Génétique et épigénétique des maladies métaboliques, neurosensorielles et du développement

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit : Génétique et épigénétique des maladies métaboliques, neurosensorielles et du développement

of University Paris 5

January 2009

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Research unit : Génétique et épigénétique des maladies métaboliques, neurosensorielles et du développement

of University Paris 5

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

January 2009

Evaluation report

The research unit :

Name of the research unit : GENETIQUE et EPIGENETIQUE des MALADIES METABOLIQUES, NEUROSENSORIELLES et du DEVELOPPEMENT

Requested label : UMR_S INSERM

N° in case of renewal : U-781

Head of the research unit : Mr Arnold MUNNICH

University or school :

Université Paris 5

Other institutions and research organization:

INSERM

Dates of the visit :

January 29-30, 2009

Members of the visiting committee

Chairman of the commitee :

Mr Nicolas LEVY, Marseille, France

Other committee members :

Mr Jacques BECKMANN, Lausanne, Switzerland

Mrs Gisèle BONNE, Paris, France

Mr John BURN, Newcastle, England

Mr Hubert DE VERNEUIL, Bordeaux, France

Mr Jean-Louis MANDEL, Strasbourg, France

Mr Geert MORTIER, Ghent, Belgium

Mr Bertram MULLER-MYHSOK, Munich, Germany

Mr Giuseppe NOVELLI, Rome, Italy

Mr André REIS, Erlangen, Germany

Mr Bert SMEETS, Maastricht, Netherlands

CNU, CoCNRS, CSS INSERM, représentant INRA, INRIA, IRD.....) representatives :

Mr Serge ANSELEM, Paris, INSERM CSS representative

Mrs Dominique SIGAUDO-ROUSSEL, Lyon, CNU representative

Observers

AERES scientific representative:

Mr Philippe BOUVET, Lyon, France

University or school representative:

Mr Arnaud DUCRUIX, Université Paris 5

Mr Paul KELLY, Université Paris 5

Research organization representative :

Mrs Chantal LASSERRE, INSERM

Evaluation report

1 • Short presentation of the research unit

- Number of lab member : 72 including
  - 17 researchers with teaching duties
  - 23 full time researchers
  - 17 PhD students, all with a fellowship
  - 15 engineers, technicians and administrative assistants
- Number of HDR : 33
- Number of students who have obtained their PhD during the past 4 years: 14
- Number of PhD students currently present in the research unit : 17
- Number of lab members who have been granted a PEDR : 4
- Number of "publishing" lab members: 39 out of 40

2 • Preparation and execution of the visit

The overall organisation of the visit was satisfactory. The whole committee listened to the general presentation by the director and the presentations of research teams by their respective leaders. However, although all the experts assisted and discussed with the teams' leaders and some of the teams members present in the audience, each research team was specifically evaluated by a group of experts including one head in charge of reporting after the visit. The committee splitted into three separate groups during presentations and discussions with respectively PhD students and post-docs, with staff scientists and with technical and engineers staff.

In addition, as a general recommendation for the future, we think that individual laboratory visits should be organized and that the researchers should provide a limited number of posters and discuss their projects with the reviewers of the evaluation panel. Actually, it is important for reviewers to meet leading post-docs and graduate students in order to appreciate the scientific potential of the groups.

The document provided to the experts was found of quality to those who were able to read it. Some of the experts neither received the minimal rules requested for downloading information and documents on the AERES website, nor the written document. A concise written document should be a pre-requisite before such visits. As a general recommendation, we think that previous evaluation reports on the groups should be provided before the evaluation and that the overall structure and funding of groups should be indicated clearly and homogeneously (e.g. Institutional funding, contracts, tenured positions, post-docs, graduate students, technicians and other supports, lab space, etc.).

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

This research unit is very well known internationally for its scientific achievements. This research laboratory has been/is a world-leading centre in human genetics. It is characterized by the presence of several technological platforms providing high quality services to groups inside.

Regarding the present proposal for renewing this Inserm/University laboratory, it is of importance to point out that 3 groups that existed in the last 3 years are not renewed in the new structure. Either they have been suppressed, or merged with top level teams. Such a remodelling of the structure appeared of pertinence to the experts.

The director has insisted on his will to maintain excellence among the different groups of his structure, and on the major importance of such an excellence towards integrating the future Institute of Genetics Diseases (IMAGINE foundation) which is planned to be built as a novel entity/building by 2012.

The record of total publications by the groups of U781 in international journals is of paramount visibility. However, there is some heterogeneity among different teams that will be pointed in more details in the reports on individual groups. In all, among the 10 proposed groups, 9 of them fulfill all the criteria for being considered as high quality and specific scientific teams in terms of scientific production, scientists and students attraction, scientific collaborations and international visibility. Three of these groups have been evaluated at an outstanding level in the international genetics landscape while five others were evaluated as excellent in the same context, with some slight differences when comparing one to the other, and one needs some improvements to maintain its important projects at the best level. One team, of real importance in the U781 structure, cannot possibly be evaluated according to the usual scientific criteria, and the committee will propose solutions towards maintaining its activities both in the structure and in the French and European genetics landscape.

All the groups applying for the structure, have technical help at the bench and also profit of several state-of-the art core facilities and dedicated technological platforms allowing them to obtain fast and high quality reagents and results.

The committee has been globally favorably impressed by the accomplishments in the last years as well as the future projects. This research centre is clearly an international reference in genetics and rare diseases. This is due to the excellent and very large team of MDs and PhDs constituting the unit, the large cohorts of patients' samples which have been made available for research studies after being developed as homogeneous cohorts by the clinical team and the excellent and dynamic leadership in the last years by the director. The impressive number of important contributions published in very well reputed scientific journals reflects the excellence of this research centre. Major grants are obtained each year by the teams, including European projects (ERA-Net, partnerships in FP6 and FP7-EU programs), ANR grants as well as numerous grants from foundations/associations and prizes to team leaders.

4 • Specific appreciation team by team

Team 1 : Embryology and Genetic Architecture of Human Neural Crest Malformations

This is an outstanding team, with a wonderfully rich and wide transversal research program (from gene hunting to functional studies), that is steadily and consistently (and over many years for now) continuously producing excellent science at the forefront of the research in this domain.

Their output and track records are of exceptional quality, both in terms of attracting substantial grant support, scientific publications and translation into clinical practice. They are highly networked, both nationally and internationally. The move from HSCR to neurocristopathies in general, is cutting edge and innovative and will

likely result in significant contributions in the next years. The team has promising young scientists and students, with excellent coaching by the senior staff.

The only minor shortcoming of this (and the other teams in this unit) is their relative weakness in computation biology (bioinformatics, statistics, statistical genetics, genetic epidemiology, algorithmics, etc), skills, which in the era of high-throughput data gathering and meta-analyses, become increasingly more important if not essential. There have been important attempts to consolidate the team in this direction. But the creation of a strong research bioinformatics team working in close proximity to the other teams would be to the benefit of the entire unit promoting new cutting edge collaborations between these scientists.

Publication's record (2005-2008) : Oustanding; 62 publications signed by members of the team. 40 publications are signed as 1st or last (or both) authors by members of the team, including 6 publications in Nature Genetics, Nature and American Journal of Human Genetics. Other high level and impact papers (HMG, Hum Mut, …). Nine reviews published.

Nom de l'équipe : Embryology and Genetic Architecture of Human Neural Crest Malformations

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: Molecular and physiopathological bases of chondrodysplasias

The team combines scientific knowledge, well-established techniques with a novel high-throughput mutation screening techniques in a state-of-the art effort to identify novel causes of bone diseases and to shed new light onto the pathogenesis of these diseases. Strengths include: 1) the high-quality of the investigators who are internationally recognized in this field; 2) the impressive collection of patient samples; 3) the logical research plan including a spectrum of studies ranging from molecular characterization of patients, cell culture analyses, and mouse model studies.

The publication record of the team is outstanding. In particular, the leading staff scientist and several others members, have published numerous seminal papers in the field of monogenic disorders of bone. The research group is among the elite in the field of skeletal dysplasias.

Each of the participating researchers provides important contributions to the team and they established strong collaborative networks.

In addition to advancing our molecular understanding of this group of disorders, more focus on developing therapeutic strategies for this group of patients, who often suffer from multisystemic dysfunction that is usually debilitating and frequently fatal, would be beneficial. Furthermore, because mesenchymal dysfunction has been implicated in the pathogenesis of several common degenerative diseases, the findings of the team may have broader implications beyond rare bone diseases.

The team has promising young scientists and students, with excellent coaching by the senior staff.

Publication's record (2005-2008) : Oustanding; 53 publications signed by members of the team. 24 publications are signed as 1st or last (or both) author by members of the team, including 3 publications in Nature Genetics, 1 in Bone, and several publications in high level and impact journals (Am J Hum Genet, Hum Mut, …). High level collaborative papers including several in Nat Genetics. Eight reviews from the team members.

Nom de l'équipe : Molecular and physiopathological bases of chondrodysplasias

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 3 : NF-κB signaling pathway in human diseases

This team first identified disturbed NF-kB signalling due to mutations in NEMO as cause of the disorder incontinentia pigmenti. Subsequently they showed that several members of the same pathway are mutated in several other diseases affecting mainly the epidermis. Consequently the group has extended their study to other pathological conditions associated with impairment of NF-kB signalling and its pathophysiology. The complexity of the pathway and the number of already identified disorders affected by it are certainly a challenge. The group though, can take advantage of interesting animal models and unique family material.

Studying NF-kB signalling and skin homeostasis and its relationship to pustular psoriasis are very interesting and important topics, which resulted in the attraction of a further very good scientist to complement the existing team of very dedicated scientists and clinicians, which is a clearly a strong point of this group together with their excellent national and international collaborations. This should add important expertise to the group and help tackle the very ambitious work programme. Given that this is a highly competitive field, developing clear objectives and focus will be very important for a small group like this. Hopefully this will aid them to reach again the excellent publication level achieved in the past. However, it is to be pointed that this group has an insufficient critical size given the complexity of the disorders and pathophysiological mechanisms studied, and the international competition in the field. The publication level has decreased in the last few years, without recent major papers by the senior staff and students in top journals and in leading author's positions.

Nevertheless, the experts found the projects convincing enough to trust that a major effort will be done to hire more scientists and postgraduate students to help reach again this previous level.

Publication's record (2005-2008) : 11 publications signed by members of the team. 6 publications are signed as 1st or last (or both) author by members of the team, including publications in Human Mutation and Hum Mol Genet, and several publications in the Am J Med Genet. High level collaborative papers include an article in Science. Eight reviews from the team members.

Nom de l'équipe : NF-κB signaling pathway in human diseases

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

Team 4 : Molecular and pathophysiological bases of mental retardation

This team's project is oriented towards molecular and functional approaches aiming to better understand mental retardation. In the last years, this group has obtained several major results in the field and their ongoing project will retain most of the previous strategies, which we consider as extremely logical in the context. After identifying molecular and functional bases for these syndromes, they constantly develop a translational activity for clinical and genetic diagnosis and, in the future, based on their basic and clinical researches, they aim, through clinical trials, to ameliorate healthcare for patients affected with mental retardation (MR). In the next years, this team will continue exploitation of high resolution CGH-arrays to investigate unexplained disorders associated with chromosomal imbalances that are not possibly observed at the karyotype level, as a way to identify molecular bases of yet unidentified syndromes. In particular, they will address MR associated to (out)growth defects. As a second aspect of the project, families affected with autosomal recessive mental retardation will be explored through a collaborating network of clinicians. As an interesting and pertinent part of the positional cloning project this group develops a candidate gene's screening approach based on a series of genes previously identified in Drosophila as being related to brain plasticity. Based on the outstanding previous results (this group has first identified Neurotrypsin in human MR), they will explore the function of proteins having been involved in related disorders. Finally, a very innovative approach, combining ChIP on Chip and high throughput sequencing, will be used towards exploring the pathophysiology of autism disorders. We have no doubt on the relevance of the projects presented by the team's leader as well as their feasibility. Indeed, the team's leader has demonstrated an excellent scientific direction in the past years, having published in the best international journals and, as other groups in the lab, can rely on a major clinical expertise on site as well as excellent collaborations in France and Europe for all the projects. The committee has considered this team as excellent and is confident that future results will provide new insights into the molecular and mechanistic bases of MR.

Publication's record (2005-2008) : Excellent; 36 publications signed by members of the team. 18 publications are signed as 1st or last (or both) author by members of the team, including 3 publications in the Am. J. Hum. Genet, and several publications in high level and impact journals (J Med, Hum Mut, …). Outstanding collaborative papers include 2 papers in Science with a major contribution of the team's leader and PhD student.

Nom de l'équipe : Molecular and pathophysiological bases of mental retardation

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 5 : Retinal dystrophies : from genes to clinical trials

This group has an excellent track record in the field and has built up a formidable clinical resource over many years. They are well integrated with a successful recent transfer of leadership to a young and promising research director. The detailed and systematic search for genes responsible for the retinal dystrophies has made an important contribution to the development of diagnostic and the research group is now well integrated with the molecular genetics service team. All the developed projects have appeared convincing to the committee for future achievement of major results. It is of importance to note that this group has developed a pertinent partnership on gene's transfer applications with group 9 in the same lab, not only pointing its interest on therapies for retinal dystrophies, but also in collaborative projects by using in-house facilities and expertise.

The level of publications over recent years has fallen below the impact of these achieved in the past, probably reflecting the search for monogenic explanations for a well defined group of phenotypes and, somehow, the lack of more functional studies. The new projects should attract young students and scientists that appear as a necessity. Hopefully the recent discoveries in relation to TMEM will be accepted in a high impact journal while the potential progress of LCA cases to exon stripping therapy could produce exciting results.

Publication's record (2005-2008) : Very good; 23 publications signed by members of the team. 19 publications are signed as 1st or last (or both) author by members of the team, including 3 publications in Am J Hum Genet, and 5 in Human Mutation.

Nom de l'équipe : Retinal dystrophies : from genes to clinical trials

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 : Mechanisms and patho-physological consequences of CTG repeat instability in myotonic dystrophy type 1 (DM1)

Team 6 aims at the elucidation of the underlying mechanisms involved in CTG-repeat instability and the pathophysiology leading to the broad variety of disease manifestations in myotonic dystrophy (DM1). A very strong point of the team is the unique mouse model they developed several years ago for studying both repeat instability and disease manifestations. Due to the group's open and cooperative attitude these animals have become a driving model for investigations in many research groups worldwide.

Team 6 is an initiator and important player in the international network on DM1 with the only concern that visibility, leadership and contribution may dilute in such an environment. They should be aware of this. The team consists of excellent senior and promising young researchers, but is still fairly small with respect to the projects scheduled. Each of the 3 projects could already require the involvement of the complete team to be competitive in the field. So the team should focus on those projects, in which they can maximally show their excellence. There is a risk of being involved in too many topics, which would negatively affect the scientific output and level. The tedious mouse work and the extreme complexity of the frequently changing pathophysiological mechanisms in DM1 have had a negative effect on amount and quality of the scientific publications, which has happened to all other DM1 investigators as well. As underlying disease processes are becoming more and more clearer, it can be expected that this will change in the next couple of years and the team is perfectly placed to be involved in key papers to come. Noteworthy, is their important effort to translate the knowledge of the molecular pathology in the mouse model into treatment options of patients. In conclusion, teams 6 is a vital team with a bright future, based on the quality of researchers and projects, if they are able to keep the right scientific focus.

Publication's record (2005-2008) : 10 publications signed by members of the team. One major paper in Plos Genetics in 2007. Several invited conferences at major meetings in the field.

Nom de l'équipe : Mechanisms and patho-physological consequences of CTG repeat instability in myotonic dystrophy type 1 (DM1)

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 7 : Genetics of Mitochondrial diseases

Over the past 4 years, this team has followed a very successful track in the field of mitochondrial disorders. The publication record is excellent with manuscripts in Nature Genetics, JCI, and the American Journal of Human Genetics. The team is very well connected both nationally and internationally, with the team and team leader enjoying highest esteem in their respective field and community. The group will be reinforced by a second strong group arriving. There are very good connections not only to other academic teams, but also to partners in the private sector. It seems noteworthy that in addition to high publication output there is also a large number of PhD theses awarded and that there are PhD theses with good to excellent first-author publications from that team.

The proposed research is highly innovative and original, ranging from basic research to clinical trials, thus actually applying the "bed to bench and back" philosophy so often and in so many places advocated but rarely practiced. All the proposed projects are very exciting with a good chance to success and high potential impact for treatment, understanding of disease processes, and diagnostics. In summary we have no hesitation to pass the highest possible recognition to the team and their research.

Publication's record (2005-2008) : Outstanding; 26 publications signed by members of the team. 10 publications are signed as 1st or last (or both) author by members of the team, including major articles published in journals such as Nature Genetics, JCI, Am J Hum Genet, Ann Neurol. Excellent collaborative articles.

Nom de l'équipe : Genetics of Mitochondrial diseases

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 8 : Genetics and pathophysiology of hypercholesterolemia

Over the past 4 years, team 8 has pursued the careful screening of genes involved in autosomal dominant hypercholesterolemia (ADH). These studies have largely contributed to the international reputation of the team. The publication record is generally good to very good. A remarkable achievement of the team is to be involved in National and International networks with "Lipid Clinics" as well as their ability to rise funding (ANR funded project and companies sources).

Altogether, the research topic is original, including their recent efforts to characterize endophenotypes, and has thus a great potential to advance the field. This field of research is highly competitive but the major

strength of this team is to screen families in contrast to US teams working at the cellular level. This approach is also their weakness given the genetic heterogeneity and paucity of such families, hence the need to securing the project by screening subjects outside ADH families. The project is very exciting with an original area of research that is destined to have a major impact on the understanding of the pathophysiology and treatment of cardiovascular diseases.

Given the past achievements and the originality and quality of ongoing projects, the viability of the team is guaranteed for the future, if the gene screening is enlarged, including their potential role as candidate genes for complex CVD, with a strong potential arising from the expectations of genes in ADH detection and the extension of any therapeutic applications. As a supplemental recommendation, this team should envisage seriously to hire post-doctoral fellows to improve and accelerate gene's hunting as well as animals based projects and thus maintain its quality and visibility at the highest international level in this highly competitive field.

Publication's record (2005-2008) : Very good; 38 articles published including 26 on Marfan syndrome and SSC and 11 publications on ADH have been signed by members of the team. 21 publications are signed as 1st or last (or both) author by members of the team, including important contributions in Hum Mut and J Med Genet. Several didactic articles have been published in the period.

Nom de l'équipe : Genetics and pathophysiology of hypercholesterolemia

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 9 : Principles and therapeutic applications of gene transfer

Gene therapy has recently held the promise of correcting genetic diseases: therefore, it is really interesting to have a team dedicated to gene transfer in support and collaboration of other teams of the unit specialized in human genetic diseases. The main advantage of the team is the excellent international recognition of the principal investigator in the field of gene transfer and gene therapy. This position allows the team to participate in research networks and relationships with the biotech industry (Cellectis SA) with numerous fundings.

The first two projects ("Targeted integration of transgenes" and "Intervention on mRNAs") are highly innovative and competitive. They tend to suppress a possible genotoxicity associated to the conventional additive gene therapy. The third project is a good application of gene transfer techniques to look at the mechanisms underlying the abnormal phenotype of different metabolic disorders.

The principal weakness of the team is a generation gap between the currently present team leader and the young postdocs and students, without an intermediate level of mature group leaders. The committee recommends active measures to recruit one or two independent group leaders over the next four years. The other weakness of this team corresponds to the very limited connections and collaborations with the other teams in the same lab, with exception of team 5.

Finally, the establishment of a gene transfer vector core for the Institut Fédératif de Recherche is an excellent decision that will necessitate laboratories, equipments and technical expertise.

Publications : The team's leader has an outstanding list of publications, including during the concerned period (48 papers signed in the period 2005-2008). However, most of them correspond to studies performed before he joined the U_781.

Nom de l'équipe : Principles and therapeutic applications of gene transfer

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+	B	A

Team 10 : Genatlas

Strictly spoken and thought, Team 10 is not a research team but rather a transversal platform or a "service team", which updates and improves constantly the Genatlas database. This database provides information for the international scientific and medical community including the structure, expression and function of genes, in addition to gene mutations and their consequences for a given illness. The specificity of Genatlas relies on the fact that it is a disease orientated database, which is different from the various existing Locus Specific databases (LSDB), different from the genome wide mutation database. It also differs from the widely used OMIM database. The added values of the Genatlas database are: (1) a thorough updating by dedicated curators (who read the corresponding references guaranteeing higher quality of data compared to automated acquisition performed in numerous DB); (2) the new link to Orphanet, the portal for rare diseases and orphan drugs and to CEMARA, the web site of the reference centre for rare diseases, and (3) the implementation of new tools adapted to the recent developments of high-throughput technologies in genetics (prediction of mRNA structure, miRs, chromosomal rearrangements, etc.).

Besides the tremendous amount of work performed by Team 10 to constantly update Genatlas and also to develop new tools, there is an important necessity to catch international visibility and to present the Genatlas structure at least at the EU level and possibly through connection with European Bioinformatics Institute (EBI). One of the main difficulties for this service team is to keep non-permanent staff members and to raise money for further maintenance and developments of this important tool. Indeed, this team may not be considered as a research team by itself since it has no possibility to hire tenure researchers from the public organisms and almost no specific publications can be produced on this specific activity. Thus, although the importance of maintaining such a platform, it cannot be evaluated on the same basis that other teams. Such service platform would certainly benefit from application and support to the current GIS-IBISA calls as strongly recommended and supported by the committee.

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

— Core facilities :

Microarrays : The microarray platform provides services for microarray analysis for Agilent and Affymetrix Chips analyses. The efficiency of its organization and the quality of its technical staff and management allows efficiency for the in-house developed projects.

Mutation screening and Sequencing : 3 D-HPLC and 2 multi-capillaries ABI PRISM 3100 automated DNA analysers and ABI377. It is recommended that the platform should anticipate evolution of sequencing technologies and begin to reallocate some of its work force to develop in-house the massively parallel sequencing technology. The sequencing capacities for such a structure have to be upgraded and this needs to be planned in the context of the foundation Imagine.

Washing staff: 3,3 full time equivalent. Washing and sterilization of the glassware.

Administration : 3.5 full time equivalent to serve as director's and groups leaders assistance, financial management, missions, etc…

Federative Research Institute and core structures on the Necker's site : The Necker's IFR is efficient in that it proposes common core facilities such as animal room, proteins analyses and identification, … One full time technical staff of the unit 781 is dedicated to the animal works for the research groups. The committee has recommended to enhance facilities for bio-informatics analyses and imaging on the site, in accordance with the development of massive data production technologies in the future.

Genatlas: As a particular and important notice regarding Genatlas, the committee has taken a long period of the visit towards evaluating Genatlas, not as research team *per se*, but as a bio-informatics core service. The committee strongly recommends maintaining Genatlas as one of the major integrated databases dedicated to genetics diseases. However, maintaining in the genetic's landscape requires some financial and strategical help from French and European public organisms, and that is clearly favored and encouraged by the committee (see specific evaluation for Genatlas).

— Human ressources:

The Students and Post-docs: Overall the students seemed to be quite satisfied from the stimulating intellectual environment and coaching they found in this Unit. They have regular meetings and easy access to their mentors. They are encouraged to participate at national and international conferences. The general working atmosphere is supportive, agreeable and uncompetitive, though it was hard to assess how vast a consensus there is on this last item across all groups. To better evaluate this point it may be advisable when confronted to such a large Unit, to have these discussions on a per team basis. There was a strong concern about the requirement for a training period abroad, which may conflict with their personal familial plans. This point was heavily discussed with a presentation of the perspectives as seen from the establishments and hiring teams (requirement for broad eclectic training, exposure to the outer world, lack of inbreeding, etc.). There is however still important room for major improvements.

- There are no generalized and effective PhD thesis committees or tutors as yet, and there was a consensus that this should be rapidly installed.

- Their knowledge of the (spoken and written) English language is often limiting, a difficulty which could be solved if internal seminars and group meetings were to be regularly held in English. They were also encouraged to apply to specific courses to which they are entitled.

- Space (and quiet space) is a major problem in the Unit. Thus when they need to write documents, they often choose to stay at home to do so.

- Access to computers is unevenly handled. Some teams have funds to buy PCs for their usage. In other teams, students need to pay for these from their own pockets.

- There are unfortunately not many interactions with scientific activities on this campus outside of the Unit.

Staff scientists : Numerous researchers belong to the lab and are affected to specific teams. All together, 24 tenured (most belonging to Inserm) and 14 Hospital-University researchers belong to the structure. Such a high number of tenured scientists certainly reflects the high quality of projects in each group, as well as the dynamism of the director and leading staff. All scientists actively participate to the life of the lab, communicate at international meetings and are invited for seminars or communications.

Technical and engineers staff : Engineers, technicians and administrative assistants (ITA) of the unit have organized a meeting for several committee members. A clear presentation made by the ITA representative was followed by a rich discussion between all participants. ITAs' participation in the Unit's life is excellent with a very good communication between ITAs, researchers and students. Their participation is regularly acknowledged through not only article co-authorship, but also oral presentations, which is rather unusual in France. At the present time, the working conditions are good; however, there was some kind of worry about the project to move in a new building ("IMAGINE"), the ITAs being afraid that the planned space will not be sufficient. The technical staff seemed satisfied from the environment and coaching they found in each team. Most of them have some common tasks for the unit. It was found difficult to assess how vast a consensus there is on the evaluated items (support, competition, etc…), in particular when comparing staff members of specific scientific teams and those dedicated to core facilities. A major point, not specific to this particular laboratory, concerns the accession of several members of this staff to tenure positions. This is a recommendation of the

committee that long term, non yet tenure staff members, must be integrated at Inserm, CNRS or Paris 5 University when working for more than 3 years in the lab and then having filled all the requirements expected from the scientific staff of the unit.

32 ITAs (corresponding to 28.4 full-time ITAs) work in the Unit. Among them 17 are state employees, of whom 7 work at bench. The remaining 15 ITA are all employed on short-term contracts (mainly through ANR funding); this was a major concern for these young people (mean age: 31 years) since in such situation long-term career perspectives are far from being clear; 11 of these ITA employed on short-term contracts work at bench, whereas the remaining 4 ITA are computer persons working in the Genatlas team (Team 10). This latter situation seemed unreasonable to the committee, especially because of the specific objectives of Genatlas.

From a general viewpoint, the ratio of full-time ITA per researcher full-time in the Unit is, at first glance, excellent (1.05). However, when taking into account full-time ITA working at bench per full-time researcher, the ratio is only 0.64 and reaches 0.24 if only the state employers are taken into account. This is another concern that is hardly compatible with the emergence of long-term and risky projects. In this regard, given the large number of academic researchers (17 from University), the committee was surprised to learn that only 3 ITA are funded by Paris Descartes University.

The technical staff is very motivated. All are ready to participate in training in order to give a better service. They organize training or seminars for the members or students of the unit. The organization of the secretarial staff is very efficient.

— Management :

The direction of the research centre for the next four years has obviously been considered very positive by the committee. Clearly the project of building the new foundation IMAGINE for genetics diseases and the major involvement of the Director in this project are essential.

6 • Recommendations and advice

— Strong points :

Identification of molecular bases of genetics diseases (world top level); High impact publications on a regular basis; Attraction of high quality scientists, physicians and students; Dynamism and excellence of most group leaders and director; International collaborations; Translational links from patients to basic research; Pertinence of the projects; Funding; Perspectives of the future foundation Imagine.

— Weaker points :

Partnership with industry; internal collaborations; Bio-informatics.

Several PhD students noticed poor supervision of their thesis work. Actually, in some groups there are a large number of PhD students under the supervision of only one or two staff scientists. An increase in the recruitment of qualified post-doctoral fellows could help to solve this problem.

— Recommendations :

Some changes in the organization of the unit seem necessary to ensure the durability of some of the research teams, their continuous excellent research and visibility at the international level. In particular, some efforts should be made on several aspects including post-genomics studies (for some groups : see specific evaluations), partnerships with industry and development of projects clearly dedicated to therapies.

— Conclusions :

This unit is an excellent instrument for basic and applied research in modern genetics. It deserves much attention by the players of public scientific research in France, in particular in this period of important changes of the French research system. However, the scientists at this research centre must maintain very high standards in their research activities in order to obtain grants to fund their projects. Also, they should react quickly to the changes of objectives and goals of modern genetics and cell biology since they wish to maintain the centre at the edge of knowledge.

This Unit must be renewed in all, without any restriction according to the excellence of the structure as evaluated during the site visit. All the specific scientific teams of the unit must be created/renewed in this structure as proposed – no restriction. The group leaders are the most pertinent as proposed in the project. The committee recommends to support Genatlas as mentionned in the report.

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 28 avril 2009

DRED 09/n° 190

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 781 Génétique et épigénétique des maladies métaboliques neurosensorielles et du développement** » rattachée à mon établissement.

L'Université Paris Descartes est consciente de ses moyens limités quant à l'affectation des ITRF (techniciens, ingénieurs et administratifs) dans les laboratoires : il existe une centaine de formations dans l'Université et seulement 250 postes d'ITRF affectés aux structures de recherche. Certaines d'entre elles sont fortes de plusieurs centaines de personnes (les centres de recherche). Néanmoins, l'Université s'engage à optimiser cette répartition.

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

Le Président de l'Université

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UNIVERSITÉ
PARIS DESCARTES

DIVISION DE LA RECHERCHE
ET DES ECOLES DOCTORALES

Paris, le 11 mai 2009

UMR-S 781 Génétique et épigénétique des maladies métaboliques neurosensorielles et du développement

Retour sur le rapport du comité AERES – Observations de portée générale

Pas d'observations.