Développement normal et pathologique du système immunitaire

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Développement Normal

et Pathologique du Système Immunitaire

University Paris 5

February 2009

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et de l'enseignement supérieur

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Evaluation report

Research unit :

Développement Normal

et Pathologique du Système Immunitaire

University Paris 5

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

February 2009

Evaluation report

The research unit :

Name of the research unit : Développement Normal et Pathologique du Système Immunitaire

Requested label : UMR_S INSERM

N° in case of renewal :

Head of the research unit : M. Alain FISCHER

University or school :

Université 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 Michel COGNÉ, University of Limoges

Other committee members :

Mr Alessandro MORETTA, University of Genova, Italy

Mr Stephan EHL, University of Frieburg, Germany

Mr Olivier NEYROLLES, IPBS, Toulouse, France

Mr Philippe GROS, McGill University, Montreal, Canada

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, Université Paris 5

Mr Gérard FRIEDLANDER, Université Paris 5

Research organization representatives :

Mrs Christine TUFFEREAU, INSERM representative

Evaluation report

1 • Short presentation of the research unit

The research unit is localized on the Necker Campus and belongs to the Medical School of the University Paris 5.

- Number of lab members : 49 including
  - 2 researchers with teaching duties
  - 10 full time researchers, all from INSERM
  - 16 postdoctoral fellows
  - 12 PhD students, all funded
  - 9 engineers, technicians and administrative assistants : including 5 for core facility
- Number of HDR : 10
- Number of PhD students who have obtained their PhD : 7
- Average lenght of a PhD during the past 4 years : 3,5 years
- Number of publishing lab members among researchers with or without teaching duties: 12 out of 12

The research unit is part of the Necker's Institut Federatif de Recherche (IFR) and linked to the University Paris 5 School of Medecine. It will relocate to a new building, called Imagine, in 2012.

2 • Preparation and execution of the visit

Day 1

Time : from 16 :00 to 16 :30

Time length : 30 minutes

Presentation by the head of the lab: past activity and projects

Time : from 16 :30 to 17 :45

Time length: 75 minutes including questions for 25 minutes

Presentation by team leader #1: past activity and projects

Time : from 17 :45 to 19 :00

Time length: 75 minutes including questions for 25 minutes

Presentation by team leader #2: past activity and projects

Day 2

Time : from 8 :15 to 9 :30

Time length: 75 minutes including questions for 25 minutes

Presentation by team leader #3: past activity and projects

Time : from 9 :30 to 10 :45

Time length: 75 minutes including questions for 25 minutes

Presentation by team leader #4: past activity and projects

Coffee Break from 10 :45 to 11 :00

Time : from 11 :00 to 12 :15

Time length: 75 minutes including questions for 25 minutes

Presentation by team leader #5: past activity and projects

Lunch : from 12:15 to 13 :00

Time : from 13 :00 to 14 :15

Time length: 75 minutes including questions for 25 minutes

Presentation by team leader #6: past activity and projects

Time : from 14 :15 to 14 :45

Time length : 30 minutes

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 :45 to 15 :15

Time length : 30 minutes

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

Time : from 15 :30 to 16:00

Time length : 30 minutes

Door-closed meeting : Committee members, AERES representative, University and INSERM representative

Time : from 16:00 to 17 :15

Time length : 75 minutes

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

The head of the unit is one of the most famous worldwide-recognized experts in the field of immunodeficiencies and all his accomplishments made him laureate in 2008 of Grand Prix INSERM de la Recherche Médicale.

His unit has developed and follows a very original and productive research track: dissecting and understanding the molecular mechanisms of rare genetic defects responsible for severe deficiencies of the adaptative immune system. The unit made an impressive number of contributions first applied to the understanding of human immunodeficiencies, but also with strong implications for basic immunology, including the identification of Artemis and Cernunnos and the description of important roles for SAP, XIAP, PMS2, Rab27a, Mun13-4, adenylate kinase 2… Altogether, this work has generated more than 230 papers since 2003, with a number of them in top ranking journals such as *Cell, Nature, Nature Immunology, Nature Medicine, New England Journal of Medicine, Lancet, Journal of Clinical Investigation, Journal of Experimental Medicine, Blood…* and also resulted into a similarly high number of invited conferences in international meetings.

The excellence of the basic research carried by the unit highly benefits from the quality of the work achieved for years by clinicians associated to the laboratory at Necker Hospital, and mostly through the large national and international network they have developed, becoming a referral centre for such rare diseases. The unit was thus able to collect both biological samples and clinical data from patients and families precisely studied. A number of phenotypically similar defects were thus dissected allowing to describe numerous subgroups in apparently homogeneous groups of patients. These errors from Nature were cleverly explored to provide better understanding of yet undescribed intimate mechanisms of cell functions and regulation. Such findings were applied to the design of related animal models to confirm and further explore these discoveries. They were also, as much as possible, targeted for prevention or attempts at repair and healing.

Mastering both clinical and basic research in the field of immunodeficiencies under the excellent guidance of the lab Head led the unit to achieve an unique international position animating national and international scientific / clinical networks and disseminating knowledge about immunodeficiencies. During discussions, this evaluation committee has repeatedly characterized the work of the unit by using the words of excellence and generosity. This generosity extends from scientific communications and collaborations rapidly built about new data, to translations of such data into new diagnostic tools and genetic counselling, to the training of young scientists hosted in the lab and to a strong involvement into teaching University students and even into regularly contributing to science vulgarization.

Finally, pioneering contributions of the unit have been achieved in the past to the setting of clinical trials for gene therapy of severe combined immunodeficiencies, and now to the molecular understanding of the initial leukemic side-effects of this therapy and in the design of more efficient and safe protocols with new self-inactivating lentiviral vectors.

The six teams included into the INSERM unit are all driven by strong principal investigators able to carry out independent and original research. The scientific focus of their research is in most instances devoted to a given type or a given aspect of human immunodeficiencies. It is quite evident the complementarity of the expertise of these different teams, a characteristic which allows bridging different areas such as V(D)J recombination, B cell differentiation, mechanisms of cell cytotoxicity, apoptosis, role of NKT cells, therapy of immunodeficiencies. Each team is very productive but these teams also have strong synergies, as manifested by a number of joint studies that resulted in major scientific contributions. The possibility to keep these teams associated also in the future appears of major strategical importance since it will certainly represent a clear added value for each of them.

One significant strength of the group as a whole is the ability to combine different scientific expertise in order to pursue "unexpected findings" from clinical and experimental observations. Continuing this kind of open-minded research in addition to the 6 defined lines of the scientific program will be useful for the future development of the unit.

The quality of the programs conducted in the unit has also attracted a fairly large amount of funding which is judged as sufficient in the current context but the unit could certainly be still more productive if being given all the space that it deserves and additional human resources.

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

Team 1: Genome dynamics in the immune system

The head of the team is a senior INSERM researcher. The team also includes a junior CNRS researcher, 1 MD, 1 postdoctoral fellow, 3 PhD students, 2 engineers and 1 technician.

— Strong points :

The team leader has brought major contributions to the discovery of new factors involved in V(D)J recombination. He has a high reputation and is recognized worldwide for the quality of his work, in the context of a very hard competition with several large and famous laboratories abroad.

One member of the team also has a very good track record and sound projects, notably on congenital dyskeratosis; he is a strong input for the team.

The team has an outstanding track record of publications, with about 20 original papers since 2003, many of them in prestigious journals such as Cell, Journal of Experimental Medicine, Lancet, Mol. Cell Biol, Blood….

Recent activity and projects show a constant ability and courage to engage in new and innovative methodologies and experimental approaches.

Projects presented for this evaluation were very clearly written, structured and orally defended.

Of note, a clear exploratory strategy was proposed to test and pinpoint DNA defects in new patients with immunodeficiency phenotypes suspected to be related to such anomalies.

— What needs to be improved :

Institution should provide much needed additional space.

— Recommendations :

The team has to stay aware of its strengths and challenges.

The team has to keep on with balanced efforts both for the exploration of new clinical defects and for the development of experimental models, while remaining sufficiently focused to stay competitive.

Nom de l'équipe : Genome dynamics in the immune system

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+	NN	A+

Team 2 : Lymphocyte interactions and B cell terminal differentiation

The head of the team is a senior INSERM researcher (DR). The team also includes a 1 junior CNRS researcher (CR), 1 postdoctoral fellow, 1 PhD student and 1 technician.

— Strong points :

The team leader is an outstanding scientist with very good international reputation. She made major contributions to the field with implications both for unraveling immunodeficiencies with Hyper-IgM and for the molecular understanding of class switch recombination, somatic hypermutation and the enzymes involved in these processes.

The recent work of the team and the projects thereof are devoted to spontaneously occuring intrinsic B cell defects in humans. These projects are of major importance for new understanding of the fine-tuned mechanisms associated with class switching and somatic hypermutations and are strongly complementary to the work carried by several other laboratories adressing these questions but only dealing with mouse models.

The team has gone very far in clinical studies and in the classification of intrinsic B cell defects, including relevant studies on germinal center alterations in secondary lymphoid organs in the patients. There are still several ongoing projects which are very promising, about new homogenous groups of patients with clearly similar molecular defects.

The work directly carried out by the team has yielded outstanding publications, with about 30 original papers since 2003, many of them in prestigious journals such as Nature Immunology, Journal of Experimental Medicine, Journal of Immunology, Blood…. with the addition of a number of good review articles.

Fruitful collaborations with top laboratories in the field, have also allowed association to studies published in journals such as Cell, Nature Immunology, Journal of Experimental Medicine…

The team is also strongly involved in genetic counselling for primary immunodeficiencies as a National Referral Center

— Weaknesses :

Institution should provide more space.

The team has not invested enough in new technologies.

The committee judged that the written report was less structured than the oral presentation.

— Recommendations :

The research program would benefit from more openness to new technologies and use of new avenues to maximize the results

Pursue current collaborations with foreign groups studying class switching and somatic hypermutation

Nom de l'équipe : Lymphocyte interactions and B cell terminal differentiation

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+	NN	A+

Team 3 : Lymphocyte homeostasis ; the role of lymphocyte cytotoxic activity

The head of the team is a senior INSERM researcher (DR). The team also includes 1 junior INSERM researcher (CR), 2 postdoctoral fellows, 2 PhD students, 2 engineers/technicians.

— Strong points :

The team leader is a worldwide-recognized scientist with major recent contributions to the understanding of the hemophagocytic lymphohistiocytic (HLH) syndrom. Her work has also yielded important breakthroughs and insights into the intracellular vesicle types and pathways as well as specific proteins that regulate the exocytosis of cytotoxic granule contents, such as Munc13-4, Rab27a and Slp2a-hem, apparently belonging to a subset of cytosolic organites distinct from perforine/granzyme containing granules.

The team is able to cope in parallel very efficiently with both human genetics, immunology and cellular biology.

Ongoing projects are very challenging, aimed at characterizing additional effectors of Rab27a or syntaxin 11, at understanding the role of the LYST defect in Chediak-Higashi syndrom or at studying a murine model reproducing HLH.

The team has an outstanding track record of publications, with more than 50 papers since 2003, many of them in prestigious journals such as Cell, Nature Immunology, Science, Journal of Experimental Medicine, Lancet, Journal of Clinical Investigation, Molecular and Cellular Biology, Blood…. with the addition of a number of good review articles, and several invited conferences in international meetings.

The team has attracted important grants from ANR, PCRDT, GIS Maladies-rares, FRM… The group leader is additionnally involved in teaching and is responsible for a clinical laboratory ensuring the molecular biology and prenatal testing of immunodeficiencies at Necker Hospital.

Efforts are made to translate knowledge from basic research to clinical application. The development as a mouse model in preparation of an interventional trial for FHL is an important step.

— Weaknesses :

Institution should provide more space.

— Recommendations :

The research program would benefit from the input of new technologies, especially such flow imaging as can be provided by Amnis® for the observation of cell-cell interactions or intracelllular localization.

Nom de l'équipe : Lymphocyte homeostasis ; the role of lymphocyte cytotoxic activity

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 4 : T cell activation and EBV susceptibility

The head of the team is a senior CNRS researcher (DR2). The team also includes 2 postdoctoral fellows, 2 PhD students, and 1 engineer. This team is a novelty in the structure of the whole research unit, having budded from team 3.

— Strong points :

The team leader is a talented scientist who produced noticeable work about signal transduction in lymphoid cells, during his stay at McGill (Montreal). He clearly maintains strong collaboration with this excellent team.

The team leader regularly produced excellent contributions as a senior author and his new position as a team leader is logical and promising.

The team leader's publication track record includes several top publications since 2003s, with 13 original papers and good review articles in such journals as Nature, Journal of Experimental Medicine, Nature Immunology, Molecular and Cellular Biology, Plos Biology, Immunity….

This new team's projects were clearly exposed and are based on further exploring the SAP and XIAP-associated pathways in lymphocyte development and genetic exploration of patients with rare XLP–like defects through a genome-wide scan.

— Weaknesses :

Institution should provide more space.

— Recommendations :

Some of the projects are risky (role of NKT cells in EBV immunity, association between SAP and XSIAP, …) and the team should be prepared to change direction if the preliminary results do not support the hypothesis or if murine models rapidly appear as inappropriate.

Nom de l'équipe : T cell activation and EBV susceptibility

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	NN	A+

Team 5: Physiopathologie de l'apoptose lymphocytaire

The head of the team is a senior INSERM researcher (DR). The team also includes 3 postdoctoral fellows, 3 PhD students, and 1 engineer/technician.

— Strong points :

The team leader is a very rigorous and talented scientist. His work has greatly contributed to unravel the variegated field of autoimmune lymphoproliferative syndroms (ALPS).

The team is able to deal very efficiently with materials available in minute amounts from patients and to carry out very sophistated cellular and molecular studies with such material.

This expertise has allowed several recent major contributions, including two original reports in the New England Journal of Medicine: one reports for the first time somatic mutations in the CD95 gene by studying the double negative T cells that accumulate in patients with sporadic ALPS and the other documents a CD3 zeta mutation in a case of immunodeficiency. Altogether the team produced about 20 international papers since 2003.

As mentioned earlier for team 1, an algorithmic approach is used here to try and segregate the numerous types of ALPS based on observed anomalies upon cell activation of new patients' cells.

Within this unit, the team has very productive interactions with the other teams, notably with team 1 and team 4, as well as with other teams outside of Necker, including one at the Pasteur Institute.

The team has attracted important grants from ANR, and PCRD (e-rare call).

— Weaknesses :

Institution should provide more space.

Dealing with several projects and approaches in such a highly competitive field may be risky for a small team like this one.

— Recommendations :

Be more focused.

Nom de l'équipe : Physiopathologie de l'apoptose lymphocytaire

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 6: Therapy of Immune deficiencies

The head of the team is a senior researcher (PU-PH). The team also includes 3 postdoctoral fellows, 3 PhD students, and 1 engineer/technician.

— Strong points :

The team leader is a worldwide-recognized scientist and clinical practitioner who regularly made cutting-edge contributions to the field of severe combined immunodeficiencies and their therapy.

The team is unique in its ability to bridge discoveries from the bench to the clinics and vice-versa,

The achievements of the team in order to learn from initial side-effects and move towards a safer and still efficient gene therapy of SCID are remarkable. The thorough follow-up of treated patients that was performed, clearly prompted by unit director's laudable pediatric attitude of high patient's awareness, yet carefully conducted, is of major importance not only for SCID but also for all future applications of gene therapy.

The team has an outstanding track record of publications, with about 60 papers since 2003, many of them in prestigious journals such as Nature, Nature Genetics, Science, Journal of Experimental Medicine, Lancet, Journal of Clinical Investigation, Blood…. with the addition of an impressive number of invited conferences in international meetings, several book chapters and a planned patent.

The team has recently discovered a new form of genetic SCID linked to a mutation in the adenylate kinase 2 gene.

Beside clinical work, the identification of a human "common lymphoid progenitor" and the discovery of human lymphoid precursors in the amniotic fluid are major basic discoveries.

The team has attracted a large number of grants from DHOS, INCA, ANR, Europe, AFM, PHRC.

— Weaknesses :

Institution should provide more space.

— Recommendations :

Keep going!!

Nom de l'équipe : Therapy of Immune deficiencies

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 all lab members are very enthusiastic about the scientific project of the team, the way the unit is run by its director and the general mood of the unit. A good indicator is that of people having been PhD students there coming back for their second post-doc.

Many, and more specially the technical staff, complained about space, both at the bench and for using computers and desk-space.

Finding an alternative solution offering more space before moving to the IMAGINE building should be a priority for the Institution.

Students and post-docs appreciated the regular teams and unit meetings and were encouraged to start a new the initiative of an additional « journal club ».

— Human ressources :

The number of technicians/engeneers hired for limited periods is quite high; permanent positions should be searched for, at least for some of them.

— Communication :

Communication within the unit appears to be excellent.

6 • Recommendations and advice

— Strong points :

The unit is internationally renowned, conjugating high standards and high productivity both for basic and clinical research with a highly innovative and rigorous approach. The unit can be depicted as a model of translational research, with a very good balance between genetic studies, immunology, cellular biology, genetic counseling, clinical studies and clinical trials.

The unit has a very regular scientific production at the highest international level, with an outstanding track record of publication.

The unit also repeatedly demonstrated its ability to pick up and furrow on unexpected findings.

The projects are innovative and ambitious but rely on a demonstrated know-how and an established bio-bank continuously implemented through active clinical networks.

The scientific homogeneity and the structure of the unit are remarkable: each team within the unit has a clearly identified focus, can be individually judged as excellent and is run by a high profile team leader; there are strong collaborations and synergies between all these teams ; the dynamics of the structure is good, allowing people to share projects, to move from one team to the other, and occasionnally to create a new team as in the case of the leader of team 4. This evolution is emblematic of the open-minded and encouraging spirit of the unit's head, allowing individualities to blossom and, when ready, engage in branching orientations while retaining a strong link with the father-tree.

Another way to grab this is to look at the authorship or the unit's papers, always carefully balancing contributions. The policy for publications and signatures is thus very favourable for the development by leading scientists of their own professional projects and careers.

The balanced gender ratio between male and female team leaders can also be noticed.

The unit is susccessful in attracting large amounts of external funding, both from Europe, from ANR and from foundations.

The unit is providing a unique environment for PhDs and post-docs. It is active in multiple areas besides research itself, including the animation of clinical networks, a referral center, teaching and communicating about immunology and immunodeficiencies…

The output of the unit for patients has been remarkable.

The outstandingly encouraging, intelligent, generous and nearly fatherly presence of the unit's director (who no longer claims leadership of his specific team) has to be acknowledged and revered.

— Weaknesses :

Work with institution(s) to find additional space.

— Recommendations :

Find a strategy to offer additional space before moving into the new IMAGINE building, while keeping all the teams associated in the same building /floor and preserving their easy access to all core-facilities (including cell cytometry). The committee recommends that everything should be done to reduce the detrimental impact of the move.

Care about the plans for careers offered to the technical staff. Engage institution(s) to provide additional permanent positions (technicians, engineers).

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+

Unité Mixte de Recherche U 768
INSTITUT FEDERATIF DE RECHERCHE
NECKER ENFANTS-MALADES
DEVELOPPEMENT NORMAL ET PATHOLOGIQUE
DU SYSTEME IMMUNITAIRE

Directeur : Alain Fischer

Inserm
Institut national
de la santé et de la recherche médicale

Paris, April 20th 2009

Other comments

Some points are missing in the report about team 4 (head Sylvain. Latour) when compared to other team reports and clarifications are needed :

-Indeed, S.L produced noticeable work during his post-doctoral stage and still collaborates with this excellent team. However, he developped is own thematic research/expertise since he was recruited in 2000 in the research unit. This expertise has allowed major conributions including one original paper in Nature and two in Journal of Experimental Medecine.

-The team has attracted important grants from ANR, GIS-Maladies rares.

Alain FISCHER

Hôpital Necker-Enfants Malades - Pavillon Kirmisson
149 Rue de Sèvres - 75743 Paris Cedex 15
Tél. : 33 (0)1 44 49 50 71 - Fax : 33 (0)1 42 73 06 40