correctors, inflammation and ion transport.

The strategic plan is very well thought out, is well supported by the expertise and track record of the principal investigators and funding for the coming years has been secured. The projects stem from several interesting recent findings that could open the door to potential clinical applications.

Conclusion

- Strengths and opportunities:

Outstanding basic studies are strongly supported by high quality translational research bed to bench and vice versa (co direction of the team and strong implication of the clinician leading the cystic fibrosis centre at Necker Hospital). The patented correctors are very promising for clinical trial within 5 years. The large spectrum of approaches (biochemistry, patch-clamp, human and animal electrophysiology) all used by the team gives credence for feasibility of the project.

- Weaknesses and threats:

No obvious weakness was identified. The committee suggests that for the application of 2018, an investigator of the quality of one of the current senior principal investigators should be attracted.

- Recommendations:

The 5-year plan will likely require participation of an industrial partner to be fully accomplished. This is still not ensured. The investigators are however planning to create a spin-off company that should address this potential threat.

The group should recruit young researcher in the next five years as one of the principal investigators is 60 year old.

Team 3 :

Inhibition of ribosome biogenesis: effects on cellular homeostasis and pathological implications

Name of team leader:

Mr Stefano FUMAGALLI

Workforce

Team workforce	Number as at 30/06/2012 U845 – E8	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	1	1	1
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**1**	**1**	**1**

Team workforce	Number as at 30/06/2012 U845 – E8	Number as at 01/01/2014
Doctoral students	2	
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
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 group joined INSERM U845 very recently (June 2011). Most of the results presented in the report were obtained during the post-doctoral stay of the principal investigator at the University of Cincinnati. The research interest of the group is to study the role of Ribosome Proteins (RP) in ribosome biogenesis and the cellular response to ribosome biogenesis inhibition. Briefly, the authors could show that RP depletion (in a mouse hepatectomy model) leads to p53 accumulation and cell cycle arrest. Systematic siRNA-mediated depletion of RP expression allowed to demonstrate p53 super-induction when biogenesis of both ribosomal subunits was blocked and to dissect molecularly the mechanism of this super-accumulation. Aims of the studies presently carried out by the two PhD students are the evaluation of p53-independent response to inhibition of ribosome biogenesis with a particular focus on IFRD1 and the regulation of RP mRNA translation through the functional characterization of 5' terminal oligopyrimidine tract (TOP) binding proteins. Both studies have been presented as posters by the PhD students who showed enthusiasm for their preliminary results. In collaboration with a group of INEM, the group will assess the effect of ribosome biogenesis inhibition on proliferation and survival of tumors. In collaboration with a group of IMAGINE, studies on experimental ribosomopathies will be conducted. This team has started to be productive with two articles (*Gene Dev* and *Mol Biol Cell*) in 2012. Two other articles (*Nat Cell Biol*) and a book chapter in 2009 and 2011 were published in the earlier laboratory. Overall, the team leader's track record is very promising.

Assessment of the team's academic reputation and appeal

The principal investigator has tight links with his former laboratory, but has already secured one "Ligue contre le Cancer" and one ANR grant in his new position. The team leader was invited at four conferences in 2009 and 2010, which shows the attractiveness of his research. Two PhD students have joined the team.

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

The team has outlined projects clearly based on and emerging from previous work in cellular responses to ribosome biogenesis. The project is original, based on several findings of the preceding period and proposes five aims, three of which have fundamental research outcomes (p53-dependent effects on cell cycle, effects on gene expression and regulation of 5' TOP mRNA translation). The last two aims are focused on applied projects and concern the pathogenesis of ribosomal checkpoints and the study of ribosome biogenesis in tumor model systems. The latter are clearly well in the frame of the new Department of Cell Biology "growth and signalling" and collaborations within this new Department should be fruitful. The project is a basic research proposal with a scarce reference to a translational approach. We recommend to strengthen the collaboration with clinical teams. This will add value to the proposal and be more attractive for future grants.

Assessment of the team's organisation and life

The group is very small and the principal investigator is doing interviews of candidates for post-doctoral positions. Meanwhile, one scientist is currently applying to CNRS for a CR1 position, supporting the attractiveness of the group.

Assessment of the team's involvement in training through research

This evaluation point cannot be addressed due to the fact that the team joined the Institute very recently.

Assessment of the five-year plan and strategy

The project is original but very focused on basic science research. It is promising based on excellent past work with documented achievement records and productive research group with solid international collaborations. There are clear prospects, with strong creative and cutting-edge research. If this small starting group is somehow reinforced during the upcoming 4 years, the prognosis should be good.

Conclusion

- Strengths and opportunities:

Excellent basic science with good translational prospects. The planned translational research should benefit from interactions inside the new Department. There is an excellent potential to collaborate with clinical scientists involved in rare diseases in Necker hospital and possibly outside.

- Weaknesses and threats:

This is still a small group, but recently reinforced by a post-doctoral fellow (ANR). The small size of the group makes international competition difficult, but the head of the group is well aware of this weakness and has chosen appropriate directions for his research. The translational approaches are still scarce.

- Recommendations:

More investigators should be attracted in the Unit.

To make the project more translational and better integrated in the context of the research of the Department, the proposed studies should be extended to ribosomopathies other than DBA and integrated with the basic research. The collaboration with clinical groups should be enhanced.

Team 4 : PRL/GH Pathophysiology: translational approaches

Name of team leader: Mr Vincent GOFFIN

Workforce

Team workforce	Number as at 30/06/2012 U845 – E3	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	1	1
N2: Permanent EPST or EPIC researchers and similar positions	1	3	3
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)	3	2	2
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff (without research duties)	2	2	
TOTAL N1 to N6	**11**	**12**	**8**

Team workforce	Number as at 30/06/2012 U845 – E3	Number as at 01/01/2014
Doctoral students	2	
Theses defended	4	
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	4	

• Detailed assessments

Assessment of scientific quality and outputs

This team is internationally highly respected, and the group is regarded as the opinion leader in the field of prolactin receptor biology and the translational opportunities offered by understanding the basic cell biology and physiology. The principal investigators have been world-leading in the field for many years, and it is particularly important that they have maintained this reputation since the retirement of the former head, and have continued to publish important papers that have led the way for other groups around the world. Publications are routinely in very good journals, usually top of their fields. The volume of outputs is very good for a group of this size, and has resulted from a strong network of external collaborations. This has certainly added considerable value to the work of the team and to the field overall. Although the team has not published in the very highest ranking journals such as *NEJM, Cell, Science* etc, they have two outstanding and strategically important papers as main investigators in *PNAS (2) and J Biol Chem (2)* in the past term as well as a key review in *Nat Rev Urol*, which lay the ground for much of their proposed future work, as well as a large number of important papers as coinvestigators in *Endocrinology, JCEM, J Mol Biol, Arthr Rheum, FASEB J, Mol Cell Biol,* and others.

A central collaboration has been established to realise the translational potential of the breast tumour work, and collaborative links are in place to facilitate the work on prostate cancer (for example access to valuable tissue collections). The prostate work is more based in animal models, but clinical translation and validation appears to be well supported by *ad hoc* collaborations.

The structural biology collaborative work on prolactin receptor structure is valuable for better understanding of the receptor function, and the resulting interaction with biophysical approaches including NMR has allowed important progress that would have been difficult or impossible otherwise.

Overall the committee would rate the team's performance in this domain as excellent.

Assessment of the team's academic reputation and appeal

The team is very well known in the field of endocrinology, and increasingly known in breast cancer/mammary biology and prostate cancer fields. In endocrinology, the group became internationally highly visible after the critical identification and characterization of the prolactin receptor by the team through the 1990s. With the development and characterization of effective PRL antagonists, the team has capitalised on this international lead to develop numerous highly effective collaborations in the past 10-15 years, and has extended the scope and wider significance of understanding PRL receptor biology.

The current principal investigator has been an active and collaborative leader of this group over the past few years, and his international leadership is exemplified by his enthusiastic nomination as the vice-chair of the former Gordon Conference, and then the Chair of the new FASEB conference on Prolactin and GH family, held in Colorado in summer 2012. The organisation of this conference has been very well received by numerous international teams. It has certainly enhanced the international reputation of the team as central to the discipline, and as leaders in the field.

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

The two lead principal investigators, have had strong interactions with the external scientific community, and both are well recognised international figures at endocrinology meetings. They have won grant awards from external agencies to support their collaborative programmes, though not very many large EU grants.

The group holds three patents, one option for exclusive licence for pharmaceutical development (with Ipsen), and several industrial contracts and consultancies (Ipsen, Pfizer etc). They have had over 30 MTAs in the past 5 years, indicating significant and valued engagement with the academic community.

Assessment of the team's organisation and life

Although this is hard to judge externally, the organisation of the team seems to function well, with effective and collaborative interaction between team members.

Assessment of the team's involvement in training through research

The unit has trained several PhD students and post-doctoral staff over the past five years as well as a number of visitors, as well as two recent clinical MD fellows.

Assessment of the five-year plan and strategy

The team outlines appropriate and exciting development of ideas regarding prolactin role in cell biology and tumour development, and lays out a sensible and translational programme that is well justified by the data gathered from the past 5 years.

The focus on prolactin (rather than GH) is appropriate, and the team has chosen to place most effort on breast disease, prostate cancer, and structural analysis of the full-length PRL receptor.

Breast cancer itself is a highly competitive area, and one that has been led by major teams that have taken a genome-wide view of the disease using broad screening approaches. Unless prolactin is found to have a clear significant role, there is a risk that it will be left behind as a relatively minor player. On the other hand, the team can argue effectively from its work with multiple fibroadenomatous disease that prolactin does indeed have a role in benign or pre-malignant breast disease that can be exploited as potentially both a biomarker and possibly a 'druggable' target. The interaction with Ipsen is extremely valuable in this regard, and may hold important therapeutic promise for the future. Indeed a recent paper in Nature (Curtis et al, 2012) indicated that breast cancer is a complex and heterogeneous mix of conditions with different molecular pathologies, therefore the team may well have a great opportunity to explore potential future therapy for a targeted group of patients, and PRLR may prove to be a valuable biomarker. The new collaboration with XenTech offers exciting new avenues to understand carefully chosen targets.

The team is relatively small but this is not seen as a big problem. Indeed the team is expanding and this will be valuable to maintain momentum and provide an exciting and competitive local environment for the investigators. The collaborative links are mainly external rather than internal within the Institute, but they are well chosen and highly appropriate for the targets of the team. There are in fact some developing collaborations with other groups in the Cell Biology group.

Conclusion

- Strengths and opportunities:

The team shows a strong international leadership in the prolactin receptor field, has established a strong network of effective collaborations, both clinical and basic, and has access to valuable biobanks. It has identified potential targets for therapy in breast and prostate disease. Funding has been secured by a good range of external income sources. New synergies and collaborative opportunities may be available with the new Institute.

- Weaknesses and threats:

The team is still quite small, with intense international competition in breast and prostate cancer.

Systemic prolactin antagonism might have unforeseen adverse effects in man (noting different prolactin gene expression patterns from rodents).

- Recommendations:

The team should sustain or even increase its size as planned in the report, with strong encouragement to junior researchers to join it.

It might be worth developing stronger collaborative links in the prostate cancer field to ensure that the team remains at the cutting edge, depending on the outcomes of the basic animal studies proposed in project 2.2.

Team 5 : Cell growth control by nutrients

Name of team leader: Mr Mario PENDE

Workforce

Team workforce	Number as at 30/06/2012 U845 – E5	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	2	2
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)	1	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	4	4
N6: Other contractual staff (without research duties)	1		
TOTAL N1 to N6	**10**	**10**	**8**

Team workforce	Number as at 30/06/2012 U845 – E5	Number as at 01/01/2014
Doctoral students	2	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	3	4

• Detailed assessments

Assessment of scientific quality and outputs

This team is internationally known for characterization of mouse mutants within the mTOR pathway, and had on this subject numerous french and international prestigious collaborations, as well as within the INEM. Specifically, the team has focused its activity on the study of nutrient sensing controling growth properties and metabolic disease. Major projects that have been pursued include : S6K/mTOR signaling, cell size control and muscle growth, nutrition and cancer. The scientific output is excellent and several new transgenic mouse models have been published. From 2007 up to now, seven publications in high quality international journals were produced in which first or last authors were members of this team. Thus, the group has generated first rated quality work published in major scientific journals as main investigator including *Nature Commun*, *Cell Metabolism,* two *J Clin Invest*, *Mol Cell Biol*, FASEB J and as collaborator in *J Cell Biol*, *Endocrinol, FASEB J, J Biol Chem, Sci Signal* and *Oncogene*.

The successful participation of the principal investigator in EU grants including a Junior ERC grant and a network participation in a EU 7th framework program have brought in third party grant money to the group and international recognition. In total, 12 grants have been attracted to the Necker campus, which causes also a diversification of multiple projects. This has strengthened financially the group and fostered attraction of new researchers.

Assessment of the team's academic reputation and appeal

This is a very attractive group well known in the field of the control of basic cell metabolism with emphasis on the mTOR pathway. The group has mastered mouse genetics and created mouse model of human diseases. The principal investigator has demonstrated an international leadership of successful collaborations.

Numerous contributions to international meetings were made, and the principal investigator has served as coorganizer of international expert meetings. Oral and poster communications at the most well-recognized scientific congresses in the field of S6K/mTOR signaling and metabolic disease have been given. For the size and composition of the group with 50% postdoctoral fellows, this is an excellent output.

Within the Necker-Enfants Malades Institute, several collaborations will develop with at least four other teams on the following topics : tubero sclerosis complex, lysosomal storage diseases and autophagy. Outside the Institute, french collaborations are ongoing with the Molecular pathology team at Hôpital Edouard Herriot, Lyon and an investigator at the Myology Institute, Paris). International collaborations are ongoing with at team at Stanford University (USA), with at team at ETH (Zürich) and with an investigator in Lausanne). Such collaborations have been quite fruitful, as asserted by numerous joint publications in high ranking journals, obtention of substantial funding from public agencies or international grant money, and several invitations of the team's principal investigator to participate as speaker in international conferences. In particular, the team leader is recognized as an international expert in the field of nutrient sensing and mTOR/S6K signaling where he achieves significant citation numbers over time (average citation number based on ISI WEB of Knowledge is 43).

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

The studies address fundamental questions, which could have therepeutic implications for several human diseases. Indeed, the group cares about rare genetic diseases with fatal consequences in patients, and brings towards a deeper understanding of disease mechanisms that could help find new therapeutic intervention strategies. This has a significant social and economic impact for affected families.

There are expected major interactions with pharmaceutical companies, and possibly with patient associations. This team has the potential to collaborate/establish partnerships with the pharmaceutical industry, although these potential collaborations are at an early phase. Typically inhibitors of YAP, mTOR, S6K or AKT could be tested in the models established by the team. To this end, contacts have been established with Lilly and Novartis to obtain specific inhibitors, and the INEM could support that further.

Assessment of the team's organisation and life

All the projets are related to mTOR signaling, and the interactions between each unit member are thus expected to be quite strong. There is one senior researcher who recently joined the laboratory and, together with the principal investigator, contribute to supervision of five postdoctoral fellows, PhD and master students. The principal investigator will supervise all six projects that were presented at the site visit.

Assessment of the team's involvement in training through research

The principal investigator has been involved in university teaching courses of up to 10 hours per semester.

Three students are expected to complete an outstanding PhD training. Given the high respectability of the group, some more trainees are expected within this program. Five PhD thesis have been defended since 2002, and were finished within 3-4 years with a publication in high impact journal, which is excellent for projects involving time consuming transgenic mouse models. In the committee's opinion, this is a significant number of students given the size of the team. In the composition of the team for the next five years, there are already PhD students enrolled, but significant international postdoctoral fellows recruitment is also planned.

Assessment of the five-year plan and strategy

The research plan is expected to yield new successful grants and implement “molecular medicine”, and eventually new molecular pharmacology.

This group has maintained a high standard for the last ten years and this will be probably increased or at least maintained in the future. The five-year plan involves a reorganization of the team, where leadership in six projects is also given towards the postdoctoral fellows or to the DR2 position present in the group. The major projects that will be pursued are based on : AKT/S6K/mTOR signaling, TSC loss of function and gliomas, metabolic and lysosomal storage disease or the study of hepatocellular carcinoma research in association with hyper AKT activation due to PTEN loss and strong activity of lipid metabolism pathways. All these topics are in line with the recent achievements of the team and clearly within the field of expertise of the team leader. The research project is logically focused on the pathophysiology of pathway defects around PI3K-AKT-TSC-mTOR-S6K signaling.

A particular emphasis could be given to research projects involving a significant number of patient samples. Here, hepatocellular carcinoma seems to be most promising target, and contacts with pharmaceutical industry could be strengthened. Most research is based on exploitation of state-of-the-art genetic mouse models and experimental interventions- technologies. In the committee's opinion, these are very interesting topics for research with clear pathophysiological impact. The projects might be quite diverse from the disease entities and a more prominent match with major human diseases should be taken into consideration, to achieve also a significant clinical impact in their model studies.

Conclusion

- Strengths and opportunities:

This is an internationally recognized leader group in mTOR research, performing very original work that integrates very well with other groups of Necker-Enfants Malades and expected to bring new paradigms and perhaps therapy in very different human pathologies. A strong collaborative network is in place.

- Weaknesses and threats:

No obvious weakness was identified by the committee.

- Recommendations:

The team could increase the number of trainees, and if possible attract PhD students by offering grant support. It could also strengthen its links with Necker clinicians especially for rare diseases which could help launching future clinical trials.

Team 6 : Mechanisms and therapeutic strategies of chronic kidney diseases

Name of team leader: Ms Fabiola TERZI

Workforce

Team workforce	Number as at 30/06/2012 U845 – E7	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	5	4	4
N2: Permanent EPST or EPIC researchers and similar positions	5	3	3
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)	1	3	3
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff (without research duties)	6	4	
TOTAL N1 to N6	**21**	**18**	**12**

Team workforce	Number as at 30/06/2012 U845 – E7	Number as at 01/01/2014
Doctoral students	7	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	7	5

• Detailed assessments

Assessment of scientific quality and outputs

The team focuses on the mechanisms involved in the progression of chronic kidney diseases (CKD). It uses a well recognized subtotal nephrectomy model of chronic kidney diseases to explore the signaling pathway involved in the compensation for reduced renal function by the remaining nephrons, the development of glomerular sclerosis and interstitial fibrosis. During the last 5 years, the team has brought insight into the understanding of cell proliferation in progressive renal injury, and identified Epidermal Growth Factor (EGF) as one of its major determinants. The future research plan is based on multifaceted approach that combines transcriptomic, proteomics, molecular biology, functional assays, cell culture and validation of the identified targets in remnant kidney mice bearing selective inactivation of the potential mediator. The project is supported by industrial partnership in order to develop possible specific pharmacological inhibitors. The team has developed in the past 5 years important collaborations with the Nephrology and Transplantation departments of Necker hospital, through several MDs playing important role in the lab. This collaboration allowed the completion of a translational approach, which has led to the study of biomarkers in the prediction of CKD progression in two different cohorts of patients, with ADPKD or kidney transplants recipients.

The quality of the scientific work is very good. More than 100 publications by the whole team in experimental and clinical topics in relation with the project were published during the last 5 years, including as main investigators *J Clin Invest, EMBO Mol Med, J Am Soc Nephrol* (2), *J Biol Chem and Blood,* and as collaborators *Nature Med, Blood, J Am Soc Nephrol*. Two patents applications are under evaluation by the European Patent Office.

Assessment of the team's academic reputation and appeal

The research team is well recognized and has a very good academic reputation. Each scientist has been invited to give conferences in national or international meeting and to participate or organize seminars. In particular, two of them were each invited in the last 5 years in at least 16 national and international conferences.

Two scientists from the team have received 3 French awards from the “Académie de Médecine” and “la Fondation du Rein”, and an impressive number of grants and funding by foundations (Fondation du Rein, Centaure, AIRG, ASTB), institutional (ANR, FRM, ABM, EEC) and industrial (Roche) partners, leading to a 5-fold increase in the income for the lab over the funding by INSERM and the University.

The very good reputation of the team has attracted an important number of post doctoral fellows from different countries.

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

The experimental project is of importance for the economic and cultural environment. chronic kidney diseases affects over 7 million people in Europe, over 300,000 people are treated either by dialysis or transplantation for end-stage renal disease, and this number is expected to increase by an average of 5% each year. Mortality of dialysis patients remains high and the risk of cardiovascular death is 4-fold higher in chronic kidney diseases patients.

A number of collaborations within the “Centre de Recherche Croissance et Signalisation”, with teams working in the Imagine Institute and outside the Necker Campus (Institut Cochin, Institut Pasteur, Europe, USA and Canada) have been implemented during the past 10 years, and should help achieve the research project.

Two patents applications are under evaluation by the European Patent Office, the first one on the identification of a novel therapeutic target and urinary prognostic biomarker of CKD progression to treat and predict the progression of chronic kidney diseases, and the second one on the discovery of an assay that could help predict the renal side effects of sirolimus. The team has developed a project supported by Roche Pharma.

Assessment of the team's organisation and life

The unit is composed of DR2 (1), CR1 (2), PU-PH and MCU-PH (4) who spend between 30 to 50 % of their time in the lab, 2 Post Doctoral fellows, 4 PhD students. Six engineers and technicians are completing the research team. The unit seems well managed by the principal investigators. It is difficult to assess the organization and life of the unit since the committee did not have the opportunity to visit the unit and meet with the administrative, technicians and engineers who are working in the group.

Assessment of the team's involvement in training through research

The unit has trained 10 PhD students, 5 Master and 2 Undergraduate students. Most of the researchers are involved with teaching within the University Paris V Descartes (Master Class, PhD Program, Medical Students, Residents in Nephrology). One scientist is responsible for the program “Hesperis” of the European Society of Organ Transplantation, with the aim of developing high level of Transplant clinician.

Assessment of the five-year plan and strategy

The research project has been dealing with the mechanisms involved in the progression of chronic kidney diseases since more than ten years. Progresses have been made by this group on the understanding of this process. This is attested by the very good scientific production during this decade.

For the next five years, the project will focus on the identification of activators and effectors of the EGF pathway driving renal injury after nephron reduction. The team will also develop research on new signaling pathways such as AKT/STAT and JNK on podocyte adaptation and survival during the process of glomerulosclerosis, interstitial fibrosis and tubular deterioration, three main mechanism involved in the progression of chronic kidney diseases in a number of experimental models and human diseases. Among the considered signaling pathways, interesting unpublished data have been recently obtained (and presented during the on-site visit as a poster), that suggest a protective role of AKT2 in podocyte damage. In addition, the team plans to elucidate the functions and the signaling cascades triggered by lipocalin 2. Finally, it will assess a panel of biomarkers able to predict the progression of chronic kidney diseases in several cohorts of patients. The tight collaborations with the physicians of the Nephrology and Transplantation Department in Necker Hospital, the expertise of this latter group in DNA and tissue collection started several years ago, as well as in biomarkers studies in plasma and urine, should help conduct this interesting project.

The project is a very nice example of translational research through the dynamic interactions established between clinicians and researchers. It should help improve our knowledge and find new treatments to avoid dialysis in patients with CKD. This effort will have a social and economical impact for developed and developing countries, for which the costs of dialysis represent an unbearable burden. The strategy is well presented. The team will need to recruit a new senior scientist in order to develop the project.

Conclusion

- Strengths and opportunities:

This is a well organized research team with a longstanding experience in the study of the mechanism of progression of chronic kidney diseases in animal models, with a good expertise in cell and molecular biology.

The team implements a multifaceted approach applied to experimental models and large human cohorts of patients with chronic kidney diseases.

It has established stimulating collaborations with other laboratories and clinicians within the Necker Hospital.

There is a very good complementarity between scientists and clinicians.

The team has secured funds from institutional agencies and pharmaceutical partners.

There is a number of young and dynamic scientists who work in the team and help conduct stimulating projects.

- Weaknesses and threats:

Two seniors principal investigators have to or will retire in the next 12 months.

The team leader will have the responsibility of a huge animal facility. She will have to manage her agenda to keep enough time to run the team, implement research plans and follow the students work.

- Recommendations:

Recruitment of a novel senior investigator as soon as possible is recommended.

Team 7 : Immunoregulation and Immunopathology

Name of team leader: Ms Lucienne CHATENOUD & Ms Maria Leite de MORAES

Workforce

Team workforce	Number as at 30/06/2012 UMR 8147 E1, E2, E3 & UMR_S 1013 E2	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3	3	3
N2: Permanent EPST or EPIC researchers and similar positions	4	5	5
N3: Other permanent staff (without research duties)	5	4	
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	6	7	7
N6: Other contractual staff (without research duties)	5	5	
TOTAL N1 to N6	**24**	**25**	**16**

Team workforce	Number as at 30/06/2012 UMR 8147 E1, E2, E3 & UMR_S 1013 E2	Number as at 01/01/2014
Doctoral students	6	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	6	

• Detailed assessments

Assessment of scientific quality and outputs

This team corresponds to the merging of two groups, working on the immunobiology of invariant NKT cells and asthma on the one hand, and on type I diabetes and immunotherapy of autoimmune diseases. During the last five years, the team has pursued in the autoimmunity field the assessment of an anti-CD3 mAb-based immunomodulatory strategy that it has pioneered and implemented new projects dealing with the role played by environmental factors on autoimmune and allergic diseases. On the NKT and allergic field, the team has characterized the differentiation pathways leading to the generation of Th17-polarized iNKT cells and deciphered the role played by human and murine iNKT cells in various physiopathological situations.

The scientific quality of these two groups is excellent, since both have consistently published in high impact factor journals over the past 5 years in their respective field. Since 2007 one principal investigator authored 73 publications including *PNAS*, *Am J Transplant* (2), *Sci Transl Med*, *Blood*, *Plos One* as main investigator. The other principal investigator authored 17 publications, including original publications as principal investigator in *PNAS*, *J Exp Med*, *Blood*, *J Immunol* (3), *J Am Soc Nephrol* and as collaborator in *Blood* (2) and *J Immunol*. Their recent merge within a single research group should help establish new synergies (eg on topics linking asthma, diabetes and innate receptor signaling, or diabetes *vs* asthma susceptibility in NOD mice).

Assessment of the team's academic reputation and appeal

Both principal investigator are well recognized experts in their field, and have been invited at more than 50 national and international conferences since 2007, including several Keystone Symposia and International Congress of Immunology, thus attesting their very high academic reputation. The team has been involved in several EU projects and was awarded a senior ERC grant focusing on the hygiene hypothesis. The reputation of the applicants is also illustrated by invited reviews or comments in prestigious journals such as *Nat.Rev.Immunol*, *Nat Rev Endocrinol*, *N.Engl.J.Med* and *J Clin Invest*. One principal investigator was awarded a prestigious prize from the French Academy of Science, and recently appointed senior professor at the IUF. The committee would rate them among the best scientists in their field worldwide.

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

The work on anti-CD3-mediated tolerance has been developed up to the level of clinical application (phase II and more recently phase III trials) with a major impact in the field. The work in asthma has also a component of potential clinical application that might have a direct societal impact. There is a credible plan to continue to develop transfer activities with strong clinical relevance.

Assessment of the team's organisation and life

The research team is a recent joint venture between the 2 principal investigators. The motivation to do so is based on a sound scientific rationale, and places the group in a very good position to establish synergies and have a strong scientific impact in their field. The unit organization is dynamic and well thought out, and has strong ties with clinical services at Necker hospital.

Assessment of the team's involvement in training through research

The track of training at undergraduate and post-graduate levels is excellent. At the post-graduate level, altogether 4 post-doctoral fellows, 7 PhD, and 13 master students have been trained and/or supervised by the research group since 2007.

Assessment of the five-year plan and strategy

The 5 year plan will be structured around four main research axes focusing on (i) analysis of the role played by iNKT cells and basophils in allergic responses, assessment of new immune biomarkers of severe asthma and implentation of immunotherapeutic strategies, (ii) analysis of the mechanisms underlying the immunomodulatory effects of anti-CD3 mAb that possibly result in a state of operational tolerance, (iii) investigation of the interplays between infections and autoimmune diseases and (iv) assessment and modulation of the immunological mechanisms controling implantation of allogeneic cardiac progenitors.

The project is well thought out and is the natural follow-up of the achievements obtained between 2007 and 2012. The collaborations recently established between the 2 principal investigators and involvement of experts in regenerative cell therapies ensures good feasibility of several projects within this quite ambitious strategic program. Nevertheless several issues will be addressed in a quite independent way by the two principal investigators and in these particular cases, the added value of the new joint venture is not always evident. Owing to the large number of issues that will be addressed, prioritization of the topics that will be addressed during the next five years and detailed description of the human and financial means allocated to each subproject would have been welcome.

Conclusion

- Strengths and opportunities:

The main strength is the high quality of the principal investigators attested by an excellent publication output during the last five years, and the fact that synergies between them have already been established. In addition, both principal investigators clearly benefit from close proximity with the clinical services, and as a consequence would be in a good position to develop their research up to a point where they might generate clinical useful information.

- Weaknesses and threats:

The current infrastructure limitations will constitute a threat over the next 2 years until the new building is completed.

A potential weakness/threat is the risk of not functioning as a team but as 2 different research groups. In this regard, the mechanisms underlying asthma vs type 1 diabetes and ways to counteract them might be very different, thus limiting the added value of merging teams working on these two fields.

There is a risk of diluting the work force into too many distinct projects.

- Recommendations:

The committee would encourage the team to better prioritize the projects that will strengthen its overall coherence and the added value of the new joint venture. There is currently a significant risk of dispersion.

Team 8 : Regulatory T cell biology and biotherapy applications

Name of team leader: Mr Jean DAVOUST

Workforce

Team workforce	Number as at 30/06/2012 UMR_S 1013 E3	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	2	2	2
N3: Other permanent staff (without research duties)	1	1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		1	1
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**3**	**4**	**3**

Team workforce	Number as at 30/06/2012 UMR_S 1013 E3	Number as at 01/01/2014
Doctoral students	3	
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

The team on "Molecular and cell biology of immune regulation" was established in 2008 and merged into the Unit U1013 in 2010. The team conducts basic and translational research in the field of dendritic cells (DCs) and regulatory T cells, in particular in the setting of gene therapy. Having established systems to generate antigen-specific regulatory T cells and adenovirus vector-mediated expression of transgenes, the team has defined conditions to induce regulatory T cells, and analyzed the interaction of these cells with dendritic cells. The results of these studies were published in two articles (*J Immunol* 2008 and *Eur J Immunol* 2010).

An interesting and more recent line of research deals with the use of miRNA-regulated lentivirus vectors to destabilize expression of transgenes in cells of the hematopoietic lineage, including DCs. The approach, originally developed by Mr Luigi NALDINI, aims at limiting induction of effector T cells by direct presentation of antigen while preserving induction of Tregs and establishment of immune tolerance. The system was used in a study on antigen processing and presentation conducted by another team within the INEM (and described in a Science paper published in 2009, coauthored by the PI).

The output of manuscripts from the work done primarily by the group has been rather limited in the last years (5 publications since 2007 in specialized journals). It appears that there was a serious limitation in the availability of mice due to a contamination in the animal facility. This has clearly impaired the possibility to run smoothly experiments and consequently to apply for grants, writing articles etc. One article has been submitted on the miRNA-regulated expression of transgenes and others are in preparation.

Assessment of the team's academic reputation and appeal

The principal investigator has gained an international reputation for his work on dendritic cells and for the development and use of cutting-edge technologies. He has been invited at a Keystone and EMBO meeting in 2007 but in the last few years, his international visibility has somewhat diminished.

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

The two main scientists of the team are co-inventors on a patent application filed in 2007 while working at Genethon.

Assessment of the team's organisation and life

This is a small team that is able to collaborate effectively with other teams, in particular with several other teams from the INEM. The principal investigators supervise together or individually the different projects that are performed by 4 PhD students and 1 Postdoctoral fellow and assistance from 1 technician.

Assessment of the team's involvement in training through research

Four PhD students are performing their work under the supervision of the two prinicpal investigators. The team also supervised the work of 3 Master students. Both team leaders have experience in training PhD and master students, the majority of which have pursued academic careers. The team leader teaches in master 1 and 2 courses.

Assessment of the five-year plan and strategy

The team aims to develop and further optimise gene therapy approaches to induce tolerance towards selected antigens ("gene transfer tolerance").

Previous work from the team leader showed that injection of HA-specific CD4+CD25+ T cells, from T-cell receptor (TCR)-transgenic animals, concomitant with gene transfer, down-regulates the anti-HA cytotoxic and B-lymphocyte responses and enables persistent HA expression in muscle (Blood 2003). Thus, he was amongst the first to demonstrate "gene transfer tolerance" as a viable therapeutic approach, and that it is possible to induce stable expression of transgene in solid tissues. The applicability of gene therapies remains controversial, as hundreds of clinical trials have been conducted withouth major success. However, the revival of the approach makes the research proposed by this team timely.

The two main aims of the research proposal are i) the dissection of Ag-presentation pathways after AAV-mediated gene transfer, and ii) the dissection of the antigen recognition properties of regulatory T cells. For the first aim, the team is studying CD8 T cell response to a model antigen (OVA) when expressed in a soluble or cytoplasmic form and in presence or absence of B cells or CD4+ T cell help. For the second aim, they are studying regulatory T cells in vivo conversion and expansion as well as interaction between Tregs and APC using confocal microscopy. One interesting aspect is the study of the cellular interactions between regulatory T cells, dendritic cells and mast cells in the dermis (collaboration with a member of CIML, Marseille).

Conclusion

- Strengths and opportunities:

The two principal investigators are long term collaborators and have complementary expertises. Thus, the decision to join forces is fully justified. External collaborations, for example with a member of CIML (Marseille), and internal collaborations within INEM, to study for example the outcome of cross-talk between plasmacytoid dendritic cells and regulatory T cells, have been very successful in the past and can continue to bring important scientific results that may lead to new therapeutic applications.

- Weaknesses and threats:

Whereas generation of new therapeutic approaches is certainly valuable (if successful it will generate substantial revenues for the Institution), the team should expand its horizon to more basic science approaches beyond regulatory T cells. Devoting all resources to a single objective, even if remarkably important, and without contemplating a contingency plan, is seen as a weakness in the team's research strategy.

- Recommendations:

Altogheter the committee feels that the output of this team and its future plans are good. Since some of the methodologies developed and used by the team are cutting edge, it is an added value to the INEM as a whole. One possibility to increase interactions would be to integrate this team within another one from INEM. To favour the initial transition the two team could share a PhD student or a post-doctoral fellow.

Team 9 : Antigen presentation by MHC molecules : mechanisms and impact of Toll-like receptors

Name of team leader: Mr Peter VAN ENDERT

Workforce

Team workforce	Number as at 30/06/2012 UMR_S 1013 E1	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)	1		
N4: Other professors (PREM, ECC, etc.)	1		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	4	4
N6: Other contractual staff (without research duties)	3	3	
TOTAL N1 to N6	**11**	**10**	**7**

Team workforce	Number as at 30/06/2012 UMR_S 1013 E3	Number as at 01/01/2014
Doctoral students	3	
Theses defended	7	
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	3	3

• Detailed assessments

Assessment of scientific quality and outputs

The research of this team has focused on proteases involved in antigen presentation by MHC class I molecules with a particular interest in antigens related to type I diabetes. During the last 5 years, this team made original and major contributions to the field such as the the demonstration that the IRAP protease is involved in MHC I cross-presentation and that TLR9 requires a proteolytic cleavage for signaling. Beside these main contributions, the studies on self antigens recognized by autoreactive T cells in type 1 diabetes and the design of strategies to restore immune tolerance are highly original. The quality of the work is reflected by the number of publications (42 original articles since 2007) including a series of publications as corresponding author in high ranking journals such as *Science* (2009), *Immunity* (2009) and *PNAS* (2012), as well as a series of co-authored articles in *Nat Immunol* (2009 and 2010), *J Exp Med* (2009) and *PNAS* (2008 and 2009).

Assessment of the team's academic reputation and appeal

This team has gained very high academic reputation by developing an expertise in original axes of research as mentioned above. This reputation is reflected by several invited reviews and comments in journals such as *Immunity*, *Curr Opin Immunol* or *Meth Mol Biol*, by many invitations to international meetings (including a Gordon conference and the European congress of Immunology), and by the fact that the head of the team is associate editor or international journals such as *J Immunol* and *Frontiers in Molecular Antigen Presenting Cell Biology*. This team also obtained a number of grants at the national (5 ANR grants) and international level, including the coordination of a EU network project and 3 grants from the US Juvenile Diabetes Research foundation.

The international reputation of the team is also illustrated by the numerous collaborations established with foreign teams throughout Europe and the US and that led to copublications in top journals as listed above.

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

The work of this team has significant socio-economical implications through its potential clinical applications. A patent application has been filed, describing a vaccination method targeting the antigen to cell surface receptors. Research agreements with pharmaceutical companies such as Servier or Medesis Pharma also underline the fact that this work has potential economical perspectives.

Assessment of the team's organisation and life

The group appears to be well structured with 2 permanent staff scientists, 3 postdoctoral fellows, 4 PhD students and 3 engineers on fixed-term contracts. Each of the 2 staff scientist is responsible for the independent supervision of the two main axes of research (IRAP-dependent antigen processing and TLR). The team appears to be organized in a way that allows the scientists to develop their project autonomously while fostering the obvious collaborations and bridges between these projects. The recruitment of a third staff scientist focusing more specifically on the thirs axis (diabetes-related studies) will likely be beneficial for this part of the project.

Assessment of the team's involvement in training through research

7 students have defended their PhD thesis since 2007 and 4 additional theses are in progress. 8 master (1 or 2) theses have been realized in the team. The principal investigator is actively involved in teaching immunology to second year medical students and in master courses.

Assessment of the five-year plan and strategy

The projects are perfectly in line with the previous achievements of the team and are based both on these achievements and on the original tools and experimental models it has developed. This provides them with a potential competitive advantage. The project is ambitious, but definitely feasible and matching the team's strengths.

Conclusion

- Strengths and opportunities:

The original expertise of the principal investigator and his international reputation provide him with a competitive position to advance further in his projects. The creation of the new institute will represent a major opportunity to extend further these projects by taking advantage of other models such as infectious models.

- Weaknesses and threats:

The committee did not identify any significant scientific weaknesses in the project.

Although the structure of the team seems appropriate and favors synergistic interactions between the staff scientists, there might be a threat that this structure does not encourage them to take their full scientific independence.

- Recommendations:

This team shoukd be encouraged to maintain its high level of scientific productivity and promote the acquisition of scientfic independence for the permanent staff scientists, which is not incompatible with keeping strong interactions with the head of the unit.

Team 10 : Normal and pathological lymphoid differentiation

Name of team leader: Ms Elizabeth MACINTYRE

Workforce

Team workforce	Number as at 30/06/2012 UMR 8147 E4	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3	3	3
N2: Permanent EPST or EPIC researchers and similar positions			
N3: Other permanent staff (without research duties)	1	2	
N4: Other professors (PREM, ECC, etc.)	3	2	2
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**7**	**7**	**5**

Team workforce	Number as at 30/06/2012 UMR 8147 E2	Number as at 01/01/2014
Doctoral students	1	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

This team includes two hematooncologists who synergize with the team leader on clinical and basic cancer research questions. Their research in the last five years have focused on lymphoid malignancies. During 2007-12 this team has yielded ~57 publications of which 25 were published in journals above 10 IF. Often first or last authors were members of this team. In particular, multiple articles were published as primary investigators in *Blood (3)*, *Leukemia*, *J Clin Oncol (2),* and some new mutational key findings on TLX homeodomain oncogenes just came out in *Cancer Cell*. This is an overall excellent track record and publication output, based on the number of people in this unit. High quality work is evident from several papers in the top journals in the field of hematology and oncology.

Assessment of the team's academic reputation and appeal

The team leader is recognized as an international expert in the field of lymphomagenesis, and more generally in hematopoietic cancer development and progression. This assertion is supported by numerous participations to international meetings. These include several oral and poster communications at the most well-recognized scientific congresses in the field of hematopoietic cancer. Most importantly, the team leader achieves significant citation numbers over time, with an average citation number based on ISI WEB of Knowledge of 28, which the evaluators call a highly significant output for a clinical research performing team. Overall, she is a well established clinical researcher that guided her group towards international standing and recognition. The implication of the team in several national grants (a total of 19 grants was successfully attracted to the Necker campus) brings in third party grant money to the group, and allows strengthening of key projects. Overall, a significant number of collaborations and the unique T-ALL (T-cel Acute Llymphoblastic Leukaemia) bank illustrate the excellent reputation of this unit and this would also suggests a strong appeal, although less evident for attracting new staff.

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

With two clinical group leaders present, this clinical research team participates in an active biobanking project on lymphoid malignancies which is of high value for the Necker campus. The three clinical researchers within this team harmonize and the team leader heads the consortium to strengthen clinical research on a high international visibility with the outpouring of many outstanding publications. Important for the INEM and the IMAGINE institutes are the provision of the biobanking of patient material. In terms of industrial partnership, the team has obtained 5 contracts from pharmaceutical industries, and licensed two patents. Therefore the overall interactions with the economical environment are excellent. Nevertheless, given the highly translational value of the work, more information could be provided on valorization of the results and how the group tries to identify new druggable targets.

Assessment of the team's organisation and life

This is a well-balanced team that sits at the interface of clinical and basic cancer research questions. This provides the team with a unique cutting edge position, resulting in highly translational work. The future organization of the Department and the unit should further strenghten and enhance the laboratory. Strategies to attract personnel are presently difficult since the Necker campus is under reconstruction and no permanent scientist with dedicated research to lymphoid malignancies exists in the group. The integration of the group into the new building will facilitate work routines and will help to attract expert personal to the group. The research interests of the three clinical prinicipal investigators are intertwined on one topic, namely mechanisms how haematopoietic cancers are generated and how they can be battled. According to the committee's opinion there has been a synergistic interaction between them over the past five years. Missing is a permanent full time scientist dedicated towards lymphoid malignancies, which could further strengthen the team.

Assessment of the team's involvement in training through research

The team leader has been involved in several lecture teaching courses, which seems justified and not taking too much of her time as a research investigator and manager. For the size and composition (the number of clinical hematologists that underwent training is 14 since 2007, where currently 2 are newly trained) of the group, this is an outstanding production with key clinical findings.

In the evaluated period, five PhD student defended successfully their studies and obtained a post-doctoral position, two master students are passing through the group per annum. Several PhD students are currently integrated in the team.

Assessment of the five-year plan and strategy

There is a good overall plan that builds on gathered expertise and that also engages novel avenues, thereby providing a challenging and ambitious concept that should lead to significant results. There is a strong clinical backbone that uses basic research for highly translational results. Funding and personnel to achieve the goals are tried hard to be renewed to support the experimental approach. The future research proposal outline is clearly written and structured towards translational research on the following central theme "how to classify and treat lymphoid malignancies, particularly of T cell or progenitor cell origin". The project is focused towards the analysis of human disease. The proposed experiments are a logic continuation from obtained results in the last funding phase. In a first project, the team will investigate which mutations and genetic aberrations are drivers for lymphomagenesis or generation of T cell leukemias. Core cancer pathways for T cell malignancies and mutations involved with disesase manifestation are studied at a molecular level. The second topic for the future project direction deals with lineage choices and transcription factors and epigenetic/chromatin regulators controling these processes. Overall this is innovative, but competitive research.

Conclusion

- Strengths and opportunities:

This is an excellent research team with a clear hypothesis in its research plan. The translational value is strong, as a result of an excellent interface between clinical and fundamental research. The team strongly benefits from the ETP-ALL database, and has established good local collaborations that allow further in depth investigation of hypotheses beyond the ‘in-house’ expertise. The team should strongly benefit from the new organisation of the Department, if appropriate reorganisation does occur.

- Weaknesses and threats:

Missing is a permanent full time scientist with dedication and passion towards lymphoid malignancies, which could further stengthen the group.

T-cell Acute Llymphoblastic Leukaemia is a competitive field, even locally in Paris and there seems to be limited interactions or collaborations with these groups, which might be improved once the new campus is refurbished. The hypothesis on the development of oncogenic thymocytes may prevent the search for alternative scenarios and should be reconsidered. Organisational restructuring should not lead to isolation of the unit, especially given the difficulty to attract scientific personnel in such a scenario.

- Recommendations:

This clinical research team should be supported without restriction and a permanent scientist position should be attracted to increase output. A relocation to a central building seems beneficial and wished.

Team 11 : Pathogenesis of systemic infections

Name of team leader: Mr Xavier NASSIF & Alain CHARBIT

Workforce

Team workforce	Number as at 30/06/2012 UMR_S 1002	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3	2	2
N2: Permanent EPST or EPIC researchers and similar positions	4	4	4
N3: Other permanent staff (without research duties)	5	6	
N4: Other professors (PREM, ECC, etc.)	2	2	2
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	3	3
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**16**	**17**	**11**

Team workforce	Number as at 30/06/2012 UMR_S 1002	Number as at 01/01/2014
Doctoral students	5	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	5	3

• Detailed assessments

Assessment of scientific quality and outputs

This team is part of the Department of Immunology, Infectology and Haematology. It studies pathogenesis of systemic infections caused by *Neisseria meningitidis* and *Francisella tularensis*. The systemic infections are very dangerous and often life-threatening, specially those caused by *N. meningitidis* and *F. tularensis*. The scope of research presented by the team is scientifically interesting and promising. The two principal investigators have made high scientific progress in their field. in particular they have studied interaction of *N. meningitidis* with microvasculature, which is a poorly explored aspect of bacterial pathogenesis. New investigation proposal approach is introduced which will in the long term contribute to still unsolved issue of drug delivery into the brain. Briefly, the group has shown that the MDA prophage is associated with invasive strains of *N. meningitides* by using a large epidemiological study on clinical isolates and that the active phage could increase the interaction between the bacteria and the host cell. It has dissected the components of type 4 pili (tfp) and shown that these tfp bind to CD147 and to the β2 adrenoceptor on endothelial cells, the latter triggering the formation of a cortical plaque and allowing bacteria to multiply at the surface of endothelial cells, eventually crossing the barrier. Finally, as there is no available animal model for the disease, *N. meningitidis* adhering only on human cells, the team has set up a very promising model by using SCID mice grafted with human skin, in which it could recapitulate the main steps of endothelial invasion. The other principal investigators expands his research on *L. monocytogenes* to *F. tularensis*, another intracellular pathogen. He has been investigating the molecular mechanisms involved in *F. tularensis* intracellular survival and *in vivo* dissemination, and have analyzed the strategies developed by these bacteria to survive and develop in the hostile intracellular compartment of the cell.

This team has been extremely productive : 66 primary research publications including several ones as primary investigators in top journals (*Science (2)*, *Cell, PNAS, PLOS Pathogen (2), Mol Microbiol*) and as co-investigators in *Plos Genet* and *J Exp Med*, several excellent reviews (*Nature Reviews* series) and two book chapters. Overall, the team track record is outstanding.

Assessment of the team's academic reputation and appeal

The team is internationally recognized. The leaders have already been involved in international and national projects, as coordinators or active partners (1 Biotox-PI, until june 2008; 1 ANRS Astrid from Jan 2013; ANR Blanc-Microbiologie, 2007-2010; ANR Blanc-Microbiologie,2010-2013; FRM contrat pluriannuel ,2010-2013; ANR Jeune Chercheur-2011-2014; Subvention Mairie de Paris, 2011-2014). The funding level is quite impressive for such a rather small team (7 permanent researchers at Inserm, CNRS or university hospital, 6 technicians, 3 post-doctoral fellows, 2 “hospital assistant” and students). Numerous fruitful collaborations have been established with several teams outside the institute, such as with 3 investigators from Grenoble University on the role of sRNAs in F. tularensis virulence, with 2 investigators at the Institute Cochin on N. meningitidis crossing of the BBB. The group’s visibility is very high with editorial duties and many invitations to speak at international meetings.

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

Projects within the team involve original methods and approaches in cell-cell-bacterial interaction, functional genomics and inflammatory signals in bacterial systemic infections. The topics addressed correspond to major public health issues and have strong biomedical implications. Translational activities are impressive with 4 patents filed during the period (two have been licensed) and the creation of a biotech (Andromas SAS), specialized in clinical microbiology.

Assessment of the team's organisation and life:

Regrouping of the department in a single building will promote interactions between the teams and facilitate collaborative research. The researchers within the team, comprising of immunologist, cell biologists and researchers in functional genomics investigating intracellular and extracellular bacterial pathogens, are synergistically organised. Many projects carried out by department teams are likely to use common technologies such as multi-parameter flow cytometric analysis, single cell PCR and Luminex assays for cytokine determination. The departmental teams plan to create a core facility equipped with a cytometer and Fluidigm machine for single cell PCR that will be dedicated to developing standardized protocols and assisting in their use by departmental members. The expertise of the team will be useful in setting up infectious disease models with natural or genetically modified microorganisms, which will be possible in the new animal facility. Collaboration with department immunologists should be welcome in some aspects of the research carried out by one of the principal investigator and a new scientist who will join the team end of 2013.

Assessment of the team's involvement in training through research

PhD training is integral part of every scientific group. During the period of 2007 and 2012, 13 PhD students defended their thesis under the supervision of 2 team professors. In addition, 2 scientists have obtained their "Habilitation à Diriger les Recherches (HDR)". Currently there are 4 postodoctoral fellows and 6 students (PhD and Master) involved in scientific research. Depending on available funds, the department will organize additional events allowing for scientific exchange, including yearly retreats, and symposia with representatives of the biotech industry and/or dedicated to specific subjects of interest. The involvement of many departmental investigators in European Concerted actions (e.g. the BLUEPRINT epigenetic consortium) will facilitate inter-European exchanges. Many team scientists devote significant time to teaching activities, being involved in organization and/or giving lectures in M1 and M2 courses, PhD programs, and training of medical students at Parisian universities (PRES Sorbonne Paris Cité including Paris Descartes and Diderot, UPMC, UPSud, Paris XII) as well as other national and international institutions.

Assessment of the five-year plan and strategy

During the next 5 years, the team intends to complete its work on the study of systemic bacterial infections. It will investigate the mechanisms of meningococcal interaction with endothelial cells, and study the pathogenesis of meningococcal infection by dissecting the interaction between meningococci and endothelial cells at three levels of analysis : the molecular level, the cellular level, using human endothelial cells from various origins, and the tissue level, using SCID mice grafted with human skin. This animal model that has recently been established in their laboratory is a clear asset and should provide a competitive advantage for the team. The team will also study the relationships between stress response and nutrition in *F. tularensis* intracellular adaptation. All of these projects are original and well described, including contingency plans. They take into consideration the collaboration with non-academic partners and translation of their basic research to clinical applied research. They have knowledge and capacity for adaptation and change in response to changes in the environment. The SWOT analyses are sound but could have been more detailed.

Conclusion

- Strengths and opportunities:

The team clearly benefits from the remarkable scientific achievements of the founding PIs in several original and specific research niches, and implementation of innovative approaches and models (eg in vivo model of infection to study the meningococcal cell interactions). Location in the hospital gives opportunity for more interactions between clinicians and basic researchers.

- Weaknesses and threats:

As possible weaknesses and threats, could be mentioned : (i) the lack of junior investigators in the group of founding PIs, (ii) the rather poor attractiveness of the team for postdocs, (iii) its temporary relocation in Broussais which will split the Institute teams between two different sites and might slow down some projects.

- Recommendations:

A new PI, who is presently group leader at the Biozentrum in Basel, is expected to join the team by the end of 2013. Her status should be clarified.

The two team leaders perform excellent basic science with strong translational output but real scientific synergism betwen their groups should be strengthened.

Team 12 : Development of the immune system

Name of team leader: Ms Claude-Agnès REYNAUD

Workforce

Team workforce	Number as at 30/06/2012 UMR_S 783	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	1	1
N2: Permanent EPST or EPIC researchers and similar positions	4	3	3
N3: Other permanent staff (without research duties)	7	4	
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	3	3
N6: Other contractual staff (without research duties)	2		
TOTAL N1 to N6	**21**	**12**	**8**

Team workforce	Number as at 30/06/2012 UMR_S 783	Number as at 01/01/2014
Doctoral students	3	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	6	3

• Detailed assessments

Assessment of scientific quality and outputs

This is an outstanding team that has made seminal discoveries in the past several years using original and innovative approaches. The present and former team leaders were the first to report the existence of marginal zone (MZ) B cells in human blood and to unravel the heterogeneity of the memory B cell compartment and the factor driving B cell differentiation. Among their recent outputs is the discovery that MyD88 and Trail are important for the differentiation of $IgM^+IgD^+CD27^+$ B cells but not memory-switched B cells. This work was done in collaboration with a member of IMAGINE Institute (Necker hospital, Paris) and was conducted through analysis of children with congenital immunodeficiencies.

Studies from the team have resulted since 2007 in many publications in high profile journals, such as *Nat Immunol* (2009), *J Exp Med* (2007, 2008), *Blood* (2008, 2012), *J Clin Invest* (2013)... Moreover several collaborative studies came out in *Nature*, *J Immunol* and *Mol Cell Biol*. In conclusion, the scientific quality and overall output of this team is outstanding.

Assessment of the team's academic reputation and appeal

The team is internationally recognised, as attested by the recent senior ERC award and integration in the French Academy of Science of the previous team leader. Moreover both present and previous leaders have been involved in the organization of large meetings, and were invited at outstanding international conferences (such as Keystone symposia, Gordon conferences, European Congress of Immunology). Furthermore they have been invited to write reviews and commentaries in prestigious journals (e.g. *Annu Rev Immunol, Nat Rev Immunol, Curr Opin Immunol*, *J Exp Med*). The previous and current team leaders have also served various evaluation committees (eg Aeres, ANR...).

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

Although the studies done by this team are primarily focused on basic issues, the biomedical implication of their findings recently drawn from analyses of some human immune-related disorders is quite significant. In this regard, the team recently issued one patent and has established several collaborative programs with industrial partners.

Assessment of the team's organisation and life

The team has attracted several talented young researchers. One of them recently left the team. It is unclear how autonomous are the two *Chargé de Recherches* and whether or not they will have the opportunity to implement their own projects within the team.

Assessment of the team's involvement in training through research

The number of PhDs trained by this team is rather low, with only one PhD thesis defended since 2007, and one PhD who left the lab after one year. The committee felt that it would be important to increase the number of Master and PhDs students in the coming years.

Assessment of the five-year plan and strategy

Overall the general questions that will be addressed in the next five years are appropriate and in line with recent achievements from the team. They will rely on implementation of sophisticated and elegant models and methodological approaches, the feasibility of which is attested by recently published and preliminary data. The project involves combination of studies in well controlled mouse systems, and more physiologically relevant (yet more difficult to study) human models, which is clearly a strength of the team. Moreover funding of these projects have been secured for the coming years.

Conclusion

● Strengths and opportunities:

The team is very well recognized for his major achievements in the field, and keeps on working on highly original research avenues both in murine and human models.

The ongoing collaboration with an investigator from the Imagine institute will undoutebly lead to more discoveries in the future on the role of specific genes in B cell development and differentiation in humans, a field which is at present very much understudied.

● Weaknesses and threats:

The current team leaders close to retirement and it is unclear whether or not the projects will be eventually taken over by younger researchers within the team or from outside.

● Recommendations:

There is no clear strategy of how these two senior scientists plan to support more established researchers in pursuing independent careers. To address this, recruitment of younger talented individuals is strongly recommended.

Team 13 : Differentiation and physiology of T lymphocytes

Name of team leader: Ms Benedita ROCHA & Ms Sophie EZINE

Workforce

Team workforce	Number as at 30/06/2012 UMR_S 1020	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	3	4	4
N3: Other permanent staff (without research duties)	3	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3	3
N6: Other contractual staff (without research duties)	1		
TOTAL N1 to N6	**10**	**9**	**7**

Team workforce	Number as at 30/06/2012 UMR_S 1020	Number as at 01/01/2014
Doctoral students	3	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	3

• Detailed assessments

Assessment of scientific quality and outputs

This team corresponds to a former INSERM Unit (U1020) conducting research in the field of T cells in normal and pathological conditions. The scientific quality of the unit is and has been historically excellent.

During the 2007-2012 period, the team has pursued several studies dealing with the in depth characterization of T cell memory. Among the major achievements of the team, can be mentioned (i) results suggesting different DNA repair capacities of primary vs secondary memory T cells, which could underly their distinct proliferation kinetics, (ii) new insights into the mechanisms regulating lymph node attraction of antigen-specific T cells and (iii) observations supporting opposite regulation of inflammatory vs cytotoxicity genes within proliferating T cells. The team also recently showed efficient and quick reconstitution of the peripheral T cell diversity accross MHC barriers following neonatal thymus transplantation. Since donor-derived T cells seem fully tolerant towards recipient MHC, these observations could have major clinical implications in the field of allotransplantation.

The team has published 12 original articles in high impact journals (such as *J Exp Med, Blood, Mucosal Immunol*) and has co-authored several original articles as a result of external collaborations (eg in *Nat Med, PNAS, J Exp MEd, J Immunol*...). The output with respect to novel research papers is expected to increase in the coming years as a number of important contributions seems to have been delayed as explained in the scientific report. Given the controversial nature of the work and the competitivness within the field, this is not uncommon.

Assessment of the team's academic reputation and appeal

The unit has an excellent reputation, as evident from the number of invited reviews and book chapters in high profile journals (*Nat Immunol, Immunol Rev*...), as well as from the invitations to give talks at international conferences, such as Keystone Symposia and International Congress of Immunology. Moreover several papers from the team have been highly cited. The team has been very successful in obtaining competitive grants not only from french agencies but also from EU (EU FP6 and FP7) and US (Gates Foundation). In 2009, one of the principal investigator was awarded the highly competitive ERC Advanced grant (over 1.9 million Euro for 5 years). She got the CNRS silver medal and received the Seeds of Science Prize from the Portuguese Ministry of Science in 2011. The team's appeal seems good based on the postdoctoral fellows that were attracted with the ERC grant. This should further improve after the building refurbishment and implementation of the novel reorganization of the whole department.

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

As already mentioned, some recent observations from the team could have exciting clinical applications, in particular those dealing with neonatal thymus transplantation or analysis of the mode of action of anti-CD25 therapeutic antibodies in ad hoc tumor models. Moreover implementation of a new project led by a new principal investigator that will join the team, which focuses on novel B cell subsets with tolerogenic properties, could have significant applications in oncohematology and organ transplantation. Nevertheless it is not explained if and how the results will be translated or valorised.

Assessment of the team's organisation and life

The unit has been historically built-up with two principal investigators with highly complementary expertise in the development and function of T lymphocytes. The addition of a new permanent scientist with which the team leader has recently established several collaborations has inspired the unit to engage in novel research areas, and should further strenghten the unit. The loss of the administrative assistant seems problematic and should be resolved to enable the scientific staff to focus on the scientific aspects of the project.

Assessment of the team's involvement in training through research

The unit has trained a high number (especially with respect to the number of postdoctoral fellows and/or permanent staff members) of master level and PhD students (11 PhD thesis defended during 2007-2012) and the quality of training is reflected by the prestigious laboratories where these students have gone for their further academic training. This highlights the strong scientific and training reputation of the unit.

Assessment of the five-year plan and strategy

The research plan is challenging and at the front-end within the field. The required expertise is available in the unit for the succesfull completion of the program and the strategic plan is logical with respect to the recently obtained results. Prominent results are to be expected with publications in high-profile journals.

Conclusion

- Strengths and opportunities:

Excellent team with complementary research expertises, that addresses highly controversial front-end research avenues within the field of T cell development and function. The strongest assets of the team are the unique molecular single-cell analyses and the expertise in in vivo T cell development and function. The additon of the novel permanent staff member provides novel strategic opportunities that the unit has embraced in its research program. The refurbishment of the lab, initially a significant weakness and threat as discussed below, should significantly improve the functionality of the unit, as well as its appeal for talented researchers.

- Weaknesses and threats:

As mentioned by the principal investigators of the unit, the biggest threat at the moment is the transient move to Broussais Hospital which might significantly hamper implementation of some projects. The impact of this move on projects based on tissue culture studies and mouse models will be difficult to predict, and require the establishement of a strong back-up plan that is not mentioned in the research plan for the coming years.

- Recommendations:

The team should get more administrative support to enable the scientists to focus on the projects. In this regard, integration of the team within INEM could help address this issue.

Possible issues with the mouse colony due to the move to Broussais hospital should be anticipated by the generation of a contingency plan.

5 • Conduct of the visit

Visit dates:

Start:	January 28th, 2013
End:	January 29th, 2013
Visit site:	Hôpital Broussais, Bâtiment Leriche Porte 9
Institution:	Assisstance publique-Hôpitaux de Paris, Université Paris Descartes, INSERM, CNRS
Address:	98, rue Didot. 75014 Paris

Conduct or programme of visit:

January 28, 2013

8 :30 – 9 :00 Door-closed meeting of the committee and AERES representative.

9 :00 – 9 :15 Introduction of the committee to the members of the Institute.

9 :15 – 10 :00 Presentation of the project (Xavier Nassif)
20 min, talk
30 min, questions

10 :00 – 10 :15 Coffee break

10 :15 – 13:00 Presentation of the departments and teams

	Sub-committee 1		Sub-committee 2
10:15 – 10:30	Presentation of the Immunology-Haematology-Infectiology department P. van Endert	10:15 – 10:30	Presentation of the Cell Biology department, "Growth and Signalling" G.Friedlander
10 :30 – 11:20	Team Reynaud (E12)	10:30 – 11:20	Team Goffin (E4)
11:20 – 12 :10	Team Nassif/Charbit (E11)	11:20 – 12:10	Team Pende (E5)
12:10 – 13:00	Team Rocha/Ezine (E13)	12:10 – 13:00	Team Edelman/Sermet (E2)

13:00 – 14:30 Lunch – Posters

14:30 – 18:00 Presentation of the departments and teams

14:30 – 15:10	Team MacIntyre (E10)	14:30 – 15:10	Team Fumagali (E3)
15:10 – 15:50	Team Davoust (E8)	15:10 – 16:10	Team Terzi (E6)
15:50 – 16:10	Break	16:10 – 16:30	Break
16:10 – 17:10	Team Chatenoud/Leite de Moraes (E7)	16:30 – 17:20	Team Friedlander/Codogno (E1)
17:10 – 18:00	Team van Endert (E9)		

January 29, 2013

9:00 – 9:30 Meeting with University, Medical School and INSERM/CNRS representatives

9:30 – 10:00 Meeting with

- researchers with permanent position (without Xavier Nassif)
- engineers, technicians and administrative assistants
- PhD. students and postdoctoral fellows

10:00 – 10h30 Coffee break

10:30 – 16:00 Door-closed meeting, committee members and AERES representative, eventually interrupted by a discussion with X.Nassif (including lunch)

Specific points to be mentioned:

Mr Tom TAGHON was not present during the on site visit but provided a full written report.

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

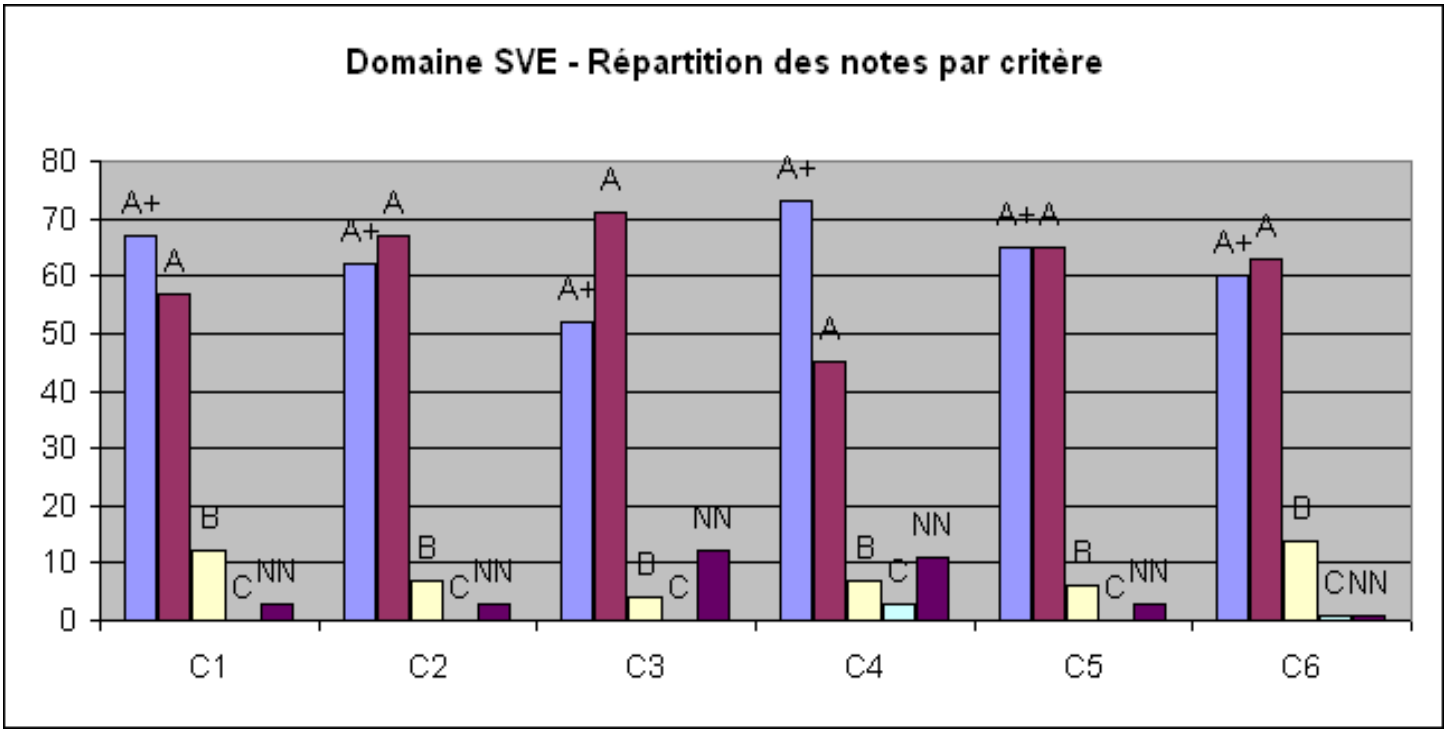
Grades

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

UNIVERSITÉ PARIS DESCARTES

Vice Président du Conseil Scientifique

Paris le 18.04.2013

Vos ref : S2PUR140006472 –Institut Necker – Enfants Malades – Un Centre de Médecine Moléculaire - 0751721N

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
Agence d'Evaluation de la Recherche et de l'Enseignement Supérieur
20, rue Vivienne
75002 PARIS

Monsieur le Directeur

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité « Institut Necker – Enfants Malades – Un Centre de Médecine Moléculaire »

Vous trouverez ci-joint les réponses du Directeur du Centre, Xavier NASSIF, auxquelles le Président et moi-même n'avons aucune remarque particulière à apporter. Nous aimerions cependant insister sur l'importance stratégique de la création de ce nouveau centre qui viendra complémenter avec le même niveau d'excellence le centre IMAGINE qui lui est dédié à l'étude des maladies rares.

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

Le Vice Président du Conseil Scientifique

Stefano Marullo, DM, DesSci

Université Paris Descartes, Vice-présidence du conseil scientifique, 12 rue de l'école de médecine, 75170 PARIS cedex 06
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Answers to the AERES report on the Necker-Enfants Malades Institute

We first wish to thank the members of the visiting committee for their time and suggestions. We certainly appreciate the effort that required the assessment of such a project. We are pleased that the visiting committee appreciated the high quality of the research that is performed by all member teams. Below we wish to address the weaknesses and threats perceived by the commission and comment on the suggestions made by it.

ANSWERS TO THE GENERAL COMMENTS

Weaknesses

(i) The teams are scattered over two campuses

The groups of INEM will eventually be housed in the medical school building located on the Necker campus. However this building has to undergo extensive refurbishment to remove asbestos and meet current fire security and general building code regulations, so that there was no other option for the majority of the INEM groups than to relocate temporarily in a new facility located in the former hôpital Broussais. It should be pointed out that the funds necessary for the refurbishing of the medical school building have been obtained and secured by the University. In addition the "permis de construire" that was necessary to start the operation was recently obtained. Renovation followed by refurbishing of the building is scheduled to start in the autumn of 2013, this should allow us to move into the renovated facilities by the end of 2015 or early 2016. So the present situation should not last more than 2 years. It is unfortunately inevitable that the INEM groups will be located in two places which will limit the informal exchanges between members of various groups. However, we are actively doing our best to enhance interaction and foster exchanges despite this adverse context. Thus although the institute does not exist formally at this time, we have started a weekly INEM seminar series and will organize a first annual retreat this fall. Furthermore the PIs from the two locations will meet on a regular basis in the steering committee which will be in charge of administering the Institute.

The initial location of the Institute on two separate campuses was a real threat until the funding for the refurbishing was obtained and secured. Now that all participants are aware that this situation is temporary, we do not feel that there is a risk of the Institute being split. In addition, we have already started actions (see below) in order to favour the exchange between the various groups.

(ii) Lack of concrete plans and budget for future organization of the center

We disagree with this comment.

- As mentioned during the site visit, all core facilities are not only shared entirely within INEM but also shared with the other Institute on the Necker campus, the Imagine Institute. These core facilities will be run administratively by the Structure Fédérative de Recherche (SFR). The budget for the SFR will be provided by the two Institutes (INEM and Imagine) and we hope to receive funds for this SFR from the University, the INSERM and CNRS. The fact that neither the source nor the amount of the SFR budget are known at this time may be a matter of concern but is due to current uncertainty about the general policies of these institutions on which unfortunately we have no influence.
- Dedicated staff. INEM has a Secretary General, Bernadette Arnoux (DR CNRS). Dr. Arnoux will be in charge of supervising the INEM administration, She will be helped by Martine Roulet as director of the administrative platform. The human resources necessary for

these platforms are provided by the founding units. Concrete planning of core facilities and administrative platform was part of the submitted INEM project.
- Recruitment of new groups. Each department has already published calls aiming at recruiting new faculty members (1 or 2 per department). Auditions of candidates for joining the Cell Biology Department have just been completed, and triage of applications for joining the I2H department is underway. These new groups will be hosted in laboratory space emptied at the end of 2013 by 3 teams relocating to the new Imagine building. With regard to start-up funding for the new teams, we anticipate that the recruited investigators, who will be selected primarily according to excellence, will have strong potential of obtaining prestigious and well-funded grants (ERC, ATIP/avenir). We will also work with the University to obtain start-up funds from the IDEX and we intend to apply for "Chaire d' excellence" positions from university, INSERM and private sources (e.g. AXA). We will also consider using a part of the lump sum funding INEM is expected to receive from INSERM, University Paris Descartes and CNRS, to fund salaries or equipment of new investigators. However this option is unlikely to be required for most new recruits and will be evaluated on an ad hoc basis as a back-up solution, so that attributing a fixed sum for it is neither necessary nor useful.

(iii) Lack of budget

It is correct that at the time of the site visit no detailed budget was ready. We are presently working to evaluate all common expenses at the level of INEM and to elaborate a detailed budget. Administrative support will evidently be funded by the common INEM budget. We are puzzled by the notion of funding meeting attendance for INEM scientists out of the common budget, as this obviously seems to be an expense to be funded by individual teams (grants usually include funds for it). While a definite budget will require approval by the steering board including all team leaders, these have already agreed to allot a significant amount to seminar series and to an annual retreat. It should be pointed out that at this stage we do not know the overall budget available to INEM from INSERM/University/CNRS, which will be determined in early 2014, a fact not facilitating detailed planning. As said above, it is also difficult to anticipate some spending items such as support for the recruitment of investigators, however this is our number one priority and we will do everything we can to attract new excellent investigators.

The committee suggested that INEM devotes funds for a PhD program. The INEM members consider that this does not seem mandatory, as Université Paris Descartes runs a well-organized PhD program in which the students trained in the INEM teams are enrolled. Establishing an additional PhD program would require first of all a clear rationale, but also significant funds that are presently not available, and administrative support.

Threats

(i) The move from Necker to Broussais and vice versa

While the necessity to move labs in two years' time obviously does not add to the attractiveness of our Institute, we do not think that this fact has a significant impact on our ability to recruit new scientists. We feel confirmed in this view by the reactions of the outstanding candidates already interviewed by the Cell Biology department who are much more concerned about the availability of core facilities and about interactions within INEM, with Imagine and with hospital than by this aspect. The laboratory space that will be made available on the Broussais site at the end of this year is newly renovated and refurbished and

thus does not lack attractiveness. Moreover, the idea of moving back to Necker to a completely renovated and refurbished building on the Necker campus is without any doubt attractive for all candidate investigators that have been in contact or are interviewed by us.

(ii) Several PIs are close to retirement : The outcome of their team when they retire remains unclear.

It is a fact that some PIs will retire soon after the end of the coming 5 years period. However, all team leaders concerned are aware of this issue and have taken steps to address it. While this written reply is not the place to name people, the team leaders and steering board are prepared to discuss details concerning each team with the reviewing committees.

(iii) Risk of creating a two-headed center with two independent departments.

We feel that this is an unjustified comment. First the set-up and administrative rules of the Institute have been conceived such that this risk is minimized. Rather than having distinct budgets, the two departments will share the same budget. The core facilities are run by a shared entity, SFR (see above). According to our internal rules of procedures that have been approved by all the founding PIs, all major decisions are taken by a vote of the "Conseil de Direction" which includes the PIs of both departments. As an example, the leaders of the I2H teams have participated in auditing all candidates for recruitment to the Cell Biology Department, and will have voting rights when it comes to selecting the candidates accepted. Other relevant measures such as our common seminar series or annual retreats have already been mentioned above.

Recommendations

(i) Attract competitive young researchers

This is already underway as detailed above.

(ii) Common internal policies and annual retreat

The policies are already adopted, and the annual retreat is planned for this fall.

(iii) Promote emergence of small teams led by young principal investigators

Insofar external young investigators are concerned, our efforts of recruitment already address this. Regarding the creation of independent teams led by young investigators already working in the existing INEM groups, the Institute will be open to the possibility of corresponding internal re-organization. The decision to split existing teams in this manner will have to be weighed against the necessity to organize the succession of retiring team leaders (another recommendation by the jury), the scarcity of technical laboratory support rendering team division more difficult, and the general funding situation.

(iv) Shared administrative support

This is already implemented, see above.

(v) Fostering interactions between PhD students and post-docs

A seminar series has been created. We will also encourage our young colleagues to propose and create additional formats of scientific exchange run by them. This could for example take the form of inter-department journal clubs or presentations of PhD and post-doctoral projects, retreats organized specifically for presentations by young scientists, and "TGIF" get-togethers.

(vi) Balanced allocation of tenured research assistants

It is correct that some INEM teams have very little or no technical support by permanent staff. It will be difficult to impose re-allocations of present technical staff between existing teams, as the concerned staff generally will have specific expertise adapted to the present teams as well as some "team loyalty" that makes moving complicated. However, the Institute will have a policy of attributing staff newly recruited by Université Paris Descartes, INSERM or CNRS, or staff wishing to change teams, with the objective of balancing technical support between the different teams.

(vii) Appoint external scientific board

We agree that an SAB will be highly valuable in guiding INEM policy and critical decisions. We will seek to appoint an SAB in the near future.

ANSWERS TO TEAM SPECIFIC COMMENTS

Team 6 (Fabiola terzi)

There is a misunderstanding concerning the role of Fabiola Terzi in the animal facility. In the weakness of her team, it is written that "she has the responsibility of a huge animal facility", which could take too much time. It has to be pointed out that Fabiola Terzi does not have this task. In fact, she is only the scientific advisor of the animal facility. A veterinary surgeon, Corina Dragu, was specifically recruited for the managing our animal facility two years ago

Team 8 (Jean Davoust)

We thank the AERES committee for their appreciation of our program and for their comments and recommendations, which adequately reflect our own perception on how to improve the insertion of our team of a small size within the INEM structure.

We wish to provide here an update of the scope of our collaborations within the INEM structure and of future scientific prospects of the team, in response to the recommendations of the committee.

History and workforce of the team

Our team was created as a new entity within UMR_S1013 with the arrival of Jean Davoust and the recruitment of David Gross in 2008 at INSERM and now comprises eight members, including one postdoctoral fellow and four PhD students. Our team acquired its current format after being granted with an ANR JC contract to David Gross in 2011 leading to the recruitment in September 2012 of a postdoctoral fellow, Pascal Chappert. Pascal Chappert previously accomplished a postdoc at the NIH Bethesda USA, and authors several first

authorship papers including a recent manuscript in final revision in Immunity. Pascal Chappert will develop his project in our team and plans to apply for a tenure track position at INSERM or CNRS in the future.

Update of our collaborations within INEM

1) Consolidation of our collaboration with the team of Peter van Endert. As stated in the ANR JC project of David Gross and in our AERES report documents, Pascal Chappert will pursue the collaboration engaged with Loredana Saveanu (team of Peter van Endert) to decipher the molecular and cellular determinants controlling the cross-priming and cross-tolerance pathways revealed in vivo with our different AAV gene therapy vectors. To strengthen this collaboration between the two teams, we have engaged a new PhD student in September 2012 on this topic (Alexandre Ghenassia under the supervision of Jean Davoust, co-supervision Pascal Chappert).

2) Extension of the collaboration with the team of Lucienne Chatenoud. Following the recommendation of the AERES committee to provide a contingency plan for our research project, we will extend our actual collaboration with the team of Lucienne Chatenoud – Maria Leite de Moraes based on our know-how on intravital imaging. We propose to breed, in the INEM mouse facility our dendritic and mast mouse models (initially engineered and used in collaboration with Bernard Malissen at INSERM CIML Marseille) with various autoimmune disease or allergy prone mouse models. This will allow us to decipher interactions between components of the innate immune system and T lymphocyte compartments. First, the ongoing collaboration initiated by Chantal Kuhn within the team of Lucienne Chatenoud on pDC-Treg interactions will be completed and second we will set up a follow up collaboration plan and engage a new postdoctoral or predoctoral fellow to pursue a jointed project.

3) Other ongoing collaborations. Importantly, as exposed to the AERES committee, we are preparing what we wish to become a land mark manuscript in collaboration with Pierre Launay (INSERM Bichat, Paris) and Bernard Malissen (INSERM CIML, Marseille) on the role of mastocytes in the skin during various immune challenge using our cutting edge expertise in intravital confocal imaging of skin dendritic cells, mastocytes and regulatory T cells.
Of note, our group has also established scientific and technical interactions with the team of Olivier Hermine belonging to the Imagine Institute (studying the role of regulatory T cells in MSC-treated mouse models of chronic GVHD and using various forms of antigens in AAV vectors to study the role of Nrp1 in CD8 T cell immunity).

Future prospects of the team in response to scientific comments raised by the AERES committee

The AERES committee has emitted a specific recommendation to initiate collaborations with other teams in order to prepare a future integration of the team within another one in the INEM. This recommendation results from the appraisal of our publications, the perception of our scientific objectives and of our skills in intravital fluorescence imaging.

We wish to bring several facts to the attention of the committee, regarding our publication list, our scientific objectives, integration of new members of the team and positioning within the INEM I2H department, all of which support our contention that our new team has reached a mature state and ought to become very productive as an independent entity in the future.

1) Our publication list has recently been implemented by two papers submitted from the team (1-2), one collaborative paper accepted (3) and one paper in final revision in Immunity by Pascal Chappert et al., (4) testifying the skill and personal achievement of our newly recruited postdoctoral fellow.

2) Importance of our project for INEM. In response to the comments of the committee, the gene therapy immunology topic we bring in the future INEM center dedicated to molecular medicine i) is at the frontiers of viral immunology and ii) is of importance for the growing field of gene therapy, where immune response to the vector and transgene represent a severe adverse effect to the treatment (Nathwani et al NEJM 2011, Hoffman et al. Front Microbiol. 2012). iii) Introduction of a foreign transgene in peripheral tissues is of general interest not only for neuromuscular disorders but also for other monogenic diseases such as hemophilia A and B (High KA, Blood 2012).

3) Fundamental scientific objectives. The AERES committee pointed out that we should *"expand our horizon to more basic science approaches beyond regulatory T cells"*. We agree and have indeed extended our horizon throughout precise collaborations listed above. However, the question addressed in our project, namely the induction of immune tolerance to a known antigen delivered in a peripheral tissue is both a challenging question in immunology and a focused one, which may pave the way for many applications. Our goal is to achieve long-term "gene transfer tolerance" to defined therapeutic gene products and delineate the underlying tolerance induction mechanisms in peripheral T cells. We concentrated our efforts on dominant tolerance mechanisms in the project and set up appropriate mouse model to transfer CD4+ Foxp3+ T cell subsets exerting suppressive activity. As exposed in the project, we benefit from the advantages of our gene transfer setting and are in a position to delineate for the first time, the antigenic motives recognized by regulatory T cells.

4) Organization of the team. We are persuaded that having organized the functioning of our team with a large independence given to David Gross with a complementary expertise with the PI, profiling him as a future group leader, allows us to share the inherent risks linked to our ambitious project. The eventual fusion of our team with another one would conversely create a situation where too many senior scientists would disperse their individual efforts to gain more visibility and independence. Therefore, we think the fusion of our team with another one would not be adequate in practical terms and would severely hamper the realization of our scientific program.

1. Carpentier M, Chappert P, Kuhn C, Lalfer M, Flament H, Burlen-Defranoux O, Lantz O, Bandeira A, Malissen B, Davoust J and Gross DA. Extrathymic induction of Foxp3 regulatory T cells declines with age in a T-cell intrinsic manner. Eur J Immunol. *Submitted.*

2. Carpentier M**,** Lorain S, Chappert P, Lalfer M, Grela F, Peccate C, Garcia L, Davoust J and Gross DA. Antigen presentation pathways, CD4 T cell responses and B cell responses govern CD8 T-cell priming after AAV-mediated gene transfer in muscle. Mol Ther. *Submitted.*
3. Boisgerault F*, Gross DA*, Ferrand M, Poupiot J, Darocha S, Richard I and Galy A. (2013) Prolonged gene expression in muscle is achieved without active immune tolerance using microRNA 142.3p-regulated rAAV gene transfer. Hum Gene Ther. *2013. Feb 21* (*) equal contribution
4. Chappert P, Bouladoux N, Naik S, Schwartz RH. (2013) Specific gut commensal flora locally alters T-cell tuning to endogenous ligands. Immunity. *In final revision.*

Team 9 (Peter Van Endert)

We are pleased that the visiting committee appreciated the high standards of the team production and did not express any criticism. Regarding the recommendation to promote independence of the permanent staff scientists, we believe that, although this apparently could not be made sufficiently clear to the committee on the occasion of the visit, the recommendation is already implemented. Bénédicte Manoury who joined the team with coworkers in 2011 routinely presents her subgroup as independent team to the outside community, publishes as senior author and funds her own research largely through multiple grants obtained by her. The fact that Bénédicte was just promoted to the grade of DR2 also attests to the recognition of her independence by the CNRs commission. Loredana Saveanu works more closely with the team leader but has started to publish as senior author and submit independent grant applications. She has also established collaborations not implicating the team leader, providing further evidence of her increasing independence.

Team 12 (Claude Agnes Reynaud)

Conclusions/ Weaknesses ans threats: The team leader is not exactly "close to retirement" since her activity will last up to the end of the next 5-year term (end of 2018). The future of the team has been planned, and is envisioned through the recruitment, as an independent investigator, of a scientist with a strong focus on B cells. This young group leader will thus benefit from the expertise of the team members who will choose to join him. Such a candidate is presently evaluated within the call for the I2H department.