Génétique humaine des maladies infectieuses

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Génétique humaine des maladies infectieuses

University Paris 5

March 2009

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

Section des Unités de recherche

Evaluation report

Research unit :

Génétique humaine des maladies infectieuses

University Paris 5

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

march 2009

Evaluation report

The research unit :

Name of the research unit : Génétique humaine des maladies infectieuses

Requested label : UMR_S INSERM

N° in case of renewal : U550

Head of the research unit : Mr. Laurent ABEL & Mr. Jean-Laurent CASANOVA

University or school :

University Paris 5

Other institutions and research organization:

INSERM

Dates of the visit :

February 12-13, 2009

Members of the visiting committee

Chairman of the commitee :

Mr Philippe GROS, McGill University, Montreal, Canada

Other committee members :

Mr Michel COGNE, University of Limoges

Mr Alessandro MORETTA, University of Genova, Italy

Mr Stephan EHL, University of Freiburg, Germany

Mr Olivier NEYROLLES, IPBS, Toulouse, France

Mr Claudio BORDIGNON, Roma, Italy (unable to attend the visit)

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

Mr Matthew ALBERT, CSS INSERM representative

Mrs Marie-Christine BENE, CNU representative

Observers

AERES scientific representative:

Mr Nicolas GLAICHENHAUS

University or school representative:

Mr Bruno VARET, University Paris 5

Mr Gérard FRIEDLANDER, University Paris 5

Research organization representatives :

Mrs Christine TUFFEREAU, INSERM representative

Evaluation report

1 • Short presentation of the research unit

- Number of lab members : 33 including
  - 3 researchers with teaching duties
  - 6 full time researchers : 6
  - 10 postdoctoral fellows
  - 4 PhD students, all with a fellowship
  - 10 engineers, technicians and administrative assistants
- Number of HDR : 3
- Number of PhD students who have obtained their PhD during the past 4 years: 13
- Average length of a PhD during the past 4 years : 3,5 years
- Number of lab members with a PEDR : 2
- Number of "publishing" lab members (among permanent researchers with or without teaching duties): 8 out of 8

The research unit is part of the Necker's Institut Federatif de Recherche (IFR). It will relocate to a new building, called Imagine, in 2012.

2 • Preparation and execution of the visit

Time : from 8 :00 to 8 :30

Door-closed meeting : Committee members and AERES representative

Time : from 8 :30 to 9 :00

Presentation by the two lab directors: past activity and projects

Time : from 9 :00 to 10 :30

Presentation by the leader and other researchers of team #2 : Genetic epidemiology

- General presentation: 10 minutes
- Human genetics of leprosy: 20 minutes
- Human genetics of tuberculosis: 20 minutes
- Human genetics of HHV-8 infection and Kaposi Sarcoma: 20 minutes
- Human genetics of HCV infection and fulminant hepatitis: 20 minutes

Coffee Break from 10:30 to 10 :45

Time : from 10 :45 to 12 :15

Presentation by the leader and other researchers of team #1: Genetic immunology

- General presentation: 10 minutes
- Human genetics of Herpes simplex encephalitis: 20 minutes
- Human genetics of Candidiasis: 20 minutes
- Human genetics of pneumococcal infections: 20 minutes
- Human genetics of infections by weakly virulent mycobacteria: 20 minutes

Lunch from 12:15 to 13 :30

Time : from 13 :15 to 14 :00

Three meetings at the same time

- Meeting with PhD students and postdoctoral fellows
- Meeting with engineers, technicians and administrative assistants
- Meeting with researchers with permanent position

Time : from 14 :00 to 14 :30

Door-closed meeting : Committee members, AERES representative, Lab directors

Time : from 14 :30 to 15 :30

Door-closed meeting : Committee members, AERES representative

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

This research unit has an outstanding research program. The two leading scientists are internationally recognized world experts in the field of genetics of Infectious Diseases, and two of the most recognized scientists abroad. They have an outstanding track record of scientific productivity and excellence with over 200 publications since 2003, with several of them published in top journals such as Science, Nature Genetics, Journal of Experimental Medicine, Immunity, etc… Their work has led them to propose new paradigms in the field of genetics of infectious diseases that have influenced the entire field. Their past work on mycobacteria (TB, leprosy) and Herpes encephalitis has proven immensely successful, and they now propose to implement the same two-prong strategies to the study of other bacterial and viral infections with a genetic aetiology component.

The two principal investigators have complementary expertise that has resulted in strong synergy in the two main research programs of the unit. Both are MDs, with distinct specialization in unique and complementary research areas, namely genetic epidemiology/statistical genetics (Team 1), and Infectious Diseases/Immunology/Genetics (Team 2). Their research programs are also uniquely complementary with Team 1 using a genetic epidemiology approach in large populations from areas of endemic disease to map, identify and clone major gene effects, while Team 2 focuses on rare cases (in sporadic or familial cases) tackled by candidate genes approaches or by genetic mapping and positional cloning in consanguinous families. The unique strength, originality and productivity of the unit's research program is highlighted by the extraordinary amount of external funding (current annual budget nearly two million Euros) they have been able to attract from France, Europe, and abroad (March of Dimes, Gates Foundation, Howard Hughes Medical Institute).

Over the past few years, the team has assembled an impressive collection of clinical material that is unique in the world. These materials include a) large collection of precisely annotated patients afflicted by different infections (TB, leprosy, hepatitis C, HTLV-1) and population-matched controls from endemic areas of disease, and b) sporadic or familial cases of rare conditions manifested by unique infections in a genetic susceptibility framework. These patients' collections have been built by coordinating the effort and expertise of many clinicans and internists in nation-wide surveys such as the one conducted in France in the case of rhinoscleroma (*Klebsiella rhinoscleromatis*) but also through field-work from the scientists of the group. For this, both teams have engaged foreign clinicians and scientists to identify, study and characterize large populations from

endemic areas of diseases for collection of clinical specimens in leprosy, tuberculosis, as well as HLTV1, HHV8, and Hepatitis C infections. Therefore, they have been extremely successfull at obtaining rare and precious clinical materials for their genetic studies, from collaborations both from France and abroad.

The team has now organized a new International INSERM unit of Human Genetics of Infectious Diseases. One branch of this unit will be based in Paris (Necker/U. Paris Descartes) and the other will be located in New York City (NYC), at the prestigious Rockefeller University. A formal agreement has been established between authorities from the two institutions, to provide a framework for work and interactions between the two sites. The head of team 2 will be spending 75% of his time in NYC, with 25% in Paris (one week per month). One of the Unit Heads will remain mostly in Paris at the current Neckers/U. Paris 5 site, but will be a visiting professor at Rockefeller, with regular visits every 6 weeks or so. This unique arrangement should facilitate knowledge and technology transfer between the two insitutions with wonderful new opportunity for training of highly qualified personels (Ph.D., PDF), as well as additional opportunitites for scientific and technical collaborations between the two institutions. This arrangement will also provide unique access to the Rockefeller's core facilities for high throughput genomics and proteomics studies (high throughput genotyping, DNA sequencing, transcript profiling by microarrays, trasngenesis, RNAi, mass spectrosocopy and so on), availability and access to with for the team is either limited or inadequate in France. Interviews with high-ranking officials from Necker, Université Paris 5 and INSERM indicated overall support for this new arrangement and associated International unit.

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

Team 1 : Genetic Epidemiology

– Strong points :

The team leader is a worldwide recognized expert in the field of statistical genetics and genetic epidemiology of infectious diseases. This is not only recognized by the many invitations he gets to attend meetings, but also by the numerous personal awards he has received.

The team has an outstanding track record of productivity, with 81 papers published since 2003. Many of these papers have been published in the most prestigious journals such as Nature, Science, Nature Genetics, Journal of Experimental Medicine, The American Journal of Human Genetics, and some important review journals such as Nature Immunology, and Annual Reviews.

The team leader has attracted considerable funding from many French, European and International sources to enable a very agressive and ambitious experimental plan.

The team leader has surrounded himself with outstanding younger scientists, including one who has himself developed a fairly autonomous research program with independent funding from the Gates foundation. Such younger investigators will insure that the team continues to build from excellence and develop new areas of research at a competitive pace.

The team has access to unique and unparalleled genetic resources for genetic studies in the form of critical patients collections in Africa, Asia, the Mediteranean basin and other areas corresponding to endemic areas of targeted bacterial and viral infections.

The team has embraced new technologies and experimental approaches and has proposed to conduct at least two whole-genome association studies. The team is uniquely positioned to lead in these highly competitive areas, but will require additional infrastructure support (see below).

The team leader continues to develop new analytical tools in the form of new genetic linkage mapping tools for complex traits and/or for populations in which genetic heterogeneity is evident. This continues to be a highly innovative area of research unique to the team leader.

— What needs to be improved :

Overall, not much needs to be improved. The team leader is using an experimental and conceptual framework that has worked well in the past and he has supplemented it with novel areas of research not only in the forms of novel infectious diseases, but also in the form of radically different analytical approaches (WGA studies).

Better access to high throughput sequencing/genotyping core facilities will be necessary to remain at the forefront of this field, but this could be attainable in the International Laboratory with Rockefeller.

Institutions should provide much needed additional space.

Additional consideration should be offered to students and post-docs to enhance their training experientce (e.g. attendance to conferences, participation in project management).

— Recommendations :

A large number of projects were presented for future work. An effort should be made to prioritize these projects along a « maturation » pipeline moving from classical epidemiology to genetic epidemiology to gene mapping and gene discovery.

Move agressively into new genomics technologies to retain a competitive edge in this field.

Nom de l'équipe : Genetic Epidemiology

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

Team 2 : Genetic Immunology

— Strong points :

The team leader is a worldwide recognized expert in the field of genetics of infectious diseases, in general, and in the identification of single gene effects in sporadic or familial cases of severe types of infections occuring outside the context of classical primary immunodeficiencies, in particular. The team leader is one of the most sought-after speakers in any conferences dealing with this topic, as acknowelded by the numerous presentations he gives at local, national and international meetings. He is a superb teacher, and a reference for this entire field. The team leader has also received a large number of personal awards including the most prestigious International Scholar of the Howard Hughes Medical Institute (one of only 6 ever attributed to French scientists).

The team has an exceptional track record of productivity, with 264 papers published since 2003. Many of these papers have been published in the most prestigious journals such as Nature, Science, Nature Genetics, Immunity, Journal of Experimental Medicine, The Journal of Clinical Investigation, and some important review journals such as Nature Immunology, and Annual Reviews.

The team has been extremely successful at attracting competitive funding from French, European, American and other International sources, close to one million Euros/year.

The experimental plan proposed by the team leader builds on previous success in the study of mycobacterial infections, herpes encephalitis, and invasive pneumococcal infections. He proposes to not only continue to work on these infections, but also to expand to additional infections (Rhinoscleroma, disseminated candidiasis), using the same conceptual and genetic framework involving sporadic or familial cases (consanguinous) of those specific infections. The proposed plan is straightforward, and likely to produce novel insight into host defense

mechanisms against such infections. In particular, tackling infections that engage different aspects of the innate and adaptive immune systems should be a fertile ground for novel discoveries.

The team includes several junior very talented scientists, who will all continue to contribute to the different projects described in the proposal.

The team is highly successful at attracting recruits, and has trained and is currently training a number of fairly large number of graduate students and post-doctoral fellows.

The team has implemented an agressive recruitment program for clinical specimens to be used for the proposed immunological and genetic studies. This is a most valuable resource. His group is using these resources to study the role of genetic factors and identifying novel genetic effects in infectious disease areas previously unsuspected to be affected by « genetic factors ».

— What needs to be improved :

Very little needs to be improved. Maybe consider additional technology platforms to identify high-value candidates for population and family studies.

The Institutions should provide much needed additional space.

Improve the recognition of collaborators' participation in key studies, including key positions in published papers (see below).

— Recommendations :

Very little needs to be changed considering the past success of the team. One would like to see a more direct promotion and career development of junior scientists in the team, in the form of increased independence. Possible additional opportunities for senior authorship on manuscripts was suggested, and should be carefully considered.

It was suggested that, for moving forward successfully in the new two-locations model, the leader of team 2 should consider reducing his travel schedule to attending meetings and conferences to maximize one on one interactions with lab members at both sites.

Additional consideration should be offered to students and post-docs to enhance their training experience (e.g. attendance to conferences, participation in project management).

Nom de l'équipe : Genetic Immunology

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

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

— Management :

Interviews with technical staff, students, post-docs and junior scientists showed that lab members were generally happy to be part of the team and satisfied with their work environment with few exceptions (see below).

A general complaint echoed by the Team leaders was the lack of space that was seen as a major impedement in recruiting additional students and post-docs to the research program, and even carrying out certain aspects of this research. Although this is not an unusual problem for highly competitive labs, this should be corrected, somehow.

A desire was expressed by students and post-docs to have a regular « journal club ». Team leaders should take the initiative in facilitating and enabling this activity.

Junior scientists wished to have some input with the Team leaders decisions upon space allocation in the unit, and other issues critical to life within the unit.

— Human ressources :

Team leaders and Junior Scientists expressed a strong view that additional technician/engeneers positions should be allocated to the Unit.

— Communication :

The Paris site has implemented a live video conferencing system that greatly facilitates communication between the Paris and NYC sites, including holding joint lab meetings.

6 • Recommendations and advice

— Strong points :

Outsanding scientific quality of the Team/Unit. One of the very best in France, with outstanding track record of productivity, original research, and scientific publications.

Proposed experimental plan builds on demonstrated success, and is very strong. It also involves continued and careful recruitment of clinical materials from unique populations that will form the cornerstone of future work by this Team for many years to come. This situation is unique worldwide.

Have been susccessful in attracting large amounts of external funding to the Team.

Have developed a superb network of collaborators both in France and abroad to gain access to key clinical material for their continued work in genetics of infectious diseases. Have developed internally and implemented abroad carefull criteria and standard operating protocols that enable them to collect and systematically classify key clinical material. They have done this in a spirit of scientific collaboration with stakeholders on the ground.

Internally, the Team leaders are seen as true scientific leaders by lab members and are deemed always available for scientific discussions and input on a daily basis.

— What needs to be improved :

Work with institution(s) to improve access to core facilities, although this challenge should be mitigated by access to the Rockefeller platforms via the NYC node.

Work with institution(s) to secure additional space, and alleviate pressure on staff.

Better promotion and career development of senior scientists within the team, in the form of increased independence, input into scientific decisions, etc....

— Recommendations :

Develop a better strategy for moving into the new IMAGINE building that would bypass the use of an intermediate site to which the labs would have to move to, while the Necker's tower undergoes renovation. This scenario was perceived unanimously as detrimental to scientific productivity of the Team.

Continue to develop Bioinformatics as a new core activity of the Team, building on the expertise and core already established at Necker's (4 engeneers forming a « core facility »). This is necessary to remain competitive and take full advantage of the new Genomics platforms (sequencing, genotyping) onto which some of the proposed work is based. In fact, this is a unique window of opportunity for this Team to develop a node of excellence that will be not only recognized locally and internationally, but would also enable training of highly qualified personnel in this key area (Ph.D, PDF, etc..). There is also a unique opportunity to work with Mathematics/Physics units at CNRS (a desire expressed by high-ranking officials at the interview). Bioinformatics should be considered a novel discipline complementary to many aspects of the current and planned activities of the group.

Engage institution(s) to provide additional permanent positions (technicians, engineers) to this unit to run some of the core technical activities being currently performed by over-qualified junior scientists and students.

Ensure that there is flawless and mutually beneficial exchange of information and technology transfer between the Paris and NYC nodes of this INSERM unit.

It would be valuable to develop a strategic plan for providing families being studied with information that concerns their child / families health (e.g. genetic counseling); in the same vein, some efforts could be made to develop novel therapeutic strategies to help genetically susceptible individuals from avoiding contraction of potentially fatal diseases (e.g. HSE).

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

UNIVERSITÉ
PARIS DESCARTES

Le Président
Axel KAHN

Paris, le 17 avril 2009

DRED 09/n° 174

Monsieur Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'unité « **UMR-S 550 Génétique humaine des maladies infectieuses** » rattachée à mon établissement.

Concernant la bioinformatique et les relations avec les mathématiciens/informaticiens, l'Université a mis en place depuis 2 ans avec l'aide de l'INSERM et du CNRS un service commun pour toutes les équipes de biologie de l'Université (les 4 ingénieurs « established at Necker ») dont les équipes de Necker bénéficient comme les autres. L'Université a prévu de faire du développement de ce service commun une priorité du contrat quadriennal à venir.

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

Le Président de l'Université

Axel Kahn

Université Paris Descartes 12, rue de l'Ecole de Médecine 75270 Paris Cedex 06
Tél. 33(0) 1 40 46 16 01 Fax 33(0)1 40 46 16 43
Email : axel.kahn@parisdescartes.fr

Inserm
Institut national de la santé et de la recherche médicale

PARIS DESCARTES

FACULTÉ DE MÉDECINE PARIS DESCARTES

The Rockefeller University

Laboratory of Human Genetics of Infectious Diseases
University Paris Descartes/Inserm Unit 550

Laurent Abel (laurent.abel@inserm.fr)
Jean-Laurent Casanova (jean-laurent.casanova@inserm.fr)

AERES

Paris, April 14th 2009

Response to the report from the visiting committee
1) General observations

We thank the committee for the laudatory evaluation of our laboratory. This visit was really the opportunity to make the laboratory's track record, and we are very 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. As noted by the committee, we will be very happy to have more space, in particular to recruit additional engineers/technicians.

We agree with the recommendations of the committee, in particular with the absolute necessity to develop Bioinformatics. This will be done in strong connection with the development of the Imagine Institute, as this aspect was also noted by the scientific advisory board who visited the Imagine Institute beginning of March.

Laurent Abel

Jean-Laurent Casanova

INSERM U 550
Faculté de Médecine Paris Descartes
Site Necker - 156 rue de Vaugirard
75730 Paris Cedex 15
France - EU

Tél. : 33 (0) 1 40 61 53 81
Fax : 33 (0) 1 40 61 56 88
mail : martine.courat@inserm.fr