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

Department for the evaluation of research units

AERES report on unit:

Imagine IHU

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

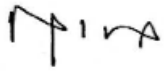
Research Units Department

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: Imagine IHU

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

- Grading table of the team 1: Laboratory of genome dynamics in the immune system

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

- Grading table of the team 2: Laboratory of normal and pathological homeostasis of the immune system

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

- Grading table of the team 3: Laboratory of pathological models of self-tolerance defects

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

- Grading table of the team 4: Laboratory of lymphocyte activation and susceptibility to EBV

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

- Grading table of the team 5: Laboratory of human lymphohematopoiesis

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

- Grading table of the team 6: Laboratory of embryology and genetics of congenital malformation

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

- Grading table of the team 7: Laboratory of molecular and physiopathological bases of osteochondrodysplasias

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

- Grading table of the team 8: Laboratory of genetic and pathophysiological bases of autoinflammatory diseases

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

- Grading table of the team 9: Laboratory of molecular and pathophysiological bases of cognitive disorders

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

- Grading table of the team 10: Laboratory of genetics in ophthalmology

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

- Grading table of the team 11: Laboratory of CTG repeat instability and myotonic dystrophy type 1

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

- Grading table of the team 12: Laboratory of genetics of mitochondrial disorders

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

- Grading table of the team 13: Laboratory of genetic skin diseases: from disease mechanisms to treatments

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

- Grading table of the team 14: Laboratory of origins and functions of skeletal stem cells in bone repair (ATIP-AVENIR Team)

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

- Grading table of the team 15: Laboratory of Human Genetics of Infectious Diseases - Genetic immunology of infectious diseases team

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

- Grading table of the team 16: Laboratory of Human Genetics of Infectious Diseases - Genetic epidemiology of infectious diseases team

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

- Grading table of the team 17: Laboratory of Hereditary Kidney Diseases - Team 1

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

- Grading table of the team 18: Laboratory of Hereditary Kidney Diseases - Team 1

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

● Grading table of the team 19: Laboratory of interactions of the intestinal epithelium and the immune system

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

● Grading table of the team 20: Laboratory of cellular and molecular basis of normal hematopoiesis and hematological disorders: therapeutic implications

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

Evaluation report

Unit name:	Imagine IHU
Unit acronym:	
Label requested:	UMR-S
Present no.:	INSERM U768, U781, U980, U983, U989, CNRS UMR 8147
Name of Director (2012-2013):	Mr Alain FISCHER (INSERM U768), Mr Arnold MUNICH (U781), Mr Laurent ABEL (U980), Ms Corinne ANTIGNAC (U983), Ms CERF-BENSUSSAN (U989), Mr Michel DY CNRS UMR 8147
Name of Project Leader (2014-2018):	Mr Alain FISCHER

Expert committee members

Chair:	Mr Michel COGNÉ, Université de Limoges
Experts:	Mr Per BRANDTAEG, Oslo University, Norway
	Mr Toni CATHOMEN, Freiburg University, Germany
	Ms Susan CHAN, Université de Strasbourg
	Mr Stefan EHL, Freiburg University, Germany
	Mr Raph EPAUD, Université Pierre et Marie Curie, Créteil (INSERM CSS representative)
	Ms Judith GOODSHIP, Newcastle University, United Kingdom
	Mr Douglas HIGGS, Oxford University, United Kingdom
	Mr Georg HOLLANDER, Basel University, Switzerland
	Mr Tobias B. HUBER, Freiburg University, Germany
	Mr Michel KOENIG, Université de Strasbourg (CNU representative)
	Mr Peter H. KRAMMER, German Cancer Research Center, Heidelberg, Germany
	Mr Jean-Louis MANDEL, Université de Strasbourg
	Mr Bertram MÜLLER-MYHSOK, Max Planck Institut, Münich, Germany

Experts:

Mr Massimo PANDOLFO, Free University Brussels, Belgium

Ms Roser TORRA, Puigvert Foundation, Barcelona, Spain

Mr Joris VELTMAN, Radboud University, Nijmegen, The Netherlands

Scientific delegate representing the AERES:

Mr David DOMBROWICZ

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

Ms Evelyne JOUVIN-MARCHE, CNRS representative

Mr Stefano MARULLO, Paris Descartes University representative

Ms Ana-Maria LENNON, INSERM representative

1 • Introduction

History and geographical location of the unit

The *Imagine* Institute project currently associates 20 research teams coming from 6 different INSERM and CNRS units of the Necker Campus and already well known for the quality of their research. IMAGINE was first funded in 2011 after the national Call (from the program "Investissements d'avenir") devoted to the creation in France of a limited number of strong and focused "Instituts Hospitalo-Universitaires" associating clinical and academic research and supported by INSERM, a University and a University Hospital (here the Paris Public Hospitals Group, AP-HP, and Descartes University of Paris). IHU foundations are intended to support research, patient care, teaching and industrial applications on a specific field, here the genetics of rare diseases. Beside the new building that will open late 2013, the IMAGINE foundation is already strongly engaged into attracting new investigators on the Necker Campus and into providing state-of-the-art equipment and core facilities in order to boost the research carried by its teams on genetic diseases.

Management team

Laboratories within Imagine agreed on **"*Imagine* principles"** warranting that they will perform independent scientific programs (as long as their scientific quality and consistency with the IMAGINE's objectives are assessed), that they will share information and contribute to the scientific work of the Institute's other laboratories, that they will seek to attract new teams, seek to promote collaborative projects between teams, and that they will all contribute to common administrative and technical support services.

Beside its director, the Institute is run by a Management Committee (in charge of strategic decisions, space allocations, common budget preparation and regulatory issues), a Council made up of all the laboratory heads, and a Scientific Advisory Board assessing the *Imagine*'s strategy and providing recommendations. A Board of Directors brings together representative of institutional partners and independent experts, while a secretariat-general coordinates the administrative and technical activities and staff.

AERES nomenclature

SVE1

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	32	34	29
N2: Permanent researchers from Institutions and similar positions	49	41	49
N3: Other permanent staff (without research duties)	46	56	25
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	10	10	10
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	67	73	34
N6: Other contractual staff (without research duties)	31	30	6
TOTAL N1 to N6	**235**	**244**	**153**

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	85	
Theses defended	49	
Postdoctoral students having spent at least 12 months in the unit*	35	
Number of Research Supervisor Qualifications (HDR) taken	16	
Qualified research supervisors (with an HDR) or similar positions	56	51

2 • Assessment of the unit

Strengths and opportunities

IMAGINE constitutes a unique project associating outstanding multidisciplinary teams in an exceptional place. Most of the principal investigators involved in the project are highly acknowledged scientists with major contributions to the fields of genetic diseases, immunopathology and immune deficiencies. Outstanding scientific contributions have regularly been made by these teams in the recent past (and for some of them for more than 20 years), although they were working in different locations and had still limited opportunities to collaborate or share expertise or equipments.

These teams have demonstrated their ability to go from clinical research to translational and basic research and then back into applications devoted to diagnosis and/or therapy. The teams have altogether built (and already found strong support through the IHU call) a well-structured and appealing project associating all of them in the same buiding, offering direct access to state-of-the-art core facilities, and reinforcing their means for exploration of human genetic diseases in close contact with Necker Hospital clinical departments.

The organisation of IMAGINE will competently support the most excellent research and will reinforce the attractiveness of the teams for young french and foreign scientists. The commitment of IMAGINE to simultaneously support clinically driven research and related basic research will obviously have a worldwide impact on the understanding, diagnosis and treatment of important genetic diseases. Exceptional progress is likely to take place in Imagine because of the current quality of the IMAGINE investigators, the attractiveness of the new institute with future oportunities to hire additional outstanding scientists, and the strength of already existing and planned international collaborations actively fostered by IMAGINE teams.

IMAGINE is part of the project of Université Paris 5 and the Necker Hospital. It will share core facilities and will be able to develop collaborations with another institute on the Necker campus, that is also home to a number of outstanding research teams.

Weaknesses and threats

As acknowledged by the head of the unit and by several team leaders, the teams will be increasingly facing the choice of either pursuing the larger possible number of gene mutations/polymorphisms involved in genetic disorders or to carry out more in-depth analysis of the pathways pinpointed by the mutations under investigation.This challenge is independent of the individual interests of basic researchers and physician-scientists with clinical duties, not least in light of the past achievements of the teams that are, for most, home to both kinds of scientists, the availability of unique patient cohorts, the strength of established clinical networking, and the current support by the IHU regarding high level core facilities. The primary mission of IMAGINE certainly remains to continue characterizing still unknown genetic anomalies. It is of essential importance for the coherence of the entire project and for the attractiveness of IMAGINE to basic scientists, that the expertise of molecular and cell biological characterization of the identified genetic defects is equally developed at the highest level. Therefore, basic science must remain strongly supported and adequately acknowledged by the unit as this constitutes the invaluable potential to perform cutting edge science (as demonstrated, for example, by the teams most recently for cytotoxic granule secretion or immunoglobulin gene recombination).

Recommendations

Reinforce the human resources available for bioinformatics, notably as a facility for the necessary analysis of whole exome sequencing (WES) and whole genome sequencing (WGS) data but also for the research and development of new methodologies. This may optimally be done under the supervision of scientists of team 16, who are experts in the development of innovative strategies and algorithms for computing and exploiting data from next-generation genetic analysis.

Keep teams focused and find additional resources and space for the strongest and most innovative projects. Given that multiple oustanding projects of the teams are currently under-staffed and need additional space, this immediately raises the question of whether IMAGINE should really go forward (as outlined by the Director) to initiate, within the confines of its new home, additional themes in cardiology, endocrinology and psychiatry. Serious thought should be given to reinforce its initial projects and attract teams and investigators to Imagine that more closely fit with the present project themes until additional space becomes available.

Use the opportunity of the new building and of amended opportunities for interactions between Imagine's staff to improve the scientific training of PhDs and young scientists. Important tools for this aim are regular journal clubs and scientific meetings aiming at creating/reinforcing links and scientific interactions between the various teams. It might be good to have a committee representative of PhD students and postdoctoral fellows to be involved in scientific animation of the site

Protect and secure the the human resources of the Institute and their exceptional know-how by securing permanent positions for technicians and engineers in charge of common facilities.

3 • Detailed assessments

Assessment of scientific quality and outputs

The main teams associating within the IMAGINE projects have previously developed outstanding research projects, unravelling the mechanisms involved in primary immune deficiencies, genetics of infectious diseases, immunopathology, hematology and the genetic/epigenetic study of diseases affecting development and physiology of kidney, joints, skin or central nervous system.

The immunology teams made seminal contributions to the exploration and treatment of multiple human immune disorders, with additional major significance for fundamental immunology and for the understanding of normal processes of DNA repair, immune repertoire diversification, molecular basis of adaptative and innate immune responses, lymphoid cell activation, function and apoptosis as well as to gut immunology, and immunopathology associated with infectious processes.

Regarding human genetics, the teams have done major work of international reputation, from identification of many novel monogenic disease genes in several areas of pathology, mostly pediatric, to functional analysis of some of these genes, understanding of pathomechanisms, and finally, especially for two teams, development of preclinical approaches to treatment (pharmacologic, cell or gene therapy). A few clinical trials have been performed or are planned and funded based on such work. In particular, gene identification has benefited from the outstanding clinical expertise either of members of the unit (also illustrated by the number of associated reference centers for specific rare diseases) or of collaborators in Necker, and also from excellent relations with clinicians in countries with high levels of consanguinity. The teams who were expert in classical positional cloning have used more recently and very successfully the efficient approaches of exome sequencing, first using outside facility, and now the high-throughput sequencing platform of Imagine. One can note also exciting discoveries of mutations in distant non-coding regulatory sequences or affecting non-coding RNAs. Functional analyses using cell or mouse models have been very well developed by some teams and should benefit from the new facilities that will be available for Imagine.

Altogether, these groups have been extraordinarily productive in delineating a collection of mutations responsible for rare diseases and exploiting these data for an understanding of key physiological processes. The past global production of these teams already puts IMAGINE as a model for their efficiency in translating clinical research into basic science and into innovative therapeutic (notably gene therapy) and diagnostic strategies.

The teams have published highly cited reports in the top bio-medical journals (*Nature, Science, Immunity, New Engl. J. Med, Nature Med., Nature Immunol, Nature Genet, JCI, J. Exp. Med...*) with IMAGINE's scientists as senior authors.

Beside the exceptional international standard of their own contributions, the teams were also successful in leading or being involved in productive collaborations and the building of strong networks with many research and/or clinical groups world-wide. This has notably allowed them to build unique cohorts of well-phenotyped patient groups both locally at the Necker hospital and elsewhere worldwide. These cohorts will be instrumental in addressing current and future challenges in genetics, both for the study of rare diseases with mendelian heritability as well as for studies of genetic variants associated with more common diseases.

Regarding methodologies, the teams have gathered strong expertise in cell biology, molecular biology, transcriptome analysis, functional genomics, deep sequencing at the whole genome level and they are in addition strongly involved in the development of new methodologies and new algorithms for the analysis of all the "big data" now coming from these technologies.

Assessment of the unit's academic reputation and appeal

Without any doubt, several of the teams are world leaders in their respective fields, specially with regards to primary immune deficiencies, immune mediated enteropathies, genetics of infectious diseases, genetics of nephropathies, skin diseases, developmental defects, etc…

While the publication track record and number of invitations is very good, the committee felt that many of the team leaders could be more active internationally, for example by taking initiatives for new collaborations to be funded by the European Union. Some of these team leaders can be more ambitious than they appear to be currently, especially given their excellent track record.

Althought the institute is not yet recognized as a very attractive place for foreign scientists at different levels in their career, the number of foreign PhD or postdoctoral fellows is low. This attractiveness is expected to increase considerably by moving to the new building and by the attraction of foreign research teams.

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

Imagine team members are strongly connected within the medical and scientic environment. They act as Editorial Board members or reviewers of several prestigious scientific journals and often serve as experts for grant agencies, charities or medical boards. They are very active in educating students as well as the general public. Many of them have strong collaborations with industrial partners specially for the design of new therapies or new methodologies. Finally, their clinically-driven research and the fact that the clinicians associated with IMAGINE project are responsible for multiple National Referral Centers for Rare Diseases at Necker, strongly link them both to care centers in France and world-wide, and to patients' advocacy groups and associations throughout the world.

IMAGINE's teams are also very efficient in fund raising and are strongly supported by French granting agencies and institutions.

Assessment of the unit's organisation and life

The fact that teams constituting the unit were dispersed in different buildings had the consequence that it was difficult for student and postdoctoral fellows to know what was being done in other teams and benefit from interactions with them. This should change with the move to the new building, especially if efforts are made to have internal seminars or other common activities (retreat, focused meetings) where student and postdocs can present their work to peers and researchers from other Imagine teams.

Despite currently complex settings of laboratory spaces (and globally a significant lack of laboratory space on the Necker campus), which required that several teams had to move to different buildings within Necker campus or to the Broussais Hospital, all the teams appear to be as well organized as possible. Laboratory members easily interact with the team leaders and seem to be highly motivated by the quality of the research they are involved in. All team leaders appear to be enthusiastic and charismatic individuals who are given high credit by other investigators, technicians and students.

Existing core facilities are shared with all the other teams from Necker and are equipped with state-of-the-art technologies although needing to be reinforced (which is a central goal of the IMAGINE project). Many technicians running core facilities are on short-term positions and worry about their future perspective to find a more stable position.

Assessment of the unit's involvement in training through research

With 86 PhD students and almost 50 thesis defended, doctoral training seems to be efficient within IMAGINE. Most investigators are teaching master students and/or PhD students through various doctoral school programs.

Assessment of the five-year plan and strategy

The five-year plan is clearly established on a very sound scientific rationale. Selection of the participating teams has been and will be done according to high standards and under the supervision of a high-level scientific advisory board. Funding appears in full adequacy with the scientific projects and the high level of the teams ensures that they will be able to attract additional support in the future.

The potential risk of being drawn into too many new directions after the identification of novel disease genes based on WGAS/WES and other high-throughput analyses has been well acknowledged by the leader of the project and by several teams. This fact should allow to find a good balance between the search for new genes and the in-depth study of a selected set of them, including when possible, development of therapeutic approaches and paving the way to clinical implementation. This will profit clinical translational researchers and basic scientists alike.

4 • Team-by-team analysis

Team 1 : Laboratory of genome dynamics in the immune system

Name of team leader: Mr Jean-Pierre de VILLARTAY and Mr Patrick REVY

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)	2	3	2
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	7	4	1
N6: Other contractual staff (without research duties)	3	1	0
TOTAL N1 to N6	**15**	**11**	**6**

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

• Detailed assessments

Assessment of scientific quality and outputs

The team is currently part of Inserm U768. It has a longstanding and excellent research record in the identification and analyses of DNA repair factors in the immune system. In the past, the group has identified Artemis and Cernunnos which belong to the Non Homologous DNA End Joining (NHEJ) repair pathway. In this evaluation period they have continued to characterize the function of Cernunnos in immunodeficiency and microcephaly, starting with the characterization of spontaneous defects in patients and they have analyzed its role in DNA repair through structure/function studies in a gene-deficient mouse models. In addition, they have identified an alternative DNA repair mechanism in B cells during class switch recombination in the absence of Non Homologous End Joining (NHEJ) after a conditional disruption of XRCC4. More recently, they identified a dominant negative variant of the DNA repair factor Apollo (having lost telomere binding) as responsible for telomere dysfunction in patients with Hoyeraal-Hreidarsson syndrome. This work pushed them to now further address the roles of DNA repair and telomere maintenance in human immuno-hemato disorders.

The team has published 10 papers with the group leaders as corresponding or senior authors in good (IF 5-10) to very good (IF 10-15) journals (J Allergy Clin Immunol, PNAS, JBC, Blood MCB, DNA Repair, JEM, Hum Mutat). They have published 15 more papers in collaborative studies (JEM, PNAS, DNA Repair, etc.).

Assessment of the team's academic reputation and appeal

The team is very successful in securing funds (>1.3 M€ during 2007-2012) through competitive grant applications at the national level (ANR, LNCC équipe labellisée, INCa, ARC, CEA) as coordinators or as partners. There appears to be no participation in international networks.

The senior principal investigator has been invited to speak at international (4) and national (1) meetings. He has given seminars at international settings. He has served in the scientific commissions of many national organizations (ARC, AERES, INSERM, ANR). He has been invited to write several reviews (Oncogene, Adv Exp Med Biol).

There were no prizes during this period, and there has been no recruitment of permanent staff. The team has a number of fruitful national and international collaborations.

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

The team participates in the molecular diagnosis of DNA repair deficiencies and telomere dysfunctions for patients at several university hospitals in France and elsewhere, through an active network of clinicians and routine laboratories. The group leaders also participate in the setting up of novel treatments for RAG1/2 and Artemis deficiencies through gene therapy in collaboration with another IMAGINE team leader. No patents were submitted during 2007-2012.

Assessment of the team's organisation and life

The senior principal investigator is the scientific advisor of the Gene Transfer Platform on the Necker campus. He has successfully contributed to the writing of an equipment grant for the cell sorting facility.

Assessment of the team's involvement in training through research

The team has supervised 6 postdoctoral fellows, 6 PhD students and 4 M2 students. The group leaders have taught at Institut Pasteur, University Paris 5 and at Porto University (Portugal). They have participated in juries to recruit a lecturer, to award PhD fellowships and to examine PhD theses. There appears to be no participation in international training networks.

Assessment of the five-year plan and strategy

The team addresses a number of important questions and proposes to continue its current work on patients and animal models, with a strong synergy and coherence between the focus of both principal investigators. In particular, they want to develop new approaches to study DNA repair and telomere maintenance through high throughput sequencing and gene-deficient mouse models. Their specific goals include: understanding the crosstalk between DNA repair and telomere maintenance, exploring "synthetic lethality" (using unique cell lines established from DNA-repair deficient patients) through the screening of shRNA libraries and of active compounds from marine microalgae, understanding telomere physiology through the screening of shRNA libraries and the study of human and murine models, analyzing DNA repair defects in cancer patients and in those patients with common variable immune deficiency of still undefined origin. The predicted results should have significant impact for both basic and applied research. However, the goals are wide-ranging and might need to be redefined unless the size of the research group increases in a near future.

Conclusion:

- Strengths and opportunities:

The team is internationally renowned, has sound vision in their approach of basic science coupled with human pathology and has good resources. The team has set up several fruitful collaborations in order to carry out molecular studies of the Non Homologous End Joining/telomere maintenance factors for which defects are simultaneously studied in patients and mice. Integration within IMAGINE and collaborations/projects with the other teams is excellent.

- Weaknesses and threats:

The field of interest is highly competitive. There is a concern that the 5-year plan would be too large for the current number of researchers unless the team is reinforced. Going after too many new targets coming out of WES would carry a risk of dispersion. The international makeup of the postdoctoral fellows and PhD student pool might be insufficient.

- Recommendations:

The team should maintain the current synergy between both principal investigators, although the institute is encouraged to support the development of the younger principal investigator's career in order for him to gain more visibility. The team should pursue its strategies towards a thorough and focused exploration of a limited number of immune deficiencies for which clinically-driven research is followed by deep exploration of the molecular and cellular mechanisms, which will necessitate additional human resources for this team.

Team 2 : Laboratory of normal and pathological homeostasis of the immune system

Name of team leader: Ms Geneviève de SAINT BASILE

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	0	0	0
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)	1	2	1
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3	2
N6: Other contractual staff (without research duties)	0	0	0
TOTAL N1 to N6	**6**	**7**	**5**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	0	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	2	1

• Detailed assessments

Assessment of scientific quality and outputs

The team has a longstanding and remarkable record in exploring the molecular mechanisms that cause severe immune disorders. The team is famous for its work in identifying actors that regulate lymphocyte homeostasis and cytotoxic activity, whose defects are responsible for hemophagocytic lymphohistiocytic (HLH) syndromes. HLH is the primary feature of various forms of Familial Hemophagocytic Lymphohistiocytosis (FHL). HLH also occurs in association with hypopigmentation in Chediak-Higashi Syndrome (CHS) and in Griscelli Syndrome (GS). In particular, the group has (i) identified a novel terminal maturation step of cytotoxic granules in lymphocytes that requires Munc 13-4; (ii) shown that HLH features can be therapeutically corrected by IFN gamma treatment in murine models of FLK2 and GS; (iii) revealed the importance of Munc 18-2 in cytotoxic granule exocytosis and its defects in FHL5; (iv) identified mutations in STK4/MST1 and in POLE1 as the cause of 2 new immune deficiencies; (v) uncovered a terminal transport step of lytic granules which depends on a kinesin complex that includes Rab27a and Sip3. This group has been extraordinarily successful in studying and identifying mutations in rare syndromes and then translating these results into an understanding of key physiological processes. Their approach is a striking example of how clinical research can impact basic science and *vice versa*.

The team has published its work in leading journals (Nat Immunol, JCI, Blood, EMBO Mol Med, EJI; 8 original articles) and also as collaborative reports. In addition, the group has published reviews in excellent review journals (Curr Opin Immunol, Immunol Rev, Nat Rev Immunol).

Assessment of the team's academic reputation and appeal

The team leader has been invited to speak at many international and national meetings (>11), and has given seminars worldwide. She is the recipient of many prizes and awards (Inserm Research Prize, EMBO membership, Prix Etancellin from the Académie des Sciences, Prix Lucien Tartois from the Fondation pour la Recherche Médicale).

The team has numerous collaborations at the national, European and international levels. This has translated into successful funding opportunities in France (ANR, PHRC, FRM équipe labelisée, ACI) and in Europe (FP7, ERC U768), both as coordinator and as partner (grant sums not disclosed).

The team has also recruited a promising young staff CR1 researcher who has an excellent publication record and is well integrated in the group. He has also begun to work at the national and international level in reviewing grants and manuscripts.

The ability of the team to attract foreign postdoctoral fellows and students could not be determined in the provided document.

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

The principal investigator is responsible for the genetic and prenatal diagnosis of several inherited immune disorders including all HLH forms in France and other countries through the Centre d'Etude des Deficits Immunitaires (CEDI) in the Necker Enfants-Malades Hospital. The CEDI is part of the Centre de reference des deficits immunitaires héréditaires (CEREDIH) which allows the rapid transfer of research progress to clinical settings. She has a partnership with Novartis (MTA) to test JAK1-2 inhibitors in murine models.

She is a regular reviewer for leading journals, and for French (Inserm, ARC, FRM, ANR, ITMO-IHP) and European agencies. She has contributed chapters in several books.

Assessment of the team's organisation and life

The team is well integrated in the unit's overall activities which is reflected in joint publications and grants. Both investigators are in charge of organizing seminars at Inserm U768. Both are in charge of the imaging core facility of IFR Necker (IRNEM-IFR94).

Assessment of the team's involvement in training through research

The team has supervised 6 postdoctoral fellows, 4 PhD students and 3 M2 students in this evaluation period. The principal investigator teaches a Master 2 course and a PhD course at Université Paris Descartes, and has also taught at the Inserm School. She is a member of the board of the Ecole Doctorale at Paris Descartes.

Assessment of the five-year plan and strategy

The group will continue its research in immune disorders to gain further insight into lymphocyte homeostasis and the cytotoxic activity of lymphocytes, and use these results to develop new diagnostic and therapeutic tools for HLH. The team will depend on its close links with the Pediatric Clinical Immunohematology Unit, the Adult Hematology Unit and the diagnostic laboratory of the CEDI at Necker Hospital. Specifically, the team proposes: (i) to identify novel protein complexes and search for new molecular causes of HLH which impact the cytotoxic activity of lymphocytes; (ii) to better understand the cellular and molecular events behind primary and secondary HLH (additive effects of partial deficiencies; role of NK cells, monocytes and macrophages; dynamics of APC/T cell interaction; effect of JAK1-2 inhibitors as therapeutic tools); (iii) evaluate the role of Munc 18-2 and other molecules in regulating the immune responses of the gut. The overall strategy is in line with the group's expertise and it is expected that the results will be highly relevant to basic and clinical research.

Conclusion

- Strengths and opportunities:

The team has outstanding international recognition. They are leaders in their field. There is an excellent connection between basic and clinical research and strong collaborative projects within the IMAGINE project (notably with regard to gene therapy of FHL3). The projects are focused, coherent and ambitious.

- Weaknesses and threats:

No obvious weaknesses detected.

- Recommendations:

Since a lot of (excellent) ideas are invested into the LCMV mouse model, the limitations of this model in reflecting the human primary HLH pathogenesis should be carefully considered. Other possibilities of inducing HLH in cytotoxicity mutants (infectious and non-infectious) should be explored.

Gut pathology associated with primary immune deficiencies is an important new field offering opportunities for several research groups. Here, it will be important to remain focused. There are developmental, epithelial, barrier and immunological gut issues (although they obviously overlap) that can be explored in part through collaborations and the group should focus on the immunological aspects.

Team 3 : Laboratory of pathological models of self-tolerance defects

Name of team leader: Mr Frédéric RIEUX-LAUCAT

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	2	2
N2: Permanent EPST or EPIC researchers and similar positions	3	3	3
N3: Other permanent staff (without research duties)	1	1	0
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3	1
N6: Other contractual staff (without research duties)	0	1	0
TOTAL N1 to N6	**10**	**11**	**7**

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

• Detailed assessments

Assessment of scientific quality and outputs

The team "Pathological Models of Self-tolerance Defects" is presently part of the INSERM Unit 768 "Normal and pathological development of the immune system" and in the future the "Imagine" Institute. The information on research group's size is contradictory in the various documents provided.

The main scientific focus is dedicated to issues concerning a loss of self-tolerance. Specifically, research encompasses (i) the identification of genetic modifiers in FAS-deficient patients with Autoimmune LymphoProliferative Syndrome (ALPS) and the evaluation of their potential contribution to ALPS "phenocopy" clinical presentions through a yet unknown mechanism; and (ii) the analysis of regulatory T cells (nT_{reg}) cells in ALPS and other severe combined immunodeficiencies. Future research of the group will build on and extend past work (see below).

In the last 5 years, the team has made a number of important contributions to primary immune deficiency research: (i) the identification of compensatory apoptosis mechanisms in ALPS-FAS lymphocytes *in vitro*, identifying a FAS-independent mechanism involved in activation-induced cell death; (ii) the elucidation of the origin of human double negative T cells (DNT), to be derived from $CD8^+$ T cells, in ALPS patients and the finding that these DNT cells overexpress granzymes A+B; (iii) the use of a combination of biomarkers (soluble FASL, IL-10, DNT cells) as a tool to diagnose ALPS and possibly to predict ALPS-onset in newborns; (iv) a detailed description of a larger cohort of ALPS-FAS patients uncovering a B cell deficiency in these individuals, suggesting the role of a protective disease modulator on the X chromosome; (v) a report concerning the first patient with a homozygous FASL mutation as the cause of a severe form of ALPS; (vi) the development of a concept of "autoimmune suppressor genes" that, when defective, favour autoimmunity; and (vii) the identification of an autosomal recessive mutation in the IL2RA gene as a cause for an IPEX-like disease presentation with severe autoimmune manifestations and predisposition to viral infections. In addition, several collaborative research activities with teams abroad have been established to investigate the FAS-mediated signalling and its role in T cell-mediated, FAS-FASL-triggered elimination of monocytes and macrophages at the end of an immune response; STIM-1 mutations as the molecular cause of disrupted calcium signalling in lymphocytes resulting in a syndrome of autoimmunity and immunodeficiency; and the consequences of IL-10 receptor mutations for gut homeostasis and the development of early onset diffuse large B-cell lymphoma.

The depth of this focused research activity is excellent and complements well with the other research in the unit as convincingly demonstrated by a number of active collaborations, that in part have already resulted in joint publications. The work presented is original and well performed taking advantage of collaborations within the unit and its unique position adjacent to the Necker Hospital with its world renowned clinical resources. Of note to the Committee is that the possible change in the Adult Heamatology Service may impact negatively on the access to clinical samples and patients beyond the pediatric age. Some of the work has provided evidence for an alternative view of a non-malignant autoimmune disease development in humans and spurred interest in extending this concept to diseases other than ALPS. This is a potentially exciting concept that has substantial support in the mouse experimental model system but seeks now solid and generalizeable evidence in the human setting.

The work of the team has without doubt international recognition and has been published in excellent speciality (Blood, JICI, Nature Genetics) and very high impact medical journals of broader scope (JCI, NEJM) providing ample evidence for the quality and novelty of the team's work. Of the 27 papers published by this team since 2007, 4 original contributions and 1 review identify the principal investigator as the senior author.

Assessment of the team's academic reputation and appeal

The team leader has been actively involved in reviewing at both the national and international level research grant proposals and applications for the appointment to permanent positions, respectively. He has presented his work at national and international conferences and has participated in European Framework 6 and 7 consortia.

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

Research partnership with the pharmaceutical company Novartis was mentioned in the documents made available for review though details concerning content, duration, exchange of technical expertise were not provided. In the oral presentation, some of these issues were clarified.

Assessment of the team's organisation and life

No specific information has been provided in the documents submitted with regards to these items; the assessement of these parameters for the entire unit are described elsewhere.

Assessment of the team's involvement in training through research

The team has trained 3 Master2 and 2 PhD students. Moreover, the team leader organises within the PhD program a course on the "Genetic and cellular basis of primary immune deficiencies" and laudably participates in outreach programmes targeting High Schools and Colleges.

The documents provided do not detail how many post doctoral fellows have been mentored by the team leader and whether he has participated in international training programs.

Assessment of the five-year plan and strategy

The research program for the next 5 years is comprehensive, ambitious, of a challenging scope and well structured for the size of the group. It foresees for the cohort of ALPS-FAS patients (i) the identification of protective and indusive modifiers of ALPS-FAS patients with haploinsufficient mutations - this is in its own right interesting but will also fuel further genetic studies of other ALPS subtypes (see below); (ii) the detailled characterisation of the B cell immunodeficiency in ALPS-FAS patients; (iii) the molecular analysis of ALPS patients with so far unknown etiologies using phenotypic, functional, and molecular inclunding candidate gene approaches; and (iv) the analysis of the molecular pathways responsible for the proliferation observed in juvenile myelo-monocytic leukemia (JMML) and Ras-associated lymphoproliferative disease, which are both driven by Ras mutations. Together, these are well designed experiments that take advantage of unique clinical cohorts and collaborations in Paris (and elsewhere, the Committee presumes) and should -together with the proven expertise of the group in that particular field of biomedicine- result in novel and significant information.

The second area concerns a new research activity for the team. This is dedicated to the analysis of paediatric (p)SLE which is in general marked by a more severe clinical presentation when compared to adult onset SLE and linked to nineteen genetic susceptability loci and a few monogenic, homozygous mutations. The planned analysis draws on a small cohort of pSLE patients. Though this is a new focus for the team, some new candidate genes have apparently already been identified, giving further support to contention that the standard approaches chosen for the genetic screen have been successful and can now be followed by molecular and cellular investigations. While this is indeed an interesting project whose success will doubtlessly depend on the methods to be employed, there is an unfortunate shortage in particulars (possibly set by space restrictions). This renders this part of the future research programme especially difficult to critically assess.

The third area of the teams new research program will focus on an in-depth analysis of IPEX and IPEX-like patients regarding the immunobiology of their nT_{reg}. These efforts also include an aim to establish a gene replacement therapy for the defective Foxp3 gene, an apparent collaboration with team 6 of the unit.

The realisation of the proposed research does not pose any particular challenges or risks that can be identified today as "no-go" criteria though, again, too few specific details are provided to assess the feasibility and the merits of the proposed research in more detail. One of the issues the Committee has, however, identified is the very competitive nature of this area of research and the need to be particularly well focused and staffed to be successful.

Conclusion

- Strengths and opportunities:

The team fits very well within the Imagine structure not least for the integrating nature of its research focus and the well established links to the clinics. The team has delivered an excellent and significant range of scientific data in the course of the past 5 years and there is no doubt, that the productivity of the research group will continue. The potential to do well will be best exploited by adapting the research group to a size that can meet the competitive challenges of the proposed research projects within internationally challenging topical areas.

- Weaknesses and threats:

The research group is currently relatively small which creates the threat not to be entirely competitive.

- Recommendations:

No specific recommendations.

Team 4 : Laboratory of lymphocyte activation and susceptibility to EBV

Name of team leader: Mr Sylvain LATOUR

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	0	0	0
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	1	0	1
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	2	3
N6: Other contractual staff (without research duties)	1	1	0
TOTAL N1 to N6	**6**	**4**	**5**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The laboratory is an integral part of the Development Normal et Pathologique du Systéme Immunitaire INSERM Unit 768. The team of 6 members is led by a permanent researcher and staffed by an additional permanent position, 3 DREM/Postdoctoral students and 1 contractual staff member. The research focuses on (i) the mechanisms of the X-linked lymphoproliferative syndromes type I and type II; and (ii) the identification of novel congenital immunodeficiencies that are associated with EBV infections and/or inpaired T cell activation. The team has made several significant contributions to the field of primary immune deficiencies, most notably (i) a first phenotypic characterisation of XLP subtypes; (ii) the description of a co-segregation of a hemizygous mutation of XIAP with a rare polymorphism in CD40LG leading to an X-linked variable immunodeficiency; (iii) the elucidation of a role for XIAP in Crohn's-like colitis via the impaired function of NOD2; (iv) the identification of a role for XIAP as a pro-apoptotic inhibitor in iNKT and mucosa associated invariant T cells (MAIT); (v) the description of a functional cluster between XIAP and SAP and its role in the development of IL-4 producing but not IL-17 secreting iNKT cells and activation of cytotoxicity by NK and $CD8^+$ T cells via SLAM-family receptor stimulation; (vi) the characterisation of a LCK gene defect as the molecular cause for a patient with early onset inflammation and autoimmune manifestations. Some of this original work has already been published in high impact journals with the principal investigator as either the corresponding/senior author (3 publications in Blood and 1 review in Immunity) or as a co-author (10 publications among them 2 J Clin Invest, 1 Plos Biol, 1 Nat Immunol, 1 N Engl J Med, 2 JACI, 1 Blood). In addition, 5 reviews have been published by the team (last or co-authorships) in the past 5 years. The journals in which the team has published are considered excellent speciality journals.

The work of the team is of international standard as reflected by the productive collaborations with research groups in Europe and overseas, the publication record with International Journals, the reviewer activity of high-impact journals of international calibre and the active participation of the PI in international meetings dedicated to his area of research.

Assessment of the team's academic reputation and appeal

The principal investigator has established himself as a leader in XLP research as witnessed by invitations to speak at national (3) and international meetings (6) as well as seminar presentations in the UK, Canada and Japan.

The principal investigator is part of collaborative networks both in France and abroad. How many of these alliances are part of national and international program project grants (or alike) is not visible in the documentation provided.

The attraction of the team to recruit foreign postdoctoral researchers and students cannot be determined as the corresponding information regarding the nationality of the team members is not provided in the documentation sent.

The principal investigator has received in 2008 two scientific prizes (Prix Jaffée, Prix de la Société Française d'Immunologie); his student has been awarded with two prizes for thesis work.

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

Some of the team's work has been supported by the XLP Research Trust, a UK charity that promotes and funds research into the cause, management and cure of XLP. Research support has also been gained from ANR and the ERC as either principal investigator or partner (grant sums are not disclosed).

The principal investigator has been invited to be a member of several committees of the national research agency that evaluate scientific projets sumitted by young researchers and applications for research chairs. He has also been member of a ARC scientific committee. These activities are testimony of the team's interaction with the National scientific environment at the level of science evaluation and promotion.

Among the partners chosen to collaborate with are internationally recognised experts and leaders in their respective fields. These interactions have been essential for some of the work published by and with the team.

Assessment of the team's organisation and life

The team's scientific focus is well placed in the unit's overall activities which is reflected in the significant number of inter-unit collaborations, some of these also resulted in joint publications. The team leader is since 2005 the responsible scientist for radioactivity in the unit. The organisation of the team as part of the unit U768 is described elsewhere.

Assessment of the team's involvement in training through research

The team leader has supervised 5 PhD, 2 M2 and 1 M1 student. In addition, 3 postdoctoral researchers have been mentored by him during the assessment period.

He has made direct contributions to institutional teaching (master level: Faculté de Médicine, Paris 5) and contributed chapters on XLP to one of the standard books on primary immune deficiency and to an encyclopedia on Molecular Mechanisms of Disease. He has also been part of thesis committees both in Paris and elsewhere in France.

Assessment of the five-year plan and strategy

The team will continue its research in analysing the molecular and cellular mechanisms responsible for the susceptibility to EBV infections and for T cell-mediated immune deficiencies. To this end, the team has access to excellent resources including well defined patient cohorts and molecular biology platforms. The overall strategy for the contiuation of the work of the team is in line with the groups expertise and the research networks' strengths.

Specifically, the program for the next 5 years foresees a focused effort in 3 areas of research: (i) the identification of new molecular causes of genetic susceptibility to EBV and of T cell activation defects; (ii) the investigation into the biology of innate-like lymphocytes; (iii) the characterization of the SAP/XIAP signaling pathways. All these areas are in a highly competitive field, but given the previous efforts, the established expertise, the know-how and the network of the team, there is no doubt that this part of the future research program will be successfully carried out.

The analysis of a cohort of 15 patients with EBV-associated lymphoproliferation but none of the so far known defects of XLP has already resulted in the identification of potentially new genes causative for the disorder. The "work-up" of these candidate genes will employ standard methods and approaches. There appears to be little to no risk in the use of the outlined methods not to gain further information on the function of the identified candidate genes.

The importance of the transcription factor PLZF and its involvement in the effector program of iNKT cells has recently been shown by the team. Further work now suggests to test the role of PLZF in iNKT and MAIT biology at the cellular and molecular levels (development, signaling, effector functions linked to the transcription factor Hobit, etc). These investigations will also be done with regards to their relevance to EBV infections and how iNKT and MAIT cells can contribute to the clinical phenotype. They are potentially very informative in further elucidating the biology of iNKT and MAIT cells. There are no obvious risks at this point and it is likely that these efforts will result in the identification of new molecules relevant for the pathogenesis of XLP-like diseases. This activity constitutes a strong and very likely successful effort, which is effectively paralleled by the patient based research program identified above.

The third research focus is based on the preliminary observation that SAP and XIAP form a physical and functional cluster (likely in the context of SLAM-R mediated signaling) which may account for the similarity in phenotype in XLP-1 and -2 patients. The proposed experiments are suitable and feasible.

Conclusion

- Strengths and opportunities:

Excellent fitting with the theme and composition of the entire Imagine Institute; ample opportunities for collaboration. Excellent research activity, international recognition and a leader in the field. Very good research publication record in a challenging field.

- Weaknesses and threats:

Weaknesses have not been identified. There are no threats that seem to jeopardize the productivity or the success of the research team.

- Recommendations

The strength and potential of this research team could take advantage of additional staff. Provision of support could be enhanced to meet the demands required to even better match international competitiveness.

Team 5 : Laboratory of human lymphohematopoiesis

Name of team leader: Ms Marina CAVAZZANA-CALVO and Ms Isabelle ANDRÉ-SCHMUTZ

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	3	2
N2: Permanent EPST or EPIC researchers and similar positions	4	4	4
N3: Other permanent staff (without research duties)	2	4	2
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	7	8	0
N6: Other contractual staff (without research duties)	2	5	0
TOTAL N1 to N6	**17**	**24**	**10**

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

• Detailed assessments

Assessment of scientific quality and outputs

The main goals of the team are to understand the early steps of lymphopoiesis in normal and pathological backgrounds, and to develop new gene therapeutic treatment options for patients suffering from primary immune deficiencies. The major achievements of the unit include the characterisation of retroviral integration sites in children treated as part of the first gene therapy protocol for SCID-X1, the preclinical development and initiation of a novel gene therapy protocol for SCID-X1, the identification and characterization of human lymphoid progenitors generated in the bone marrow that are capable of colonising the thymus after birth, the ex vivo expansion of human T-cell progenitors on immobilised Notch Delta-4, and the identification and role of AK2 in proliferation and survival of lymphoid progenitors and neutrophils in the context of reticular dysgenesis.

The scientific output of the unit has been extraordinarily high with more than 80 publications over the last five years. On 17 of these publications, which were published in journals like JCI, Nature, Science and N Engl J Med, the principal investigators are listed either as first or senior authors. Moreover, these publications underline the fruitful collaborations that have been established by the unit heads. Importantly, also the new people joining the team (former Inserm U768 team 2; see below) have been very productive and made major contributions towards the understanding of class switching and somatic hypermutation B cell defects.

Assessment of the unit's academic reputation and appeal

Without any doubt, the team belongs to the leading groups in cell and gene therapy worldwide, with an outstanding reputation of translating basic research into successful clinical trials. This fact is well documented by more than 120 invitations to present the group's findings at national and international meetings, including the Annual Meetings of the American Society of Gene and Cell Therapy and the American Society of Haematology.

Moreover, Ms Marina CAVAZZANA-CALVO has been awarded several prizes, including "Outstanding Achievements Award of the European Society of Gene and Cell Therapy", "Jean-Pierre Lecocq Award on Gene Therapy – French Academy of Sciences" and "American Society of Haematology Award for Clinical Research in Gene Therapy". Furthermore, she is a member of the Board of Directors of the American Society for Gene and Cell Therapy (ASGCT), a member of the Editorial Board of Stem Cells Translational Medicine, and member of the Editorial Board of Blood. and serving as reviewers or experts for scientific journals, grant agencies or medical boards.

Noteworthy, one of the team leaders was awarded a prestigious ERC grant on Regenerative Medicine, with a total funding sum of 2.5 million €.

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

In addition to their clinical activity, members of the team are very active in fund raising, TV and radio appearances, and collaborations with cultural institutions.

Assessment of the team's organisation and life

This team is based on a fusion between Inserm U768's former groups 2 and 6, which combines strong expertise in B-cell and T-cell lymphopoiesis with a compelling translational research focus. The complementary background and expertise of the two principal investigators was certainly the foundation of the extraordinary success of this research team.

A total of six permanent research positions in the unit will ensure that crucial knowledge will be maintained on the one hand and allow the research team to quickly engage in new projects on the other hand. The laboratory is not divided in sub-teams but rather in 3 thematic subunits, with various team members contributing their relevant expertise to all 3 lines of research. This integrated approach ensures easy exchange of ideas and technologies between the different projects.

Assessment of the team's involvement in training through research

The team is actively involved in training of PhD students, teaching of medical students, Master students in various programs as well as students in paramedical courses. The team leaders have supervised 4 Master's students, 2 Ph.D. students, and 2 postdocs.

Assessment of the five-year plan and strategy

The research plan for the next five years builds nicely upon the successful lines of research of the previous period, abandons projects that ran into a dead-end, and defines new focal points by expanding novel research developments in the lab. The projects can be subdivided into three major lines: the studies of (1) healthy lymphopoiesis and (2) pathological differentiation of B and T cells, which is complemented by (3) a strong emphasis on translational medicine.

Parts (1) and (2) will combine novel technologies, such as deep sequencing and transcriptome analysis, with conventional complementation screens to study stem cell maintenance and expansion as well as defects in B and T cell differentiation. Part (3) focuses on the development of cell and gene therapeutic approaches.

On the one hand, the planned research projects will answer fundamental questions that aim at understanding key issues in haematology and immunology, on the other hand novel concepts of combining cell and gene therapy will be established. Importantly, the three lines of research are well connected with each other and progress in one aspect of research will advance the efforts in the other areas.

Although the research plan seems ambitious overall, it is built on both know-how and technologies well established in the lab and collaborations with well-renowned partners inside and outside the organization. There is no doubt that the unit will achieve most or all of their set goals.

Sufficient funding is available until 2015, which will give the principal investigators enough time to apply for additional grants to cover the gap until 2018.

Conclusion

- Strengths and opportunities:

The team has an outstanding track record in stem cell biology, B/T cell development and gene therapy. The unit is well connected within the respective fields and one of the leading labs in hematopoietic gene therapy. The combination of strong basic research with superb translational medicine and strong collaboration partners puts this unit in an excellent position to remain on top of the field.

- Weaknesses and threats:

The lack of administrative and technical support could endanger the worldwide leading position of this unit.

- Recommendations:

The team has an outstanding track record in the fields of haematology, immunology and gene therapy, and will be one of the main pillars of success of the Imagine Institute. Consequently, the unit should be supported with high priority to further expand its activities within the Institute.

Team 6 : Laboratory of embryology and genetics of congenital malformation

Name of team leader: Mr Stanislas LYONNET

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	10	10	7
N2: Permanent EPST or EPIC researchers and similar positions	8	2	8
N3: Other permanent staff (without research duties)	8	6	3
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	2	3
N6: Other contractual staff (without research duties)	2	0	0
TOTAL N1 to N6	**32**	**21**	**22**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	11	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	17	10

• Detailed assessments

Assessment of scientific quality and outputs

The group has an excellent scientific production in the last 5 years, with many publications in the top scientific journals (since 2007, 2 PNAS, 5 Nat Genet, 5 Am J Hum Genet as first and last authors etc). The group combines expertise in next generation sequencing with functional genomics and clinical genetics and applies this to cohorts of well-phenotyped patients to identify novel disease genes, in particular in fetal development diseases and ciliopathies (Putoux et al. Nat Genet 2011). This combination is of great importance for current and future challenges in genetics. In particular, has made original discoveries on novel types of mutations accounting for monogenic diseases: very distant regulatory point mutations (upstream or downstream of Sox9) in a developmental disease (Nat genet 2009), distant deletions or duplications affecting Sox9 in disorders of sex development (J Med Genet 2011) or mutations affecting a non-coding RNA encoded by a retroposon (PNAS 2012), deletion of a miRNA gene cluster in a developmental defect (Nat Genet 2011) It plays an important role in the major international collaboration on Hirschsprung disease.

Assessment of the team's academic reputation and appeal

The scientists working in the unit are well-known in the field, not only for their expertise but also for their collaborative spirit, as can be seen from the many international collaborations and the fact that the team leader, is the current President of the European Society of Human Genetics, a very prestigious position in genetics in Europe.

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

Very good. Team members are active in teaching, both for science students and medical residents (notably fetal medicine), in reference centers for rare developmental diseases, and participate in a joint training program with Marocco. They are active in national and international (Germany, Canada) review boards, and are members of editorial boards (notably Hum Mol Genet, Eur J Hum Genet, Clin Genet). One US patent has been obtained. There is important translation to diagnosis (fetal ciliopathies).

Assessment of the team's organisation and life

The team is well embedded in the Imagine Institute, with availability of all technological platforms and biobanks. Most members have a dual University/Hospital position which guarantees links to the clinic, but they mention too few full time high level researchers We had no time to assess team's life…

Assessment of the unit's involvement in training through research

The team is very active. It has trained 8 completed PhDs and 11 M2 Master students, and is active in training of MDs in medical genetics, fetal pathology, etc…

As stated in their own SWOT analysis, the team however does not have a good formal training program for young scientists.

Assessment of the five-year plan and strategy

The group is ready to move to more complex genetic disorders in the coming years, moving from monogenic to more complex genetics (as already initiated since many years for *Hirschsprung disease*) and pursue more deeply their already successful exploration of the disease implications of the non-coding parts of the genome. The team will pursue research in their field of excellence (neurocristopathies, fetal ciliopathies and other developmental anomalies) using high throughput genomics and increased emphasis on functional genomics and model organisms. This is essential for the group: they have a unique expertise in a combination of genomics technologies needed for this, but it is also faced full of challenges (niatbly as they note, the risk of having multiple topics) The team will rely on mouse facility in Imagine, and would benefit from an implantation of the zebrafish model.

Conclusion

- Strengths and opportunities:

Excellent research group with international expertise in number of well-defined diseases for which well-defined clinical cohorts have been collected for many years. This, in combination with novel functional genomics approaches and focus on non-coding genomic variation offers many opportunities.

- Weaknesses and threats:

There is little bioinformatics expertise currently in the group, which is a threat for progress in genomics. As for other genetic groups in Imagine, the drawback of their success in identifying new disease genes is a risk of pursuing too many genes at the functional level, but team members are aware of this.

Furthermore, no new fulltime researchers were attracted to the team since 2004. This is dangerous as science needs new talents and the EU funding scheme is also focussing more and more on young scientists through ERC grants for example.

Little international funding for a group that is so succesfull when you look at the scientific output.

- Recommendations:

The team is very much focused on France, all scientists coming from France. Why not expand and look globally for talented scientists?

Investment in bioinformatics essential to make the most of the powerful genomics technologies.

Team 7 : Laboratory of molecular and physiopathological bases of osteochondrodysplasias

Name of team leader: Ms Valérie CORMIER-DAIRE

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3	2	3
N2: Permanent EPST or EPIC researchers and similar positions	3	2	3
N3: Other permanent staff (without research duties)	2	1	1
N4: Other professors (PREM, ECC, etc.)	0	1	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	0	0	0
N6: Other contractual staff (without research duties)	0	0	0
TOTAL N1 to N6	**8**	**6**	**7**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	7	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	2	3

• Detailed assessments

Assessment of scientific quality and outputs

The team is a world-leader in clinical and genetic analysis of bone diseases (osteochondrodysplasias), with, for the period 2008-2012 identifications of genes defective in acromicric and geleophysic dysplaisias, Myhre, Marshall Smith, Desbuquois, Ghosal and 3M syndromes and ATD/SRPIII and acrodysostosis. Some exciting and unexpected findings are: the involvement of missense mutations affecting a small domain (exons 41 and 42) of the well known FBN1 gene (the Marfan syndrome gene) as causing geleophysic or acromicric dysplasias in 29 patients (AJHG 2012), while the team had previously identified the ADAMTSL2 gene as a major gene in geleophysic dysplasia (Nat Genet 2008). Another such finding is that all the mutations responsible for Myrhe syndrome are SMAD4 gain of function *de novo* missense mutations affecting a single codon and leading to impaired ubiquitination (Nat Genet 2012). These findings would not be possible without the superb clinical expertise and use of efficient molecular strategies (now exome sequencing). The clinical connections are key to the success, and the team is heavily involved in the National reference center for skeletal dysplasia and with access to consanguineous families. The team has in parallel developed strong expertise in analysing the implicated pathways in cellular models and in mouse models. The co-principal investigator has in particular developed the analysis of pathomechanisms in FGFR3 related chondrodysplasias, and developed very interesting preclinical pharmacological approaches (new FGFR3 inhibitor, in collaboration with pharmacochemists) or a CNP petide analogue inhibiting downstream signaling , tested in femur explants or in the mouse model. This has led to a phase 1 clinical trial and a phase II will start in mid 2013 (with Biomarin). The team has published as major author or coauthor about 100 papers in the period, including 7 Nature Genet (3 as Corr. Auth), 11 Am.J Hum Genet (4 as CA), 4 Hum Mol Genet (3 as CA). 3 patents have been deposited.

Assessment of the unit's academic reputation and appeal

The team leader has made the biggest contribution internationally to identifying genetic causes on osteochodrodysplasias.The team in involved in European and international networks. The teamleader has been twice invited speaker at Gordon conferences, and got a prize from FRM. Very good grand funding, mostly french (one 6th PCRD european grant) and industrial funding (BioMarin).

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

- Strong links with patient groups,
- Industrial partners – Biomarin and Genzyme, implication in clinical trials,
- Creation of a Biotech start up – Selkies 3 patents for the period,
- Member of European Skeletal Dysplasia Network (ESDN), which provides expert diagnosis to radiologists, paediatricians and geneticists. Organisation of international meetings in 2007 and 2010,
- Specialised teaching on constitutional bone diseases (DU, created by the team leader, 100h teaching).

Assessment of the unit's organisation and life

Not assessed.

Assessment of the unit's involvement in training through research

Very active: 7 PhD students, 10 Master 2 during the period.

Assessment of the five-year plan and strategy

Excellent – still genes to be found for rare osteochondrodysplasias; these will increase knowledge of biology of cartilage and bone formation and is likely to be relevant to more common disorders. Novel mouse models are being constructed at Clinique de la souris, and the team has the necessary expertise to characterize them and use them in pathomechanisms and preclinical studies, especially with the improved future facilities in Imagine. The pharmacological approaches to develop therapies to increase growth from birth to teenage are promising with clinical trials commencing for achondroplasia and a good plan for developing therapies for other chondrodysplasias.

Conclusion

- Strengths and opportunities:

Strong achievements. Excellent project.

- Weaknesses and threats:

No specific weakness identified.

- Recommendations:

Recommend that this team (E7) and team E14 are sited together in IMAGINE to facilitate cooperations.

Team 8 : Laboratory of genetic and pathophysiological bases of autoinflammatory diseases

Name of team leader: Ms Asma SMAHI

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	3	2
N2: Permanent EPST or EPIC researchers and similar positions	2	1	2
N3: Other permanent staff (without research duties)	1	2	0
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	2	0
N6: Other contractual staff (without research duties)	4	5	2
TOTAL N1 to N6	**11**	**14**	**7**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	0	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	5	5

• Detailed assessments

Assessment of scientific quality and outputs

The group is studying auto-inflammatory skin diseases. It made in the past (2000-2004) very important scientific contributions to the understanding of the genetic basis of important monogenic diseases affecting skin or skin appendages, *incontinentia pigmenti* and *anhidrotic ectodermal dysplasia* and the functional implication of NF-κB signaling pathway in these diseases. Since 2007, the team has published about 15 papers, most as main or major contributor. The most important and original published results concern the identification in a severe monogenic form of psoriasis (generalized pustular psoriasis) of a missense mutation in the IL36RN gene encoding an interleukin-36-receptor antagonist (interleukin-36Ra), an anti-inflammatory cytokine. This mutation affects stability of the protein and the mutant protein is thus defective in inhibiting a cytokine-induced response, leading to enhanced production of inflammatory cytokines (interleukin-8 in particular) by keratinocytes. This was published as a full paper in New England Journal of Medicine in august 2011, with the team leader as last and corresponding author, and her younger collaborators as first two authors, and this paper has been cited already more than 30 times, which is exceptional for such a recent publication. The significance of course lies in the potential of the IL36 signaling pathway to be implicated in more common multifactorial forms of psoriasis or other autoinflammatory skin diseases, and this hypothesis is central to the project of the team in years to come. The team also showed that a single patient carrying this mutation was improved by treatment with an IL1b antagonist, supporting a link between IL36 and IL1 pathways. More recent work has shown that the initial mutation results from a founder effect in the Maghreb, but other cases of IL36RN mutations have been observed in Europe and Japan, as well as in other forms of psoriasis. The group has excellent expertise in molecular epidemiology and genotype phenotype studies of incontinentia pigmenti and anhidrotic ectodermal dysplasia, published notably as papers in Human Mutation, or in more clinical genetics journals. Very interesting functional analysis of NEMO missense mutations in IP led to demonstration of the importance of NEMO/TRAF6 interaction and polyubiquitination of NEMO (Hum Mol genet 2010 by an investigator, who has since left the team). Functional analysis of NEMO has been pursued in both IP and EDA (sharpin/NEMO interactions and linear polyubiquitination, cross talk between Wnt/βcatenin pathway and Ectodysplasin receptor EDAR, both submitted for publications). Thus this team has used human genetics, cell biology and immunology approaches to learn about the mechanisms underlying these diseases and ultimately aims to develop new therapeutic strategies to their management.

Assessment of the team's academic reputation and appeal

Little information is provided to make an evaluation (invited international lectures, prizes, membership of Academic Institutions etc). Publications indicate several important collaborations with clinicians (National reference center in rare dermatology diseases) and scientific groups in Italy, Scotland, and teams in Maghreb that identify informative consanguineous families for identification of novel genes for inflammatory skin diseases etc…

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

Strong collaboration with National reference center in rare dermatology diseases, and for molecular diagnosis of *incontinentia pigmenti and anhidrotic ectodermal dysplasia.*

Assessment of the team's organisation and life

Information provided on the organizational structure of the laboratory is scarce and was not investigated further.

Assessment of the team's involvement in training through research

Not assessed. Two PhD students and 2 postdocs currently in training. Apparently no PhD theses defended in the past 5 years from provided statistics.

Assessment of the five-year plan and strategy

Studies of this research team now focus on psoriasis, particularly on *generalized pustular psoriasis* (GPP). Although therapy in psoriasis has improved lately, the pathogenesis of this disease is still unclear. Thus, the team uses a rather poly-pragmatic approach to gain more insight into pathophysiologic phenomena: -omic approaches, genetic approaches, and analysis of a multitude of cytokines. Emphasis is put on the IL-1/IL-36 system. This system will also be manipulated by monoclonal antibodies or small molecules. Genetically engineered mice in this system with a comparable skin disease phenotype shall be studied in detail. Finally, the group also takes on a new project and plans to study the role of inflammation in metabolic diseases.

Overall this appears to be a well-focused program with considerable scientific interest and clinical relevance. A major aim of the study will be to detect new mutations underlying autoinflammatory skin diseases using both candidate gene and genome-wide approaches, using their proven competence in human genetics approaches and excellent recruitment of families, both through ongoing collaborations with clinical teams in Maghreb, and through their involvement in the National Reference centre for rare genetic skin diseases in Paris. They propose a particularly interesting program studying Majeed syndrome. They also plan to use ex vivo studies to investigate candidate immune pathways using serum and monocytes derived from patients. Finally they also plan to study mouse models with mutations of IL-36. They are also planning to develop therapeutic antibodies (mini-antibodies) and small molecules.

Taken together, the group relies on a defined patient cohort and on mouse models to study *generalized pustular psoriasis* and will continue its contribution to the elucidation of this disease.

Conclusion

- Strengths and opportunities:

A focused program addressing an important group of human diseases, based on a major discovery, expertise in human genetics and cell biology approaches, and excellent clinical recruitment, and participation of clinicians experts in the diseases targeted. A collaboration with a pertinent immunology team in Imagine would be profitable.

- Weaknesses and threats:

While the expertise in human genetic approaches is well proven, and expertise has been acquired in cell biology studies, the ambitious program will require extending the expertise of the team, and/or establish efficient collaborations with other groups within or outside Imagine.

- Recommendations:

The group should be encouraged in developing this program, and its ability to acquire the required expertise and initiate pertinent collaborations might be monitored in 2 or 3 years.

Team 9 : Laboratory of molecular and pathophysiological bases of cognitive disorders

Name of team leader: Ms Laurence COLLEAUX

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	0	2
N3: Other permanent staff (without research duties)	1	3	0
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	0	0	0
N6: Other contractual staff (without research duties)	0	1	0
TOTAL N1 to N6	**5**	**6**	**4**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

This relatively small team that specializes since many years in the study of genetic mechanisms of monogenic syndromic or non syndromic mental retardation (intellectual disability/ID), their genotype phenotype correlations and in some cases the downstream pathomechanisms has had an excellent productivity since 2007, identifying singly or as major collaborator more than 10 novel ID genes. They have nicely shown that contrasting phenotypes of mutations affecting the same transcription factor is linked to differences in NMD (nonsense mediated mRNA decay) response, giving either a loss or a dominant negative effect and indicating a role in both ossification process and brain development. Another gene pinpointed the role of NF- kB signalling in brain development and CNS myelination. The team is very good to initiate collaborations with expert teams to study functional aspects (at IGBMC, Strasbourg, for transcription effects of MED23 or MED12 rare mutations, published in Science), in Yale for the KCNT1 channel mutations that cause a specific form of epilepsy (benefitting also from superb clinical expertise of neuropediatrics in Necker (or earlier with another team for drosophila studies). The team has published as firt and/or last authors in the best high impact factor journal journals (Science Nat Genet) and, in collaboration, in Mol Cell.

Assessment of the team's academic reputation and appeal

Excellent reputation. The team is now member of a wide international network on autosomal recessive ID. Very good funding from competitive French sources (ANR, jeune equipe FRM) but surprisingly no international funding, and the team that has 3 permanent researchers (2 with dual hospital/teaching duties)/ appears only French.

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

Involvement in autism policy groups in France. Clinical involvement of 2 team members. No patents (this is understandable given rarity of individual causes of ID).The team leader has scientific responsibility in the Imagine genomic platform. Maybe could be more involved in development of diagnostic applications.

Assessment of the team's organisation and life

Not assessed.

Assessment of the team's involvement in training through research

Appears very good: 3PhDs completed, 2 running.

Assessment of the five-year plan and strategy

The team has recruited a senior permanent French researcher who has worked for the past 5 years in UCSD and who will develop a new project (cerebellum and cognition, dolichol biosynthesis and glycosylation defects). This project is at least in part a follow-up of his project in the US (1st author of Cell paper 2010), using a mouse model generated there, and will likely bring new expertise in pathophysiology studies.

The 3 other projects: 1) pursue genetics and molecular pathology of ID, where this team has unique expertise. However explosion in the field of exome sequencing makes competition more difficult, as its use appears for the moment somewhat more limited (for probably financial reasons) than in other leading international centers. And while the unique clinical expertise of Necker is of paramount importance for syndromic ID, it may be less so for non syndromic ID. 2) Project on functional analysis of some ID genes at synaptic level, relies on a collaboration with an excellent electrophysiologist in Bordeaux, and on characterization of a Kcnt1-deficient mouse (construction under way at ICS). 3) Very interesting approach on studying epigenetic correlates of autism using a very original tool, olfactory mucosa stem cells from patients and controls that can be differentiated in neurons and glia. However, a full epigenomic characterization of such cells starting from only 11 ASD patients and 11 sex matched controls may appear under-powered, especially given the extreme genetic heterogeneity of autism, and probably also some expected heterogeneity of the cell populations.

Conclusion

- Strengths and opportunities:

Excellence of clinical recruitment. Recruitment of a new permanent researcher. Member of an international network on autosomal recessive ID. Very good collaborations. Being in Imagine should improve access to state of the art genomic technologies and interactions on functional studies at organism level (mouse, hopefully zebrafish…).

- Weaknesses and threats:

The autism project is original, but risky. The competition on gene identification may become harder. The team is still relatively small, and although is chosing very well its collaborations, has to avoid the risk of dispersion.

- Recommendations:

The principal investigator should try to find international funding and should be careful not to carry a too dispersed project.

Team 10 : Laboratory of genetics in ophthalmology

Name of team leader: Mr Jean-Michel ROZET

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	0	0	0
N2: Permanent EPST or EPIC researchers and similar positions	3	3	3
N3: Other permanent staff (without research duties)	2	3	1
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	4	2
N6: Other contractual staff (without research duties)	1	1	0
TOTAL N1 to N6	**8**	**11**	**6**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

This is a leading team in the field of ophthalmogenetics. The group has identified numerous genes causing Leber congenital amaurosis and hereditary optic neuropathy. The group has also moved recently towards the development of gene therapy for the most common mutation found in Leber congenital amaurosis (a deep intronic mutation in the CEP290) by antisense oligonucleotide-mediated exon skipping. The scientific production is very good with publications in excellent journals such as Nature Genetics (IF 35.5), Am J Hum Genet (IF 10.60) and Brain (IF 9.46), including a novel gene identification published in 2013 (anopthalmia gene, ALDH reductase gene, Am J Hum Genet).

Assessment of the team's academic reputation and appeal

The team has a very high reputation and appeal in the field, as testified by invitations at international congresses and by prizes awarded to the team leader and to other investigators (including the former head of the group).

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

The team has submitted 4 patents during the evaluation period. The team is part of several collaborative networks (national PHRC, national network of referral centers, occular gene therapy network (R-TGO), European Vision Institute (EVI-GENORET)).

Assessment of the team's organisation and life

The team leader became head of the ophthalmogenetics group in 2009 (that is during the course of the evaluation period) in replacement of the previous principal investigator, now staying in the group as a consultant. This was a logical move that apparently went uneventfully.

Assessment of the team's involvement in training through research

Training of Master (7) and PhD (1) students. Teaching in Master programs and in DIU (diplômes interuniversitaires) and DU (diplômes universitaires) of the Necker faculty of medicine.

Assessment of the five-year plan and strategy

The project of the team for the next five years is mostly devoted to the identification of new genes involved in syndromic and non-syndromic Leber congenital amaurosis and in hereditary optic neuropathies, by next generation sequencing. These projects are well funded by national agencies (national PHRC, ANR, EC-IP-EVI-GENORET-WP7).

The project also involves fonctional characterisation of the TMEM126A gene product, a mitochondrial protein, in collaboration with the team 12 of the same institute, defective in the first identified cause of autosomal recessive optic neuropathy.

A third aspect of the project involves pre-clinical trials with antisense oligonucleotides (AON) for the treatment of the most common form of Leber congenital amaurosis, namely the deep intronic mutation c.2991+165A>G mutation. This involves either the use of single injections of U7-AAV2/5 vectors or repeated injections of naked AON. Preclinical tests will be performed on mouse models provided by collaborators in Nijmegen. These projects are well supported by patients organisations such as Retina France and AFM, and are fully feasible with the recent recruitment of an experienced post-doc in the field.

Conclusion

- Strengths and opportunities:

20 years of clinical experience in inherited vision disorders and gene identification, and strong interactions with the French ciliopathy network.

Excellent publication record.

- Weaknesses and threats:

Recent and limited experience in functional analyses and therapeutic development.

- Recommendations:

Continue.

Team 11 : Laboratory of CTG repeat instability and myotonic dystrophy type 1

Name of team leader: Ms Geneviève GOURDON

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	0	0	0
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)	4	3	3
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	3	0
N6: Other contractual staff (without research duties)	1	0	0
TOTAL N1 to N6	**9**	**8**	**5**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

This is a comparatively small team of 8 people, including 2 permanent Inserm researchers, 1 permanent research assistant, 1 research assistant funded by grants (fixed term contracts), 2 post-doctoral scientists, 2 PhD students. The team leader is Ms Geneviève GOURDON, who has been active in the field of repeat expansions and myotonic dystrophy (DM1) mechanisms for more than 15 years, which also sets the focus of this team. In particular the team has focussed more recently on their development and study of the DMSXL mice, which carry very large repeats (>1000 CTG repeats) in the gene for myotonic dytrophy (DM protein kinase (DMPK)).

In these mice developed in the lab and released to the community quite extensively (as witnessed by 13 MTAs) they have studied many effects of the genetic variations introduced on the mice, eg CNS dysfunction in general, modulation of CTG instability both by *cis*- and *trans*-acting factors , as well as the effects on DMPK expression very recently.

The team has published some 19 papers in the period under review (2007-2012), including some papers in high impact factor journals (Plos Genetics, Nature Structural & Molecular Biology, as well as Human Molecular Genetics). Two commercial licenses for the use of the DMSXL mice are also noted. This must be seen also in context as the team will have moved twice in the past few years, and will soon move once more, to the Imagine new building, which makes the productivity quite remarkable in a positive sense.

Assessment of the team's academic reputation and appeal

Investigators from the team are well known internationally (as well as nationally), among other things via their role in the international DM consortium meeting (IDMC). Here especially, the team leader has been known for her participation in the organizing committee. The team has been successful in attracting funding both internationally (Marigold foundation, Marie Curie fellowship) and nationally (AFM, ANR). A permanent resarcher and co-principal investigator was trained in Portugal and had a long posdoctoral training in Glasgow, in a team also well known for research on myotonic dystrophy.The team has attracted a foreign postdoctoral fellows and foreign students.

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

The team leader is active also in contacts with patients networks and interaction with the general public.

Assessment of the team's organisation and life

State weekly lab meetings or journal clubs, mainly in english.

Assessment of the team's involvement in training through research

Since 2007, the team has supervised 1 completed and 2 ongoing PhD theses and has supervised several master students. The team regularly participates in teaching courses in Paris.

Assessment of the five-year plan and strategy

The team will continue to use their mouse model to study a whole variety of questions related to DM1. They partly also directly work with material from interesting human families, thus ensuring a certain translational aspect in their work.

The questions they propose to study aim, as stated, at a) factors and mechanisms that could favour CTG repeat contractions, and b) molecular and pathophysiological consequences of the CTG expansions.

The study of factors and mechanisms that could favor CTG repeat retractions involves the mouse model and also the study of 2 DM1 families (identified by the Necker diagnostic lab), which have been found to exhibit unusual stable transmission patterns over a few generations (and perhaps also more somatically stable), while carrying a pure CTG repeat. While these families are indeed very interesting ones, it may be difficult to pinpoint the precise cause of the unusual stability using only these 2 families (while they hypothesize that one of the closely neighboring genes involved in DNA replication or repair might be the modifiers, *cis* acting non coding sequences might also be involved in the stabilizing effect). Strategies should thus be used to identify additional such families.

The second part of the project is totally within the experimental animal paradigm: try to explain the neonatal lethality in their XL model and compare it with mechanisms of the very severe congenital form of DM1, and study also the effects on CNS (vesicle trafficking, synaptic and cerebellar dysfunction) of the large expansion, as indeed cognitive and behavior anomalies are a hallmark of the human disease.

Finally, the team will continue to collaborate to various preclinical therapeutic projects using their unique mouse model, and will perform in house some of the therapeutic tests.

Conclusion

- Strengths and opportunities:

The team has very good international reputation. Funding does seem to be increasing nicely. Collaborations locally and internationally are visible and credible. The mouse model is unique, and appears the most physiologically relevant worldwide, which is a very strong asset indeed.

- Weaknesses and threats:

Reliance on a single mouse model bears a certain risk. Apparently, this particular mouse model is also difficult to breed and thus quite costly.

- Recommendations:

The potential benefit here is quite large, the reliance on the single mouse model (which has proven to be of considerable relevance and applicability) and on a single disease, albeit complex, may carry a certain risk. Hence assuring access to other mouse models (on which the team has written a review article [TIMM 2011] would appear to be a prudent thing to do for some specific applications. Another way to broaden the scope of the group to avoid the danger of overly relying on a single model, which might be implemented without too much dispersion: do similar work on another toxic RNA expansion disease (for instance Amyotrophic Lateral Sclerosis), or be more actively involved in developing more therapeutic strategies for DM1.

The project is very nice, but also ambitious. A prioritisation might be worth thinking about, even if it might be possible to fulfill the program in the time frame set.

Team 12 : Laboratory of genetics of mitochondrial disorders

Name of team leader: Ms Agnès RÖTIG

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	1	2
N3: Other permanent staff (without research duties)	3	4	3
N4: Other professors (PREM, ECC, etc.)	2	0	2
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	5	0
N6: Other contractual staff (without research duties)	0	0	0
TOTAL N1 to N6	**11**	**11**	**8**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	0	
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 main goal of this group is to identify novel genes and mechanisms responsible for mitochondrial dysfunction and improve our understanding of the physiopathology of mtDNA disorders. This represents the first step for investigating the physiopathology of these highly heterogeneous diseases with the ultimate goal of identifying pharmacological molecules improving respiratory capacity.

The team has made major contributions to the field of mitochondrial medicine. They have published several papers in the top genetics journals (Nature Genetics, AJHG) reporting new gene discoveries. The team has also made important observations on the transmission of the mitochondrial genome during gametogenesis and embryogenesis, a fundamental area of investigation in mitochondrial medicine. In addition, they have contributed to studies on pathogenesis, genotype-phenotype correlation and clinical genetics.

Assessment of the team's academic reputation and appeal

The team leader is without any doubt the top expert on mitochondrial diseases in France. She has an excellent international reputation, as demonstrated by invitations at international meetings and courses. She has established productive collaborations at the international level, as indicated by co-authorship in important collaborative studies. It is recommended that team utilizes this international visibility to obtain European funding.

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

The team leader has established in her institution an excellent structure to work with clinicians for the identification and diagnostic workup of patients with mitochondrial disorders. With the CARAMMEL network, she has contributed to extend this model to the entire country. Therefore, the team provides an extremely valuable service in this highly specialized area of genetics and molecular medicine.

Assessment of the team's organisation and life

The unit is very well organized, both internally and in its interaction with the clinic.

Assessment of the team's involvement in training through research

The team is effectively engaged in the training of undergraduate and graduate students and postdoctoral fellows.

Assessment of the five-year plan and strategy

Thanks to the excellent link with the clinic and the expertise in molecular, it is expected that the team will discover more genes causing mitochondrial disorders in the next few years. However, there is a clear need to move more and more toward functional studies, investigate pathogenesis and eventually explore potential therapies. The team is moving forward very well in the areas of the transmission of mitochondrial genomes in gametogenesis and embryogenesis, and of the molecular pathogenesis of the disorders of mitochondrial protein synthesis. They should be strongly encouraged to pursue this research lines, and also to increase their direct involvement in the study of the defects of RNA import in mitochondria, a very interesting novel subject. In the therapeutic field, they should be encouraged to continue providing proofs of principle in model systems for potential therapeutics for mitochondrial disorders, as they have done so far with quinone derivatives and iron chelators.

Conclusion

- Strengths and opportunities:

A unique web including well known pediatric division with international expertise of mitochondrial diseases constitutes a reservoir for identification of new genes involved in these diseases. Almost all of the techniques to assess the functional relevance of the mutations are available in the site of the IHU IMAGINE.

Excellent publications.

- Weaknesses and threats:

As mentionned in the proposal, the large genetic heterogeneity of mitochondrial diseases makes that the identification of new genes is most often restricted to few patients and the concurrence is rude in the field of mitochondrial disorders. The creation of the IHU/IMAGINE Institute may give the opportunity to explore more deeply the functional consequences and the physiopathological mechanisms of mt impairment in different organs such as liver or cardiac muscle.

- Recommendations:

Go into in-depth studies of biological mechanisms.

Team 13 :

Laboratory of genetic skin diseases: from disease mechanisms to treatments

Name of team leader:

Mr Alain HOVNANIAN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	1	1
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	1	1	1
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	4	2
N6: Other contractual staff (without research duties)	7	7	2
TOTAL N1 to N6	**14**	**14**	**7**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

This is a leading team in the field of inherited skin disorders. After identifying numerous genes causing skin diseases, the group now focusses on COL7A1 dystrophic epidermolysis bullosa, Netherton syndrome, atopic dermatitis and Darier disease. The projects focusses on the understanding of the physiopathology of the diseases, including construction and studies of mouse models and identifications of modifier genes, and on therapeutic approaches, including ex vivo replacement gene therapy and exon skipping for the recessive diseases and allele-specific si-RNA mediated degradation for the dominant diseases. The scientific production is outstanding with 37 research articles published over the 5 years period including 18 publications as senior authors, and 10 reviews and 5 book chapters. Many research articles were excellent and were published in high-impact journals such as Journal of Experimental Medicine (IF 13.85 : the demonstration that Netherton mutations cause kallikrein 5 desinhibition, leading to atopic dermatitis-like lesions through thymic lymphopoietin expression) and Journal of Clinical Investigation (IF 13.07 : the demonstration that kallikrein 5 desinhibition also causes elastase 2 overexpression and subsequent skin damages).

Assessment of the team's academic reputation and appeal

The team has a very high reputation and appeal in the field, as testified by invitations to many international congresses as well as participation and coordination of many international projects, including two EU consortia on preclinical and phase I/II clinical trial for ex vivo gene therapy for epidermolysis bullosa (FP6 THERAPEUSKIN and FP7 GENEGRAFT).

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

During the evaluation period, the team has submitted 4 patents on therapeutic applications for the treatment of inherited skin disorders, including one on gene therapy of recessive dystrophic epidermolysis bullosa by exon skipping strategy. The team has numerous industrial contracts: Novartis for the treatment of Netherton syndrome and of atopic dermatitis with kallikrein7 inhibitor, Regeneron for the treatment of Netherton patients with Anti-IL-1, GSK for the development of samll kallikrein inhibitors (mostly KLK5 innibitors treatment of Netherton syndrome and of atopic dermatitis), and Cellectis for the corrective gene therapy of recessive dystrophic epidermolysis bullosa by Meganuclease mediated homologous recombination.

Assessment of the team's organisation and life

Despite a move during the evaluation period from Toulouse to Paris and the loss of several permanent team members, including permanently recruited INSERM scientists, the team appears to be well organized, with newly hired permanent staff and bright perspectives.

Assessment of the team's involvement in training through research

Training of Master (9) and PhD (3) students. Teaching in Master programs.

Assessment of the five-year plan and strategy

The project of the team for the next five years is strongly devoted to the advancement of ex vivo gene therapy for dystrophic epidermolysis bullosa by various innovative strategies, including replacement therapies with SIN COL7A1 retroviral vector, Meganuclease mediated gene targeting and exon-skipping strategies. These projects are well funded by agencies (EU-FP7, AFM-strategic project) and a private company (Cellectis) and should rapidly lead to a benefit to the patients affected by these dramatic diseases.

The future plans are also aimed at improving diagnosis of Netherton syndrome and its therapy by kallikrein inhibitors, as a result of the observations made by the team on the physiopathology of the disease. This includes the investigation of immunological abnormalities in patients, the development of new murine models and their crosses with candidate modifier gene KO (KLK5, KLK7, KL14, Tnf-alpha, Il1-r) in order to validate therapeutic strategies, and the design and implementation of clinical trials using new therapeutics. The project also plans to expand findings made for Netherton disease to the considerably more common skin disorder atopic dermatitis, through multifactorial gene studies of large cohort of trios. This part of the project is also well funded by private companies (Novartis, Regeneron, GSK). For Darier disease, pathophysiological past results and future plans also suggest potential strategies for therapeutic intervention.

Conclusion

- Strengths and opportunities:

Extensive network of scientific collaborations, contacts with pharma companies and patients' organisations for the implementation of clinical trials in inherited and genetically predisposed skin disorders. The team is owner of several patents on the subject. This is a high performing team that will find a perfect scientific environment in the frame of the Imagine institute for the study and treatment of serious genetic skin disorders.

- Weaknesses and threats:

After the move from Toulouse, the team will have to attract and recruit permanent scientists and engineers. The move to the new Imagine institute also appears to be complicated for logistic reasons, including the need of a proper GMP facility to produce the gene therapeutics for the clinical trials.

- Recommendations:

An outstanding team, that needs to be supported. In particular, the need for a GMP clean room facility will have to be taken into account in the near future.

Team 14 :

Laboratory of origins and functions of skeletal stem cells in bone repair (ATIP-AVENIR Team)

Name of team leader:

Ms Céline COLNOT

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	0	0	0
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	1	2	0
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1	0
N6: Other contractual staff (without research duties)	0	0	0
TOTAL N1 to N6	**3**	**4**	**1**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	0	
Theses defended	0	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The team has developed an independent research program aiming to identify the origins and functions of skeletal stem cells in bone regeneration.

They have established several models of bone repair in mice with genetic labeling and bone transplantation which allow tracking of the fate of tissues and cells during bone development and repair. They use these methods to study stem cell recruitment from periosteum, bone marrow and surrounding soft tissues such as muscle during bone regeneration.

The team leader has joined INSERM U781 on June 1st, 2010 and supervises an ATIP-AVENIR team since January 1st, 2011. Her research activities at INSERM are in continuation with those at UCSF. The principal results since the creation of the group include the role of Matrix metalloproteinases in fracture callus remodeling and inflammation during skeletal regeneration, the Identification of the cellular contribution of bone marrow and periosteum during bone repair, the role of BMP2 and BMP7 in skeletal cell fate decisions during the early stages of skeletal regeneration and the comparative effects of bisphosphonates (zoledronic acid) during long bone and mandibular bone regeneration.

These results lead since 2007 to 14 articles (5 since 2011), 4 reviews and 2 book Chapters. The 4 main publications of the team were in PLoS ONE (2007), Bone (2010) and Dis Model Mech (2011), as a last author and J. Bone Miner Res (2009) as a single author.

The team has been successful in securing funds through competitive grant applications (FP7 marie Curie, SANOFI, Ostheosynthesis and trauma Care fondation) but most of all she has obtained a NIH/NIAMS grant before living UCSF.

Assessment of the team's academic reputation and appeal

The influence and attractiveness of the team is illustrated by 11 invitations to international conferences. The team also has several internal collaborations with american laboratories.

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

The 2011-13 ATIP-AVENIR program was co-sponsored by Sanofi.

Assessment of the team's organisation and life

The team recruited one technician in 2010, one post-doctoral fellow in 2011 and several master students.

They are currently recruiting a technician based on the funding from OTC foundation and anticipate the recruitment of a PhD student based on fellowship or extramural funding.

New grant applications in order to reinforce the research team in the future are ongoing.

Assessment of the team's involvement in training through research

The team is actively involved in training PhD and Master students in various programs (Master of Experimental Biotherapies, Paris 13 University) at a national or European level (European Master of Genetics), and teaching medical students.

Assessment of the five-year plan and strategy

The global project is in line with the previous work with a global focus on the implication of stem cells in bone repair. The functional role of muscle in bone repair using cell lines or mice as well as its interaction with progenitor cells is added to the program. Another new aspect explores the role and the possibility of targeting the FGF pathway in order to stimulate bone repair again using cell lines and mice models.

Conclusion

- Strengths and opportunities:

As mentioned in the report, the team has shown an expertise and an international status in the field of stem cells assessment in bone. They will also take advantage of their environment at Imagine Institute in term of facilities.

- Weaknesses and threats:

The group points out that the development of cooperation among IMAGINE institute will help to initiate genome wide analyses and epigenetic studies but this studies dos not appear in the project which clearly lacks genetic tasks. Similarly, “effort to communicate” with the orthopaedic group is mentioned. In this purpose, it could be of interest to integrate orthopaedic surgeons in the team. Giving the strong international competition, the team is quite small and should expand. Similarly, the topic is very “hot” and one could expect the group to publish in better impact factor journals.

- Recommendations:

Include in the team an academic surgeon from the orthopaedic department.

Try to better integrate in the IMAGINE project by making interactions and collaborations with the associated teams.

Team 15 :

Laboratory of Human Genetics of Infectious Diseases - Genetic immunology of infectious diseases team

Name of team leader: Mr Jean-Laurent CASANOVA

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	1	1
N2: Permanent EPST or EPIC researchers and similar positions	4	4	4
N3: Other permanent staff (without research duties)	3	3	0
N4: Other professors (PREM, ECC, etc.)	2	2	2
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	9	11	7
N6: Other contractual staff (without research duties)	4	2	0
TOTAL N1 to N6	**23**	**23**	**14**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	8	
Theses defended	2	
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	2	2

• Detailed assessments

Assessment of scientific quality and outputs

The program of the team is very compelling. The team aims to discover single-gene errors of immunity explaining life-threatening infectious diseases in children and characterize the underlying primary immunodeficiencies. The principal microorganisms studied are mycobacteria, pneumococci, herpes simplex virus and *Candida albicans*. The idea is that the responsible Mendelian genetic defect can be analyzed by cutting-edge strategy combining whole-exome sequencing (WES) with functional tests which the team has pioneered for infectious diseases. The functional analyses focus on the TLR and IL-1R pathways of NF-κB activation in children with primary immunodeficiency (PID), or on TLR3 and IFN-α/ß pathways in children with *herpes simplex* encephalitis (HSE). Another project is to decipher the mechanism by which the gain-of-function mutations in STAT1 alleles impair the development of IL-17 T cells (Th17 cells).

Altogether, the team has a strong scientific record of discovering new genes that influence the immune system using this approach and in the future their simple but effective strategy will be further enhanced by exploiting next generation sequencing approaches. Over the last four years the team's strategy has led to several major achievements in the fields of bacterial (mycobacterial and pyogeneic bacteria), viral (oncogenic viruses and HSV1) and fungal (*Candida albicans* and dermatophyte) infections. These results supported the proposal of new hypotheses and concepts in the field of human genetics and infectious disease, which have been published in several editorials and reviews. In particular, the novel idea of "one gene, one disease" underlying the single type of infection in at least a group of primary immunodeficiences, was published by the team leader in *Science* as early as in 2007.

Thus, the team has produced results that are well recognized internationally, and many of their studies appear as publications in excellent journals . During the last five years the team leader has been the senior or first author on at least 10 articles published in high-impact journals, such as *Science, New Engl. J. Med., Nature Med., J.Clin. Invest, and J. Exp. Med*. Therefore, the report together with the oral presentation provided a very satisfactory basis to assess the productivity and high scientific quality of this team's scientists. Also,"Scopus" lists 404 publications for the team leader with an h index of 70.

Assessment of the team's academic reputation and appeal

It appears from the above section that the team is well known internationally. There seems to be synergy with the team of genetic epidemiology and several important collaborations with clinicians and different scientific groups are mentioned. During the last couple of years the team leader has been invited to give several international keynote lectures and other honorary lectures, and since 2004 he has received six international prizes or awards. During the period 2006-2009 the team leader was the President for the European Society for Primary Imunodeficiencies.

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

The medical applications of the team's discoveries are important in terms of diagnosis, prevention and treatment. Molecular diagnosis and genetic counseling might be offered to families and the development of personalized medicine is a hot topic. However, no direct information of the team's efforts to this end is given in the proposal -- that is, it is not clear to what extent the team is involved in clinical diagnostic activities and contributes to genetic patient advice.

Assessment of the team's organisation and life

Most of the researchers in this team have an MD-PhD, and they work in close collaboration with those who have a PhD and special training in genetics, immunology or virology. The team has a unique access to patient cohorts. The team has a long-standing history of scientific and clinical collaboration, and operates in a cooperative network of expert clinicians throughout the world.

The team also has collaboration with a sister team at Rockefeller Laboratory in New York (USA), where the team leader spends part of his time. This transatlantic set-up provides outstanding opportunities for high-standard research, facilitating access to high-quality technology platforms and enhancing funding possibilities.

Interaction with the new IMAGINE Institute will further enhance the scientific environment and access to core facilities. The Paris-based part of the team is divided into four groups (6-8 people in each) covering mycobacterial, bacterial, viral and fungal infections. In their SWOT analysis they highlight the need for more space and more opportunity to secure long-term funding.

Assessment of the team's involvement in training through research

The team has currently 8 PhD students and one postdoctoral fellow. There are two qualified research supervisors, and two theses have been defended. The transatlantic axis promotes exchange of students, postdocs ans researchers between the two laboratories, increasing the knowledge base for the team. A weekly seminar is held, common to the two branches of the team, via a videoconfernce system.

Assessment of the five-year plan and strategy

Overall this appears to be a very strong program in molecular medicine with a sound balance of basic scientists and clinicians with expertise in infectious diseases. In the past they have made important contributions to the field and the present program is an extension of their previous work. The proposal states that over the next eight years the team will peruse the lines of research followed over the last years, and in addition “uncharted territories” will be explored – that is, other severe childhood infectious diseases will be studied to discover potential single-gene inborn errors of immunity. The use of next generation sequencing should provide a substantial impetus to the program and reveal many new candidates to address the team’s interesting hypothesis, and the team appears to be uniquely placed to deliver to this program. However, it would be interesting to see a plan for integrating all of the new findings into a more comprehensive immunological system to understand the genetic contribution to patients who develop these severe forms of infection.

Conclusion

- Strengths and opportunities:

An outstanding team with major past contributions to the genetics of infectious diesases and with an outstanding program.

- Weaknesses and threats:

The team lists as potential weaknesses or threats that there is an increasing bureaucracy in academia/hospitals and that study protocols are quite complex as they have to adhere to the ethics guidelines for clinical trials. The applicant should also have discussed that their adherence to WES (largely the coding sequences) as their major genetic molecular tool might be a potential weakness or threat in the future. Many centers are now enrolling patients in studies that either perform whole genome sequencing (WGS), WES or use a combination of approaches including SNP arrays. As a matter of fact, WGS is being increasingly used based on its availability and improved cost efficiency.

- Recommendations:

Continue.

Team 16 :

Laboratory of Human Genetics of Infectious Diseases - Genetic epidemiology of infectious diseases team

Name of team leader: Mr Laurent ABEL

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	0	0	0
N2: Permanent EPST or EPIC researchers and similar positions	3	2	3
N3: Other permanent staff (without research duties)	0	0	0
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	6	7	3
N6: Other contractual staff (without research duties)	3	4	0
TOTAL N1 to N6	**12**	**13**	**6**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6	
Theses defended	3	
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	2	2

• Detailed assessments

Assessment of scientific quality and outputs

The Team II of the Laboratory of Human Genetics of Infectious Diseases, Inserm U980 focuses on the genetic epidemiology of infectious diseases. The team has a truly outstanding track record in using linkage analysis and association studies to explore the complex genetic basis of infectious diseases. This includes work on leprosy, tuberculosis and some oncogenic viruses, *i.e.* HCV, HHV-8 and HTLV-1. Important work on the main topic of the laboratory in the period 2007-2012 included (i) the identification of LTA+80 and a number of additional SNPs as leprosy susceptibility loci, (ii) the identification of TOX as a susceptibility factor for pulmonary TB, (iii) the demonstration of genetic control of tuberculin skin reactivity and the identification of two important loci, (iv) the demonstration of genetic predisposition to HCV infection, the identification of IFNγR2 gene variants in chronically HCV infected patients with liver fibrosis and the impact of IL28B variants on HCV clearance.

This work has significantly improved our understanding of the role of gene variants in determining the susceptibility to and the clinical phenotype of human infectious diseases. It opens new avenues for research on the functional implications of the gene products in disease pathogenesis. Original work on genetic epidemiology has been published in excellent journals (*Nature Genetics, J Exp Med, Gastroenterology, Gut, J Med Genet, Clin Infect Dis, J Pediatr,…).*

In addition, the group has contributed significantly to the work of Team I of Inserm U980. This contribution is well documented (34 common original publications focussing on “mendelian” infection susceptibility), reflecting that the organization of the unit with two outstanding teams dedicated to the study of the human genetics of infectious diseases is an exceptional opportunity. In contrast, contribution of the genetic immunology group to the epidemiological work is less obvious (4 common original publications focussing on “complex” infection susceptibility). An attempt to more extensively look into the functional immunological validation of SNPs and a common choice of pathogens (as beautifully exemplified in TB/NTM) could be interesting possibilities to further improve the interaction towards the epidemiological side.

Assessment of the team's academic reputation and appeal

Members of the team have been invited speakers at numerous national and international meetings. The principal investigator has received the Prize Jean Valade in 2009 and another investigator was awarded two scientific prizes in 2007 and 2011. The award of an ERC advanced grant to the principal investigaor is a high recognition not only of his work in the past, but also of his future scientific concept. The team has succeeded in attracting significant additional funding as a solid basis for the years to come.

The team leader is active in editorial boards, scientific advisory boards and scientific committees and has many international collaborations.

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

The common work of the Laboratory of Human genetics of infectious diseases has received significant international recognition including several articles in the lay press. The principal investigator contributed two book chapters. He has filed two patents and has developed software for genetic linkage analysis that is accessible for the scientific community.

Assessment of the team's organisation and life

The team was part of the “Laboratory of human genetics of infectious diseases”. This laboratory, with a Rockefeller and a Necker branch aims to identify the susceptibility genes for human infectious diseases. The set-up of a genetic epidemiology and a genetic immunology team has been very fruitful in the last years and has not suffered from the trans-atlantic set-up. It is not completely clear to which extent *this set-up benefits the epidemiological research.*

Assessment of the team's involvement in training through research

Since 2007, the team has supervised 3 completed and 3 ongoing PhD theses and has supervised 9 master students. The team participates in teaching courses in Paris as well as at Montreal and McGill Universities in Canada.

Assessment of the five-year plan and strategy

The team will continue to use genome-wide approaches based on linkage analysis followed by linkage equilibrium and/or association studies (GWAS) for the analysis of genetic predisposition to *tuberculosis, leprosy, Burulli ulcer* and *HCV* infection phenotypes. Furthermore, the group will contribute to the genetic dissection of "mendelian" susceptibility to infectious diseases using whole exome sequencing and homozygocity mapping. The epidemiological studies are placed in the context of large field studies and appropriate cohorts with a good definition of the phenotype are available. The work on tuberculosis is focussed and extends previous observations on susceptibility loci to pulmonary tuberculosis and on T cell independent resistance to *Mycobacterium tuberculosis*. Importantly, for these studies, not only family based population samples are available, but also samples from additional independent populations. Work on leprosy will be extended from leprosy *per se* to particular leprosy phenotypes. The definition of more specific phenotypes is an important strategy for the future work. Similar approaches are used for disease and phenotypes induced by *M. ulcerans, HTLV1, HHV8, HCV* and *HBV*. Validation of the variants by functional studies are planned and this will be an important endeavour in collaboration with the other team of the unit. The continued involvement in the methodological work is an important prerequisite to stay ahead in this fast moving field. The scientific portfolio is large, but the plan to support a young investigator, who is seeking independence as INSERM researcher with the HBV and HCV projects, justifies this current diversification. Overall the five-year plan is convincing and the strategy is well developed in the context of the established setting.

Conclusion

- Strengths and opportunities:

The team has excellent international reputation. The ERC advanced grant provides the perspective needed to further develop the main lines of scientific research. The structural setting with a genetic epidemiology and a genetic immunology laboratory is excellent in principle, but its full potential for understanding the genetic basis of more common infectious diseases in adults remains to be explored (see below).

- Weaknesses and threats:

With 6 infection models and several phenotypes per infection, in addition to the contributions to the genetic immunology team, the program of the epidemiology team may get too diverse to remain focused.

- Recommendations:

Even better use the full potential of synergies of the combination of epidemiology, statistics, functional immunology and genetics for understanding the "non-mendelian" susceptibility to infectious diseases. This should also give rise to, once more, important methodological output in terms of methods and publications.

Validation of functional immunological (or other) significance of detected SNPs is of key importance and should be actively pursued in collaboration with the genetic immunology lab.

Team 17 : Laboratory of Hereditary Kidney Diseases - Team 1

Name of team leader: Ms Corinne ANTIGNAC

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	2	1
N2: Permanent EPST or EPIC researchers and similar positions	0	1	0
N3: Other permanent staff (without research duties)	5	6	3
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	2	2
N6: Other contractual staff (without research duties)	2	1	1
TOTAL N1 to N6	**14**	**13**	**8**

Team workforce	Number as at 30/06/2012	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	0	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The Team belongs to the world wide leading groups in renal genetics. Over the last two decades they have made seminal contributions to the field of hereditary kidney diseases. Among them the identification of genes causing steroid resistant nephrotic syndrome, nephronophtisis, Bartter syndrom and cystinosis. In the last funding period this team continued with genetic landmark discoveries such as identifying INF2 mutations in Charcot-Marie-Tooth disease (NEJM 2011). These genetic discoveries are well documented by highly cited publications in international top journals like *Nature Genetics and New England Journal of Medicine*. Furthermore, this team has been more and more active in generating and analyzing models to elucidate the pathophysiology behind the mutated genes. Highly recognized examples are the work up of multiple transgenic mouse models targeting podocin (J Am Soc Nephrol 2009), WT1 (Hum Mol Genet 2010) and cystinosin (Nephrol Dial Transplant 2010). These mouse models deepened the insight in the molecular mechanims of respective kidney diseases. Next to the work mainly been done by this lab this team contributed and co-authored to over 20 publications with many of them being published in top journals like *Nature Genetics*, *Journal of Clinical Investigation* and others.

Assessment of the team's academic reputation and appeal

With its international reputation this team has attracted several scientists from Europe and North America. In addition, this team was very successful in securing national and international funds (>1.4 Mill. € 2007-2012). The national funding includes mainly funding from the ANR as well as from the FRM foundation. At the European level this team participates in two very successful international collaborative programs: The FP7 project Eunefron and the Erare Project Podonet. The principal investigator has been invited to speak at the most important international meetings in the field (e.g. ASN, WCN, IPNA, ERA-EDTA among others) and national meetings. Furthermore the principal investigator served in national and international scientific committees. It can be anticipated that this group will continue to significantly contribute to the appeal of the Imagine Institute.

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

The proposal documents a close cooperation with several pharmaceutical companies, international research consortia and foundations. Examples are the grant from the Cystinosis Research Foundation (USA). Furthermore, there is a close cooperation with Novartis.

Assessment of the team's organisation and life

The principal investigator is the scientific manager of the Biological Resource Center on the Necker campus. She has successfully contributed the unique collection of patient samples including 22.500 samples from children with rare genetic disorders. Furthermore, the principal investigator will be part of the Imagine Executive Committee, which will be majorly important for the scientific and organasitory decisions of the Imagine Institute.

Assessment of the team's involvement in training through research

The team has supervised several postdoctoral fellows and PhD students. The group leader is actively teaching in different programs. There appears to be no participation in international training networks.

Assessment of the five-year plan and strategy

The research plan is excellent. The strategy is based on the identification of further yet unknown genes causing hereditary nephrotic syndrome as well as on the functional understanding of protein functions of already identified genes. More specifically, the team aims to characterize the protein interaction network of cystinosin with particular focus on already identified targets of the V-ATPase and TORC1 complex. In addition, functional assays has been set up to elucidate the intracellular transport fo nephrin and podocin. Furthermore, the role of the INF2 complex for the vesicular transport in podocytes will be examined. Of importance will be the integration of new team members (with cell biology expertise) and the collaboration with the animal platforms (e.g. Zebrafish facility) within the Imagine unit.

Conclusion

- Strengths and opportunities:

Worldwide reputation in the field of genetics.

Large patient cohorts.

Excellent genomics facilities & gene identification unit.

Well established international research network & collaboration.

The envisioned animal facilities (zebrafish, transgenic mice) in the Imagine Institute could facilitate the mechanistic research part of this group.

- Weaknesses and threats:

Some of the functional studies being proposed rely on cell culture models, which might not perfectly reflect the complex in vivo situation of podocytes.

The team leader seems to be much involved in the administrative work of the Imagine Institute, which could negatively influence her research activities.

- Recommendations:

Establish strategies for the “post-monogenetic diseases discovery” era, e.g. further strenghten the functional unit.

Need of an administrative support for the team leader, which will allow her to efficiently combine organisatorial work within Imagine as well as basic research.

Team 18 : Laboratory of Hereditary Kidney Diseases - Team 1

Name of team leader: Ms Sophie SAUNIER

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	1	2
N2: Permanent EPST or EPIC researchers and similar positions	2	3	2
N3: Other permanent staff (without research duties)	3	1	1
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	1	2
N6: Other contractual staff (without research duties)	1	1	1
TOTAL N1 to N6	**10**	**7**	**8**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	0	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	1

• Detailed assessments

Assessment of scientific quality and outputs

This is an international highly recognized team with excellent scientific publications. The team leader has established a group with two main interests: nephronopthisis and renal hypodysplasia. Nephronophthisis is one clinical feature of a group of disorders known as ciliopathies. The group has identified three genes encoding intraflagellar transport proteins (IFT139, IFT140, IFT144) that, when mutated, lead to ciliopathy phenotypes and another encoding TCNT3 that they have shown to be required for hedgehog signalling. As indicated by the name, abnormalities of primary cilia are thought to be the cause of ciliopathies including the renal phenotype. However the nephrocytins (proteins mutated in nephronophthsis) also localise to junctions between epithelial cells and between the epithelial cells and basement membrane. The team leader has used three-dimensional collagen matrices to demonstrate anormalities of tight junction (TJ) formation. In zebrafish she has shown that NPHP4 acts as a switch form the Wnt/beta-catening pathway to the Wnt/planar cell polarity pathway. She has also published that NPHP8 favours Wnt/planar cell polarity signalling.Moving to their work on renal hypodysplasia (RHD), the group has identified two new causes of autosomal recessive RHD – fibroblast growth factor 20 and integrin-alpha3 mutations. This is a highly productive group with excellent outputs. 1 publication in Nat Genet as first and.or last author, and, as collaborators, publications in Cell, Nat Genet (3), New Engl. J Med, J Cell Biol.

Assessment of the team's academic reputation and appeal

The team has a good international reputation and is involved in International networks such as EURENOMICS and in addition to European collaborators has collaborators in US and Australia. They have international students and post-doctoral fellows from Hungary (K. Tory post-doc 2006-2009), UK (M. Muorah M2-2011), Italy (V. Grampa PhD 2011-present). This young team has an excellent track record of international funding.

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

The team has an interaction with the pharmaceutical industry (Novartis). The team has a lot of interesting international partners supporting specific areas of research. No collaboration with patient associations is stated but their findings have translated directly to diagnostic tests. For both of the disease groupings they have access to large collections, >800 NPh families and 700 RHD patients. No partnership with SME is commented.

Assessment of the team's organization and life

No rated

Assessment of the team's involvement in training through research

The Unit has 2 doctoral students. An investigator who will join the group in 2013, is director of a Master in Paris Descartes University (Cell and Developmental Biology) and may attract new doctoral students.

Assessment of the five-year plan and strategy

The team leader presented exciting unpublished results to the panel that will undoubtedly lead to strong publications and enhance their reputation further. The team is following two major aims, which are NPHP- and RHD-related diseases. They have access to genomic facilities that will allow them to achieve their goals. The project overall is outstanding and will improve the quality of health care for children with some renal genetic conditions. The group will include 2 new people in 2013 and 2014. These persons have a great expertise in their field and will improve and enhance the skills of the group. The research plan of the group is well elaborated and extensive and promises highly interesting results and advance in the field of kidney diseases. The EURENOMIC project fits within the 5 years period.

Conclusion

- Strengths and opportunities:

High level of expertise on nephronopthisis and renal hypodysplasia and huge cohorts of patients are the basis for a promising future of this team. Also they are very well positioned within the international networks. Having a clinician in the team, also belonging to MARHEA, is a great asset. The incorporation of two new people will increase the team skills and knowledge and will allow carrying out some of their objectives.

- Weaknesses and threats:

Although well-funded their funding does not match their ambitions; the budget is at this moment not sufficient to develop all their projects.

There is a very strong competing group in Ann Arbor (USA).

The size of the group may be a bit too small to achieve all their goals.

- Recommendations:

Collaborate with patient associations.

Try to increase the budget.

The group does not need to follow up ALL newly discovered genes. If the size of the group and the budget does not allow it, they could focus in just some of them.

The group would benefit from an expert in bioinformatics.

Team 19 : Laboratory of interactions of the intestinal epithelium and the immune system

Name of team leader: Ms Nadine CERF-BENSUSSAN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	5	5	5
N2: Permanent EPST or EPIC researchers and similar positions	4	3	4
N3: Other permanent staff (without research duties)	5	5	3
N4: Other professors (PREM, ECC, etc.)	1	2	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	6	6	6
N6: Other contractual staff (without research duties)	0	0	0
TOTAL N1 to N6	**21**	**21**	**19**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	14	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit	6	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	7	7

• Detailed assessments

Assessment of scientific quality and outputs

The team focus has always been the pathophysiological role of intestinal lymphocytes and their interactions with the gut epithelium. Coeliac disease (CD), a relatively common childhood enteropathy, has been a very useful clinical model for studies of these interactions. The team made seminal contributions in this field, leading to a changing paradigm of the immuno-pathogenesis of CD. It was previously believed that this disorder was caused by interactions between wheat gluten, genes and the adaptive immune system. The PI clearly showed that the pathogenesis, in addition, involves an important contribution of innate immunity. Certain gluten peptides can directly activate the gut epithelium so that it secretes IL-15; this cytokine next activates intraepithelial lymphocytes to secrete the disease-promoting cytokine IFN-γ and drive them into cytotoxic activity, while at the same time blocking the effect of the suppressive cytokine TGF-ß.

CD is a model disorder to analyze how interactions between environmental and genetic factors can trigger intestinal inflammation in response to a dietary antigen, induce autoimmunity and promote T lymphomagenesis. Past work had shown the key role of adaptive immunity orchestrated by HLA-DQ2/8 molecules. These molecules that confer a major genetic risk, present gluten peptides to lamina propria CD4+ T cells and can thereby induce their activation in the small intestinal mucosa. The main contribution of the team has been to demonstrate the parallel severe alterations of lymphocyte homeostasis in the gut epithelium and to disclose the important role of innate immunity orchestrated by the cytokine IL-15.

The team has shown that IL-15 synthesis is massively increased in the gut epithelium and lamina propria of patients with active CD and refractory CD (not responding to a gluten-free diet). Epithelium-derived IL-15 is necessary and sufficient to drive the survival and expansion of clonal intraepithelial lymphocytes (IELs) in refractory CD. Due to their high sensitivity to IL-15 and to the potent anti-apoptotic properties of this cytokine, clonal IELs survive and probably accumulate genetic alterations that sometimes promote the progression to high grade T-cell lymphoma. Thus, IL-15 orchestrates epithelial damage in refractory CD by inducing the secretion of IFN-γ by IELs and their perforin/granzyme-dependent cytotoxicity against enterocytes.

All these original findings have been well received by the international scientific community. The results have been published in well-known journals with a relatively high impact, and have been elaborated in several good review articles.

It is always difficult to obtain acceptance for novel ideas in a well-established field. However, the research of the team has been so solid and penetrating that the changing paradigm of CD is now widely accepted and substantiated by other eminent scientists. It is impressive how this team has been able to apply clinical knowledge from the paediatric field to basic scientific work. These efforts represent true translational research which requires the dual skill that the PI possesses, being trained both as a clinician and a mucosal immunologist.

The team published in 2004 (in *Immunity*) that IL-15-dependent cytotoxicity of IELs against enterocytes in refractory CD requires the interaction of the activating NK receptor NKG2D on IELs with its ligand MIC abnormally expressed by enterocytes both in active CD and refractory disease. This work also showed that expression of MIC on enterocytes is induced by gluten peptide 31-49 via IL-15, which fits with other results obtained for the pathogenesis of CD, implicating this peptide as being “toxic”. Altogether, these results indicate that IL-15, induced (directly or indirectly) by peptide 31-49, orchestrates an innate immune response that promotes an autoimmune attack on the gut epithelium by IELs.

Another role of IL-15 in CD was also suggested when her team demonstrated that IL-15 impairs activation of the TGFβ-Smad3 pathway, a key control mechanism of both T lymphomagenesis and intestinal inflammation. The effect of IL-15 was ascribed to a long-lasting activation of Jun-kinases that induces phosphor-c-jun which is able to interfere with Smad3 binding to the promoters of TGFβ target genes. The effect of IL-15, observed in IELs and lamina propria lymphocytes may initiate not only the activation of IELs but also the HLA-DQ2-adaptive CD4 T cell response to gluten peptides. This role of IL-15 might more generally explain the deleterious effects of this cytokine in other inflammatory or autoimmune disorders. However, her team has so far been unsuccessful in explaining the upregulation of IL-15 in CD.

More recent work from the team, has demonstrated that secretory IgA (SIgA) antibodies may contribute to uptake of gluten peptides from the gut lumen by exploiting the transferrin receptor (CD71) which becomes apically expressed on activated gut epithelium. This is a novel concept that in the future may facilitate therapeutic intervention in CD, particularly by blocking the enzyme transglutaminase 2 (TG2) which the team recently has shown to promote the retrotranscytosis of CD71-SIgA complexes. Such complexes can carry toxic gluten peptides (e.g., particularly the immunostimulatory 33-mer, peptide 56-89) in a protected manner into the mucosa. This transport is not observed in patients on a gluten-free diet or healthy controls, where the peptides are almost entirely degraded after entering the enterocytes. In contrast, in active CD a large proportion of the peptides is rapidly translocated intact into the lamina propria. This work shows that intact peptides in the intestinal lumen bind to cognate SIgA antibodies which then mediate their retrotranscytosis via the CD71 and TG2, both of which are upregulated at the apical surface of enterocytes in active CD.

The retrotranscytosis of gluten peptides may maintain intestinal inflammation in active CD, although the role of this process in the onset of the disease is not clear. Thus, enterocyte expression of CD71 is markedly up-regulated in response to a decrease in iron stocks, a condition observed in young women following pregnancy, a period classically associated with the onset of CD. The team has also shown that food-derived peptides endocytosed by enterocytes can be loaded on MHC class II molecules and be extruded as exosomes with strong immunostimulatory properties. The results of all this work have potential therapeutic implications, and are to be taken into account to optimize the recently proposed oral therapy with enzymes able to digest gluten. This possible therapeutic approach has been reviewed by the team.

The team also performs complementary projects designed to gain insight into the cross-talk between intestinal microbiota and the host. Bacterial adaptation in the mouse has been described. However, in studies of IgA responses in the mouse gut, it is a complicating issue that mice, in contrast to humans, have a prominent T cell-independent B-cell population (B1 cells) which migrates to the gut from the peritoneal cavity. The host-microbiota studies are performed in a gnotobiotic mouse model. The team also uses transgenic mice with CD4+ T cells specific for ovalbumin and overexpressing IL-15 in the gut epithelium as a pseudomodel for CD. A future aim is to generate a humanized B6 stain with human HLA-DQ2 expression and overexpression of IL-15 to more accurately reflect CD. The team also plans to use this mouse model to investigate if IEL proliferation may result in lymphocyte transformation and development of lymphoma, which is a very severe complication of refractory CD.

Major publications of the team include Immunity (3), J Clin Invest. (1), J Exp Med (1) Gastroenterology (7), Gut (4), Plos Genet (2) Nat Rev Immunol as first and/or last authors.

Assessment of the team's academic reputation and appeal

Many studies of the team had major impact and were well recognized internationally while they have been elaborated in several good review articles. The team's research has promoted a network of excellent collaboration with access to an extensive infrastructure which will be expanded when the team in September will be located in the new IMAGINE building at Necker Campus.

The principal investigator and her colleagues have been regularly invited to dozens of international conferences over the last five years. The principal investigator acts as a reviewer for Gastroenterology, Gut, J. Clin. Invest., Eur. J. Immunol J, Am. J. Physiol., Blood, J. Exp. Med., Science, Nature Review Immunology.

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

The team plans to set up a new industrial partnership to produce humanized anti-IL-15 to be tested in clinical trials on patients with refractory CD and malignant lymphoma development. The team has already an approved trial with autologous stem cell transplantation ongoing in such patients. The principal investigator also wants to exploit the expertise of the Department of Pediatric Gastroenterology in the care of children with untractable diarrhoea. Her hypothesis is that most of these disorders are caused by single-gene mutations. In collaboration with exome sequencing teams of genomics and bioinformatics at IMAGINE she is in the process of testing her hypothesis by whole exome sequencing (WES). As a follow-up goal, she wants to develop links between adult and paediatric CD patient cohorts to improve diagnosis and care of those who are affected by severe enteropathies.

Assessment of the team's organisation and life

The team appears to be organized in a logical manner with its main scientific objectives in mind. The access to pooled resources seems to be good and interactions on a collaborative basis are promoted to enhance innovative research. The team generally presents clear scientific goals. The new IMAGINE building will clearly boost all of this.

Assessment of the team's involvement in training through research

From the number of PhD students (14), postdoctoral fellows (6), and qualified research supervisors (7) listed under the team work force at present, the training situation in the team should be quite good. Defended theses up till now are eight.

Assessment of the five-year plan and strategy

The long-term goal of the team is to perform competitive research on the mechanisms controlling intestinal immune homeostasis and to provide guidelines to treat immunopathological disorders in the gut. The first major goal is to pursue studies on CD and its complications, particularly refractory CD and malignant lymphoma complication, both with regard to the pathogenic role of the discovered retrotransport of IgA-gluten complexes across the gut epithelium and the biological significance of IL-15. Similar analyses may be performed with IgG complexes binding to FcRn, as described for patients lacking IgA in a recent review article from the team. The second major goal is to expand the work initiated on host-microbial interactions in the gut, including local and systemic effects on immune homeostasis. This work will include studies on regulatory T cells and dendritic cells.

The study of autoimmune intestinal disorders should be encouraged because of the team's unique expertise and access to clinical material. To go more in depth as to revealing the biology and pathological properties of IL-15, the team describes various mouse models that appear to be well designed. The same applies to continuing human studies of refractory CD where the team possesses excellent expertise and access to a unique clinical material, especially for genetic studies. The described mouse studies may support the clinical studies, although the team as yet has failed to develop a badly needed mouse model that truly reproduces CD.

One may be sceptical to some of the research described with regard to intestinal homeostasis influenced by host-microbial interactions. These studies are first of all based on mice and colonization with the segmented filamentous bacterium (SFB) which particularly grows in the distal ileum. The group has observed that SFB adheres to the Peyer's patches (PPs) and stimulate T-cell as well as IgA responses. Here a distinction is important between B1 and B2 (classical T cell-dependent) responses when comparing PPs and the lamina propria. This distinction is not discussed in the application, neither is the fact that SFB has not been yet formally identified in humans.

Conclusion

- Strengths and opportunities:

The team has up till now published a great number of original papers in journals with impact factor >10. It is a strength of the team that it combines basic science and clinical expertise promoting translational research.

- Weaknesses and threats:

The impact of the clinic may, however, lead to distraction and a scattered scientific interest. Thus, the team would clearly benefit from being more focused in its scientific efforts. For instance, the mechanistic explanation for the postulated role of TG2 in retrotranscytosis of CD71-SIgA complexes through the gut epithelium is not dealt with in detail, not even in the last paper on this issue from the team (Gastroenterology 2012), and how the uptake of such complexes could be involved in the initiation of CD remains unknown.

Also, although it is useful to combine mouse studies with the exploitation of clinical material, the team needs to pay attention to the fact that many biological features in mice are different in humans, for instance the effect of microbial activation of pattern recognition receptors and the mucosal IgA system.

- Recommendations:

The planned work should take the abovementioned issues into account. Nevertheless, the value of combined approaches in immunology should not be underestimated. There are too few groups performing immunological studies on clinical material, and combining this approach with mechanistic studies. This can generate valuable information which can not be obtained with any other approach. This team deserves strong support.

Team 20 :

Laboratory of cellular and molecular basis of normal hematopoiesis and hematological disorders: therapeutic implications

Name of team leader: Mr Olivier HERMINE

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		1	
N2: Permanent EPST or EPIC researchers and similar positions		3	
N3: Other permanent staff (without research duties)		6	
N4: Other professors (PREM, ECC, etc.)		0	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		5	
N6: Other contractual staff (without research duties)		0	
TOTAL N1 to N6		**15**	

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

• Detailed assessments

Assessment of scientific quality and outputs

CNRS UMR 8147 – Team 3 represents the laboratory of haematological research in the Imagine Institute of Genetic Diseases. The research group is well established and headed by an experienced and well regarded principal investigator. Their research philosophy includes the integration of basic and applied clinical research in haematological conditions affecting both children and adults. Their four main areas of interest include; (i) erythropoiesis and the regulation of iron metabolism (supervised by another investigator) ; (ii) lymphoproliferative diseases; (iii) diseases affecting mast cells and (iv) graft versus host disease in bone marrow transplantation (all supervised by the PI).

This group has been very productive, publishing well cited papers in high impact journals.

Assessment of the team's academic reputation and appeal

Anecdotally, the team leader is a well-regarded principal investigator. However, the documentation given does unfortunately not provide the information for objective evaluation concerning several other important measures including scientific achievements, invited international lectures, prizes, membership of Academic Institutions, etc. He is clearly very well known throughout France and internationally and he is very highly regarded by his close colleagues. Research scientists in his current laboratory are extremely supportive and appreciative of his leadership and mentorship.

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

No information was provided in the paperwork but it was clear from the oral presentation that this group fulfilled the criteria for strong impact on the social and economic space, for example with contributions to the formation of two biotech companies and the development of therapeutics in the area of mastocytosis.

Assessment of the team's organisation and life

The division of labour in this area of research is distributed between a large group studying erythropoiesis and iron metabolism, and three smaller groups studying lymphoproliferation, Mastocytosis and Stem cell transplantation. The involvement of researchers in specific programmes is also detailed although individual skills and roles are not summarised. There is no breakdown of how research funds are divided between the different projects and therefore it was difficult to assess whether the resources are adequate. During the course of the presentation it became clear that although the group has diverse interests they have made important contributions in each of the areas being studied. The team leader explained his research philosophy which is somewhat unusual (covering many topics). Nevertheless, he convinced the committee that he has the drive and enthusiasm to carry several and diverse projects forward whilst remaining internationally competitive in each of these areas chosen to study in detail.

The unit is structured into 4 interacting project areas with a total of 4 senior scientists/PI, 2 engineers, 4 PhD post-doctoral fellows, 3 MD/PhD scientists, 2 MD researchers, 2 ITA, 11 doctoral students, 1 engineering student, 7 students at the Master level and 5 staff members at the technician level. Individual members are often part of more than one project area. How the resources are organised and shared is not reported. The internal organisation and the present state of the premises for this relatively large laboratory is not divulged. Given the large group of researchers (~40) and the huge diversity of projects, the level of support needs to be substantial.

Assessment of the team's involvement in training through research

No information is provided.

Assessment of the five-year plan and strategy

The breadth of topics covered under the four themes of the laboratory is huge and diverse with no fewer than 33 deliverables. Although each deliverable is described in just a few sentences, the topics each represent complex problems that would involve at least 2-3 people; so, from the written report it was not clear how they could all be delivered by the researchers as presented. Many of the proposals are potentially interesting but were not described in sufficient detail to make an assessment of their feasibility, likelihood of success, etc... Some of the proposals are very imaginative. The focus, priorities and scientific details were clarified during the presentation and we were convinced that, despite the wide ranging nature of the programme, the 5 year plan is deliverable and original. The PI highlights the lack of focus as a potential weakness of the programme and the committee agrees with this self-assessment which should be corrected by a focus on fewer project areas, which in turn may also increase the man power available for each of the project areas of the future.

The research planned for the next 5 years is documented in detail and apparently constitutes a continuum of the activity carried out in previous years. 4 project areas are defined:

Research is planned on the molecular mechanisms resulting in specific defects of erythropoiesis with a specific focus on the role of HSP70, the transferin receptor 1, serotonin, neuropilin 1 and adenylate kinase 2 (AK2) deficiency. The latter research focus provides a logic link with the IMAGINE team E5, and has the potential to make essential contributions to the understanding of the presentation of reticular dygenesis.

The focus on lymphoproliferative diseases caused by viral infections (HTLV-1, EBV, HCV) is covering a fairly broad spectrum of specific and timely research questions but is, in comparison to the work in other project areas, in particular erythropoiesis, less concise. Moreover, there is a significant potential that this research is challenged by its significant range given the relatively small size of the research group in charge.

The third focus is dedicated to the pathogenic role of mast cells in various pathologies including the entity of mastocytosis. This is a very strong and well recognised research activity where the team has also served as a National Reference Centre for mastocytosis. One aspect of this work seeks to employ GWAS to identify gene mutations causative for the familial form of mastocytosis (other than c-kit and c-kit activating mutations) while another aspect of the program seeks to establish the cellular role of mast cells in cancer, inflammatory disorders and neurological diseases.

The fourth project area concerns mechanisms of GVHD in allogeneic bone marrow transplantation with a specific focus on MKT cells and the identity and mechanisms of myeloid suppressive cells in the context of allogeneic bone marrow transplantation.

The projects outlined are in general of high originality and very likely to provide essential new insight into a number of important issues in haematology. In addition, several research deliverables propose to investigate specific mechanisms/molecules in distinct disease contexts, a strategy of inter-related approaches that provide obvious coherence and added value. The methodological approaches chosen are credible (though only limited information is provided to be able to judge this in detail). A significant number of research activities are carried out in collaboration with biotech companies. This partnership with the private sector is not entirely well described in the documentation with regards to its governance. The committee understands that this is structured by Institutional rules and regulations in order to dissipate concerns of a potential conflict of interest given that this individual academic leader is also a stakeholder of private companies in the research partnership. The productivity of the laboratory may suffer with possible changes of the provision of adult medicine services at the Necker.

Conclusion

- Strengths and opportunities:

This is a highly original and interesting set of proposals. The programs are initiated from the clinic and are consequently of medical importance. The principal investigator is imaginative and original but in our opinion his talents are spread too thinly. The committee would advise that the projects are reduced in number. The committee also suggests that the on-going projects will be aligned with the aims of the Imagine Institute remit. Finally the committee suggests that some of the responsibilities involved in running each project might be devolved and delegated to the appropriate senior scientists in the laboratory.

- Weaknesses and threats:

None identified, except for the risk of dispersion.

- Recommendations:

The team should benefit from focusing on a maximum of two themes corresponding to erythropoiesis (supported by the “Red Cell “ LABEX network) and mastocytosis (which can allow genetic studies ideally fitting with the IMAGINE project).

5 • Conduct of the visit

Visit dates:

Start: January 30th, 2013

End: February 1st, 2013

Visit site: Hôpital Necker Enfants Malades

Institution: Assistance Publique-Hôpitaux de Paris, Université Paris Descartes, INSERM

Address: 149, rue de Sèvres - 75743 PARIS cedex 15

Conduct or programme of visit:

30 janvier 2013

9h00 Accueil du comité

9h10 Réunion à huis clos du comité

9h40 Présentation des membres du jury et rappel sur le rôle et la procédure d'évaluation par l'AERES

10h00 Présentation bilan et projet IHU (gouvernance)

11h10 Pause

11h25 Réunion du comité et des tutelles (INSERM, Université) en présence de l'AP-HP

12h00 Déjeuner

13h00 Début des présentations

Immunologie		**Génétique**	
13h00	Bilan U768 – Mr Alain FISCHER	13h00	Bilan U781 – Mr Arnold MUNNICH
13h20	Laboratoire Mr Jean-Pierre de VILLARTAY	13h30	Laboratoire Mr Stanislas LYONNET
14h20	Laboratoire Ms Geneviève de SAINT-BASILE	14h40	Laboratoire Ms Valérie CORMIER-DAIRE
15h20	Pause	15h40	Pause
15h40	Laboratoire Mr Frédéric RIEUX-LAUCAT	16h00	Laboratoire Ms Asma SMAHI
17h00	Réunion à huis clos du jury		

31 janvier 2013

Immunologie		**Génétique**	
9h00	Laboratoire Mr Sylvain LATOUR	9h00	Laboratoire Ms Laurence COLLEAUX
10h00	Laboratoire Ms Marina CAVAZZANA CALVO	10h00	Laboratoire Mr Jean-Michel ROZET
11h10	Pause	11h00	Pause
11H30	Bilan U989 – Ms Nadine CERF-BENSUSSAN	11h20	Laboratoire Ms Agnès RÖTIG
11H50	Laboratoire Ms Nadine CERF-BENSUSSAN	12h20	Laboratoire Mr Alain HOVNANIAN
13h00	Déjeuner	13h20	Déjeuner
14h00	Bilan U Mr Olivier HERMINE	14h10	Laboratoire Ms Céline COLNOT
14h20	Laboratoire Mr Olivier HERMINE	15h00	Laboratoire Ms Geneviève GOURDON
16h00	Entretiens parallèles avec Chercheurs/Enseignants, Etudiants/Postdoc, ITA		
17h00	Fin de la journée		

1 février 2013

8h30 Bilan U980 – Mr Jean-Laurent CASANOVA et Mr Laurent ABEL

8h50 Laboratoire Mr Laurent ABEL

9h50 Laboratoire Mr Jean-Laurent CASANOVA

8h30 Bilan U983 – Ms Corinne ANTIGNAC

8h50 Laboratoire Ms Corinne ANTIGNAC

9h50 Laboratoire Ms Sophie SAUNIER

11h00 – 17H00 Réunion à huis clos du comité

Specific points to be mentioned:

Ms Fathia MAMI-CHOUAIB, Institut Gustave Roussy, was an observer for CNRS during the presentation and related discussions of the comittee for team 20.

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

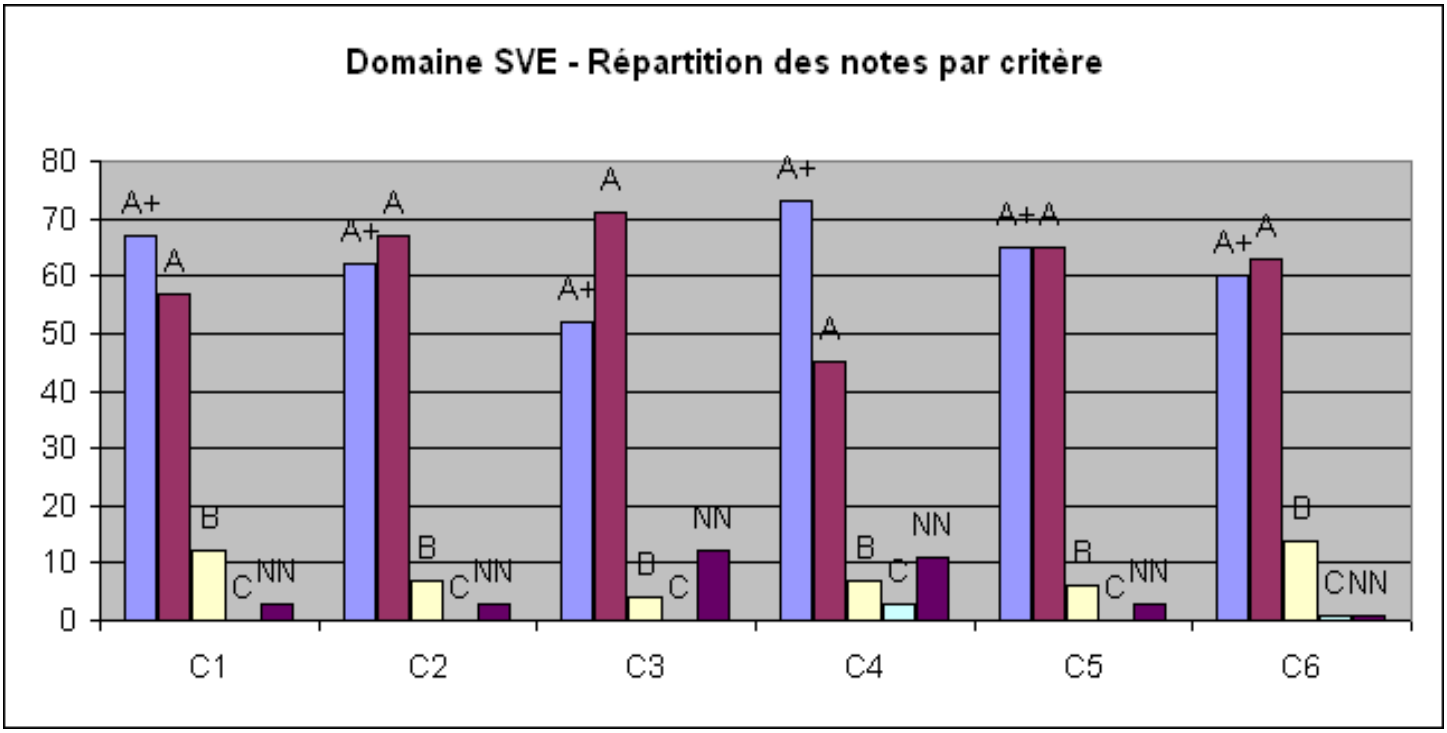
Grades

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 23.04.2013

Vos ref : S2PUR140006465 – IHU Imagine – Institut des maladies génétiques – 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 « IHU Imagine - Institut des maladies génétiques »

Vous trouverez ci-joint les réponses du Directeur de l'Institut, Alain Fischer, auxquelles le Président et moi-même n'avons aucune remarque particulière à apporter.

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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INSTITUT DES MALADIES GÉNÉTIQUES

Responses to the AERES report from the visiting committee
Volet 2

Team 6 – Laboratory of embryology and genetics of congenital malformation (Stanislas Lyonnet)

Page 28: "As stated in their own SWOT analysis, the unit however does not have a good formal training program for young scientists."

Response: The team has trained and will continue to actively train scientific and medical students (see the Table p. 27 for instance with 8 PhD theses in the 2007-2012 period). What has been pointed by the PI is that an effort for improving the training format should be done collectively by the IMAGINE Institute in cooperation with the Paris Descartes University.

Page 29: "Furthermore, there appears to be no new fulltime researchers attracted to the team since 2004."

Response: A full time researcher, Mrs A. Henrion-Caude (CR1 INSERM), joined the team in 2007 and other regroupments are also envisioned once the team has moved to the IMAGINE building. Another full-time researcher (Mrs H Etchevers), recruited in the group in 2004, left Paris to Marseille for familial reasons in 2010.

Team 7 – Laboratory of molecular and physiopathological bases of osteochondrodysplasias (Valerie Cormier-Daire)

We have only a small comment concerning the unit 's organisation and life section, which has not been assessed

1) We have an internal meeting every Monday with all members of our team discussing results of specific project

2) We are actively participating at the weekly seminar of our unit and at the weekly seminar of the Imagine Institute.

3) The team has strong links and collaborations with others teams of the Imagine Institute as illustrated by :
   - Cilia disorders and the Ciliome project shared by 2 other teams from the unit (JM Rozet, T Attié) and one other unit (S. Saunier) from the Imagine Institute or
   - by the shared project with Laurence Colleaux on NFIX.
   - our involvement in other projects for our expertise in skeletal dysplasia (from the clinical to cellular levels)

4) Finally, the team is well integrated in the Imagine Institute and used all technological platforms available (Animal facilities, Genomic, Bioinformatic, histology and imaging platforms and biobanks).

Team 20 – Laboratory of cellular and molecular basis of normal hematopoiesis and hematological disorders: therapeutic implications
(Nadine Cerf-Bensussan)

We thank the experts for their positive evaluation of our group and the emphasis put on the excellent capacity of our team to combine basic science and clinical expertise and promote translational research. We do hope that joining IMAGINE will provide us with the best possible environment to foster our research along these lines.

We specifically thank the AERES committee for acknowledging how difficult it has been for us to establish a new and original paradigm concerning the role IL-15 in celiac disease, a role which is no widely accepted.

The reviewers showed concerns on projects which have been initiated more recently.

- We confirm that we intend to dissect in depth the interactions between Transglutaminase, CD71, SIgA and gluten peptides in celiac disease. We have already obtained a series of new exciting results which point out to the key role of this pathway in celiac disease, not only in the transport of peptides but also likely in the activation of the local immune responses. A new article is in favorable revision. For on-going and future work, we intend to rely on our past expertise in biochemistry and endocytosis, on new expertise in imaging developed by C. Lebreton, Research Engineer, as well as on collaborations with groups working on CD71-IgA interactions in erythropoiesis (O. Hermine, I Moura, Imagine) or in nephropathy (R. Monteiro, Bichat), with specialists in endocytosis (G. Montagnac, I. Curie) and collaborations with groups producing specific polymeric IgA, transglutaminase inhibitors and transglutaminase KO mice.

- We are fully aware that we have to be careful in translating our results on host-microbiota from mice to humans. Yet we want to stress that gnotobiotic mice provide today a most powerful tool to mechanistically dissect these interactions and are used by some prestigious groups in the field (A. McPherson). Using this tool, we have established to the general surprise of the community (and to ours) that only a restricted number of host-specific strains, the prototype of which is

Segmented Filamentous bacterium, can drive the full maturation of the gut immune barrier. This important important finding has been largely confirmed by others since our publication in 2009 in Immunity. Very likely this property depends on the capacity of only very few commensal strains to adhere to the mucosa via a host specific receptor. Gnotobiotic mice have thus allowed to establish a new paradigm that likely can be translated to the human situation. Strikingly, Segmented Filamentous bacterium was shown to exist as host-specific versions in many species including in humans as shown recently (in two articles published in november 2012 and february 2013). Recent results of our on-going collaboration with P. Sansonetti suggest the feasibility of cellular microbiology approaches to identify the epithelial receptor. Concerning the IgA response and the possible and controversial role of the B1 pathway described in mice, we have already obtained a series of results which plead against a significant role this B1pathway in the response to the microbiota. The mechanisms of intestinal IgA production may thus not be drastically different in humans and mice. Moreover, these studies in mice will provide us the assets necessary to set up appropriate mouse models to investigate the consequences of the genetic defects that we expect to identify in a cohort of children with very early onset inflammatory bowel diseases thanks to exome sequencing.

Laboratory of Human Genetics of Infectious Diseases (U980)

We thank the committee for the laudatory evaluation of our laboratory of Human Genetics of Infectious Diseases and of the two constitutive teams of Jean-Laurent Casanova (Genetic Immunology) and Laurent Abel (Genetic Epidemiology).

This visit represented a unique opportunity to discuss the laboratory's track record in an open-minded and interactive manner, and we are pleased that the committee did appreciate all the work that has been done and the projects we are planning.

We do not have any substantial observations to make with respect to this report but only a few comments and precisions to bring with respect to the following points raised by the committee.

Team 15 - Genetic Immunology of Infectious Diseases (Jean-Laurent Casanova)

In the section "Assessment of the team's interaction with the social, economic and cultural environment" (page 55 of the document)

"The medical applications of the team's discoveries are important in terms of diagnosis, prevention and treatment. Molecular diagnosis and genetic counseling might be offered to families and the development of personalized medicine is a hot topic. However, no direct information of the team's efforts to this end is given in the proposal - - that is, it is not clear to what extent the team is involved in clinical diagnostic activities and contributes to genetic patient advice."

We fully agree that the medical applications are an essential part of our work. We have mentioned both in the “Results” (conclusion section) and in the “Project” (Perspectives-Implications section) documents of our team that one of our major aims is to provide to the families molecular diagnosis and genetic counseling. We also would like to clarify that Dr Capucine Picard, a research associate in our team, is responsible of the "study center of immune-deficiencies” (CEDI), which is the immunological and genetic diagnosis laboratory at the Necker Children's Hospital. Moreover, Dr Jacinta Bustamante, another research associate in the lab, works in CEDI too. This laboratory is well recognized in France and abroad, for the diagnosis of more than 180 primary immune-deficiencies. The CEDI is also one of the major interface between clinical units and our laboratory of Human Genetics of Infectious Diseases. The collaborations between these structures are sources of synergy for the identification of new genetic causes of primary immune-deficiencies as well as for the molecular diagnosis and the genetic counseling to the patients and their families.

In the section “Assessment of the team's involvement in training through research” (page 56 of the document)

“The team has currently 8 PhD students and one postdoctoral fellow. There are two qualified research supervisors, and two theses have been defended.”

We just wanted to update the number of qualified research supervisors (HDR) as three additional researchers of the laboratory (E. Jouanguy, G. Vogt, A. Puel) have recently obtained their HDR from Paris Descartes University, and another one (J. Bustamante) will defend her HDR in the next month.

In the section “Weaknesses and threats” (page 56 of the document)

“The applicant should also have discussed that their adherence to WES (largely the coding sequences) as their major genetic molecular tool might be a potential weakness or threat in the future. Many centers are now enrolling patients in studies that either perform whole genome sequencing (WGS), WES or use a combination of approaches including SNP arrays. As a matter of fact, WGS is being increasingly used based on its availability and improved cost efficiency.”

We fully agree with this suggestion too. As we mentioned in the Project document of our team (perspectives-implications section), we already plan to carry out WGS in patients for whom WES has not been successful. In fact, we have now performed 15 WGS and their analyses are in progress, searching in particular for the role of non-coding variants. In the near future, we will progressively apply the WGS approach to more patients, depending on its availability and its cost efficiency, as mentioned by the committee. We would like to remind the committee that our lab has been the first to exploit the power of next generation sequencing in the field of immunology and infectious diseases, as early as in 2009 for WES and in 2010 for WGS, with papers published from 2010 onwards (Bolze et al. Am J Hum Genet 2010; Buyn et al. J Exp Med 2010). We have since published numerous papers based on this approach that was pioneered in our lab (Liu et al. J Exp Med 2011; Bogunovic et al. Science 2012; Bolze et al. Science 2013). We are well aware of the pros and cons of both WES and

WGS. Finally, we want to stress that the quality of the phenotype of the patients is what matters the most in any such research project. A large number of WES and WGS programs have failed due to the poor quality and definition of phenotypes.

Team 16 – Genetic Epidemiology of Infectious Diseases
(Laurent Abel)

In the section "Weaknesses and threats" (page 60 of the document)

"With 6 infection models and several phenotypes per infection, in addition to the contribution to the genetic immunology team, the program of the epidemiology team may get too diverse to remain focused."

Although we are studying a number of infection phenotypes, we are indeed investigating a limited number of infections *per se*, namely those due to common mycobacteria and oncogenic viruses. It has been shown repeatedly in the last few years that tackling the issue of host genetics in the control of infections through different phenotypic angles was the most efficient strategy (e.g. time to onset may contain more information than the binary infection phenotype yes/no). In addition, working on different but closely related infections allows testing the hypothesis of some common genes/pathways being involved in the pathophysiology of these infections. As an example, we are planning a meta-analysis of our different GWAS performed in tuberculosis, leprosy and Buruli ulcer to search for host genetic factors shared by these three most common mycobacterial infectious diseases. In addition it is important to note that we are using similar methodological tools to investigate the different infectious phenotypes irrespectively of the nature of the pathogen. Therefore, any methodological development is benefiting to all the phenotypes in a straightforward manner. Stated differently, we have indeed a much more substantial homogeneity in both the microbes we are studying and the methods we are using than could be thought at first glance. Finally, this increase in the number of phenotypes under study also reflects our ongoing efforts to recruit additional scientists. As noted by the committee, this is best exemplified by the presentation of a young investigator at the next Inserm competitive entry examination.

In the section "recommendations" (page 60 of the document)

"*Even better use the full potential of synergies of the combination of epidemiology, statistics, functional immunology and genetics for understanding the "non-mendelian" susceptibility to infectious diseases. This should also give rise to, once more, important methodological output in terms of methods and publications.*

Validation of functional immunological (or other) significance of detected SNPs is of key importance and should be actively pursued in collaboration with the genetic immunology lab."

We fully agree with the recommendations of the committee, in particular with the need of actively pursuing and amplifying the interaction with the genetic immunology team. As an example we are

starting an in-depth functional dissection of SNPs located in the *TOX* gene and that we recently found associated with pulmonary tuberculosis by a positional cloning strategy (Grant et al, Am J Hum Genet 2013). As this gene is involved in the development of T-cells, our genetic immunology team is now conducting a number of experiments in several immunological cells to investigate the impact of these polymorphisms in TOX function. This is a first example, and we are currently setting up similar *ad hoc* functional experiments for the most significant signals identified though association studies of other common infection phenotypes.