Génétique du développement normal et pathologique

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Genetics of normal and pathological development

From the

University of Nice Sophia-Antipolis

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

January 2011

Research Unit

Name of the research unit: "Genetics of normal and pathological development "

Requested label: UMR-S

N° in the case of renewal: UMR_S636

Name of the director: Ms. Minoo RASSOULZADEGAN

Members of the review committee

Committee chairman

Ms. Margaret BUCKINGHAM, Pasteur Institute, Paris, France

Other committee members

Ms. Paola BOVOLENTA, CSIC, Madrid, Spain

Ms. Blanche CAPEL, Duke university, Durham, USA

Mr. Pascal DOLLE, Université de Strasbourg, Illkirch, France

Ms. Anna-Katerina HADJANTONAKIS, Sloan-Kettering Institute, New York, USA

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Mr. Patrick BLADER, Université Paul Sabatier, Toulouse , France (représentant INSERM)

Observers

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Ms. Catherine LABBE-JULLIE, INSERM

Mr. Jean-Marc LARDEAUX, University of Nice - Sophia-Antipolis

Report

1 • Introduction

- Date and execution of the visit

The visit of the AERES committee took place on the 25th January 2011, in the Centre de Biochimie where the INSERM UMR636 is located. After a meeting between the AERES scientific advisor and the committee, all the members of the UMR636 participated in a brief explanation of the evaluation procedure, followed by the presentations of the current and future directors of the Unit. The committee then heard presentations by the five team leaders which took place, together with questions and discussion, in the presence of the members of the team concerned. Later in the afternoon the committee met with scientific researchers (permanent scientists, post-docs and PhD/Master students) followed by a meeting with technical staff. They then had two successive meetings first with the Vice-President of the University of Nice, in charge of research, together with the INSERM representative and then with the director of the CNRS UMR6543, which is also mainly located in the Centre de Biochimie, in the presence of the future director of the INSERM Unit. There was further discussion with the future Director alone before a concluding closed door meeting of the AERES committee.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

At the time of the last review, four years ago, the INSERM Unit consisted of three teams namely team 1 (RNA mediated epigenetic heredity in development), team 2 (kidney organogenesis) and a third team working on PPAR signalling and muscle physiology which left the Unit in 2008 to join the Faculty of Medicine INSERM U907, which the team leader now directs. This re-location was appropriate in regard to the more metabolic re-orientation of their research. The departure of this team permitted the emergence of research team 3, directed by a senior member of team 2 who had driven the excellent work on sex determination in this group, a theme now pursued by team 3. In 2009, the Unit succeeded in recruiting a young team leader who had previously done outstanding work on the transcriptional regulation of pancreas development as a PhD student and post-doc in the Max Planck Institute in Göttingen, Germany. He obtained an INSERM Avenir start-up grant, together with other awards, and now directs a research group (Team 4) focussing on the regulation of endocrine cell specification and re-programming in the pancreas, in the context of diabetes. In 2009, the Unit recruited a 5th team leader, a senior researcher in the Telethon Institute of Genetics and Medicine (TIGEM) in Naples, Italy, with a strong reputation for work on neural development and brain patterning. Her installation in the UMR636 has been facilitated by an ANR chair of excellence award. All five teams use the mouse as an experimental model. As the new title of the Unit states, the focus is on developmental genetics and cellular reprogramming. The teams work on different tissues and organs, but share common interests in genetic regulation and cell behaviour which make this a coherent ensemble.

The Unit is housed on the first two floors of the Centre de Biochimie on the Parc Valrose campus of the University of Nice. The mouse animal house is located at level -2 in the same building, and has been under the supervision of members of the Unit which provides the majority of the manpower. Furthermore the Unit has now established a platform for generating transgenic mice. A histology laboratory is also installed at this level. Other facilities shared with the CNRS UMR6543, include a washing-up service on floor 2 and a microscopy platform housed by the CNRS Unit which occupies floors 3-5 of the building.

- Management team

The Unit is managed by the director in close collaboration with the other four team leaders. This steering committee meets monthly and there is a bi-annual meeting of the laboratory council, which includes all team leaders and representatives of the different categories of scientific and technical personnel. Management of this relatively small Unit does not appear to pose problems. There is one full time and one half time secretary for the Unit which, as the number of teams increases, is minimal. Additional support comes from the regional administration of Inserm but since it is located in Marseille, despite good relations, the distance is a complicating factor.

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	3
Number of full time researchers from research organizations (Form of the application file)	7	7
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	11	13
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	9	10
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	8	
N6: Number of Ph.D. students (Form 2.7 of the application file)	7	
N7: Number of staff members with a HDR or a similar grade	8	8

2 • Overall appreciation on the research unit

- Summary

During the last four years the Unit has been very productive, with some outstanding scientific contributions. They have succeeded in recruiting two excellent new team leaders at junior and more senior levels. The scientific projects build on this strength and are ambitious while remaining realistic.

- Strengths and opportunities

The focus of research on the mouse model, together with overlapping interests of the teams in cell programming and organogenesis during development as well as cell reprogramming in the adult, confers scientific cohesion. Clearly the Unit functions well as a whole. The recent recruitments strengthen and stimulate research, bringing in new approaches and concepts. Increased interaction with the neighbouring CNRS Unit provides opportunities for sharing facilities and seminar programmes and also for benefitting from the excellent cell biology practised in this Unit. The creation of a federative research structure betweeen the two Units receives strong support from the committee, as do plans to strengthen links with the University.

- Weaknesses and threats

The Unit needs more permanent scientific staff and technical support, a lack which has been exacerbated by the recruitment of new research teams. They have been very successful in rising outside financial support, but it is essential that internal funding and salaries should be assured for maintaining essential facilities such as the mouse animal house. The latter is especially important in the context of a future fusion with the neighbouring CNRS Unit. The question of space for expansion of the INSERM UMR 636 is an issue, as is the capacity of the mouse house in the medium term.

- Recommendations

The Unit should consolidate their infrastructure before further team recruitments. Given the perceived need for bio-informatics, the committee encourages them to concert with the CNRS UMR 6543 Unit in this respect. In general, the establishment of co-operative interactions with this Unit is strongly encouraged by the committee. The development, with the University, of a follow-up on the successful international PhD programme (InterDec) is encouraged.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	2
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	7
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	0.9
A4: Number of HDR granted during the past 4 years	3
A5: Number of PhD granted during the past 4 years	4 (+2 in Dec. 2010)

3 • Specific comments

- Appreciation on the results

The Unit has produced important scientific results, which have contributed to the progress of research. All the team leaders are international figures in their fields. In the last four years, the Unit has published over 45 papers in peer-reviewed journals. These include journals of the highest impact, such as Nature or Cell, as well as excellent journals such as Developmental Cell, Current Biology, J. Cell Biology, PNAS, Human Molecular Genetics, FASEB Journal or Development. In addition to these publications, which primarily emanate from teams in the INSERM Unit, they have also participated in other prestigious publications. Members of the Unit have also published reviews in high impact periodicals such as Nature Rev. Genetics. One of the team leaders is also responsible for a patent on his work. Seven PhD students have successfully defended their theses. All the teams are engaged in external, mostly international, collaborations. This is evidenced by joint publications and also by grants from the European Union or NIH for collaborative projects between teams in the Unit and European or American laboratories. Collaborations also extend to Japan.

- Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners

Team leaders are invited as speakers in international meetings, such as Keystone and Gordon conferences in the USA or EMBO meetings in Europe, as well as to give seminars in Institutes in France and abroad. In the last four years, they have obtained prestigious awards and prizes, such as the election of Team 1 leader as a member of EMBO, Team 2 leader as a member of the Faculty of 1000 for Medicine, or Team 4 leader as a winner of the Foundation Schlumberger and the Juvenile Diabetes Research Foundation career development awards. Team 5 leader was awarded a distinguished professorship (Chaire d'Excellence) by the ANR and one investigator in the team 3 received the Albert Sézary prize of the French Academy of Medicine. Furthermore, students and postdocs have been awarded competitive fellowships, including a Boehringer Ingelheim PhD fellowship.

The recruitment of two excellent team leaders from Germany and Italy as well as students and postdocs from within France and internationally, clearly indicates the attractiveness of the Unit.

The teams have all succeeded in obtaining ANR grants and are also partners in European Union or other international consortia. Strikingly more than 85% of their current funding (excluding permanent salaries) comes from external sources. Many of them have on-going international collaborations, with research laboratories and also industry, for example with the RIKEN Omics Science Center, Japan, with laboratories in the University of Queensland, Australia; Harvard Medical School, USA; MD Anderson Cancer Center, Houston, USA; UCSF, USA, as well as many European Institutes/Universities and with the company NOVONORDISK, Denmark, to cite a few examples. Many collaborations have resulted in joint publications.

- Appreciation on the management and life of the research unit

This is a small Unit so organisation and communication are straightforward. The current and future directors appear to work well together and to have very good relations with the members of the Unit. The committee was impressed by the positive attitude of the team leaders and personnel. Difficulties that have been encountered, for example the lack of personnel in the washing-up facility, which created a serious problem, have been tackled collectively. Different teams have invested time and effort into setting-up and maintaining common facilities, like the transgenic service. Problems which were raised by the technical or scientific personnel did not reflect on the internal management, but rather on the need for more external support. This included technical positions to ensure the running of common facilities such as the washing-up service or the animal house and to permit the establishment of more core facilities. The recruitment of more senior scientists to the Unit is also required to reduce the burden on post-docs of over-seeing the work of PhD students and other laboratory responsibilities. It also emerged that all PhD students would benefit from an external tutor in addition to their supervisor, as practised by many doctoral schools.

Internal scientific meetings take place regularly at the team and Unit levels, the latter in conjunction with the CNRS UMR 6543 when post-docs or final year PhD students present their work in monthly seminars. In addition, they organise seminars for external invited speakers. The Unit has high scientific ambitions, and their ability to promote cutting edge projects is evidenced by the recent team leader recruitments from within and outside the Unit.

At present one member of the Unit holds a University position as a lecturer with major responsibilities for teaching courses in cell biology. A number of the team leaders, senior researchers and post-docs of the Unit participate in teaching Master degree courses in developmental biology and disease pathologies. Some also participate in Master programmes at other Universities. Students and post-docs would appreciate more possibilities for paid teaching in the University of Nice. In the future, the Unit hopes to increase the interface with the University, by the recruitment, for example, of additional University scientific staff. A notable initiative taken by the Unit has been the establishment of an international PhD programme (InterDec) financed by an EU Marie Curie grant, run jointly with the CNRS UMR 6543. Financing of this programme has now come to an end, but the Unit is very keen to find alternative ways to continue such an international programme with the CNRS Unit and the University in the future. Within this Marie Curie programme, foreign students were assisted administratively on their arrival. Post-docs and students from overseas currently in the Unit expressed their regret that there is not an infrastructure on the campus that facilitates the installation of foreigners.

In addition to academic teaching, members of the Unit have also been active in talking to the general public about scientific issues.

- Appreciation on the scientific strategy and the project

The scientific project over the next four year period focusses on the theme of developmental genetics and cellular reprogramming which is now the new name of the Unit. The aim is to build upon the research achievements of the existing teams who, as indicated in the comments on individual teams, present projects at the forefront of their area of research. Expansion of the Unit is envisaged, with recruitment of a bio-informatics group as a priority, potentially in conjunction with the CNRS Unit. Reconciling excellence in research, which also ensures state of the art bio-informatics, with the need of the Unit for computation analyses applied to the data they generate, may prove difficult and requires careful thought. Recruitment of team leaders with AVENIR type start-up grants is also envisaged in the general area of mammalian genetics. The attractivity of the Unit makes this possible, but current restrictions in space and technical support do not make this immediately feasible.

Recruitment at the University level to the Unit in this area would facilitate their expressed desire to contribute to an improved curriculum in mammalian genetics. Restructuring of research on this subject is proposed with a re-localisation of teams on the Valrose campus working on mouse genetics in the Centre for Biochemistry where the mouse facilities are housed. This would require re-location to the Natural Sciences building of some CNRS UMR 6543 teams. Such a regrouping of teams that work on the mouse model would certainly stimulate scientific interactions and improve the visibility of mouse genetics in the University of Nice. However interactions with the excellent cell and molecular biologists of the CNRS UMR 636 are also very important for the INSERM Unit.

The proposed integration of research activities of the two Units in a Federative structure is a good way forward towards an eventual fusion, clearly favoured by the University. An ambitious aim towards greater expansion and integration is to obtain a major grant from the French government for the Federative structure, as a Laboratory of Excellence (LABEX). This would permit refurbishing of the Natural Sciences building, with the perspective of new recruitments, as well as providing considerable resources. Requirements of the INSERM Unit for a FACS core facility or for a high-end central server for high performance backup and analysis of data or even for expansion of the mouse animal house would be more easily satisfied in such a prestigious LABEX context. With or without a LABEX, a Federative structure which includes both CNRS and INSERM Units would constitute a centre of scientific excellence with heightened visibility.

4 • Appreciation team by team

Team 1 : Non-Mendelian heredity of an epigenetic state, role of RNAs and micro RNAS

Team Leader : RASSOULZADEGAN MINOO

- Staff members

	Past	Future
N1: Number of re searchers with teaching duties (Form 2.1 of the application file)	3	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	1	3

- Appreciation on the results

The research carried out during the last 4 years by the group has been exceedingly original and of remarkably high standard. This highly original work has resulted in some very exciting findings hinting at novel mechanisms that regulate not only development but also non-Mendelian modes of inheritance. The relevance of the work is reflected in the production of 11 original articles (4 data papers) and 6 reviews in the past five years, mostly in top tier journals including Nature and Dev. Cell as well as Development. The impact of this research is significant as it may lead to the establishment of a new paradigm in the field and help to shed light on human disorders with a non-Mendelian inheritance pattern. Central to the past work has been the extraordinary powers of observation of the team leader that have allowed for these very interesting findings to emerge.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The importance of the group's findings is reflected in a series of publications in outstanding journals. The resulting meeting invitations, and the fact that the group leader has recently been elected to EMBO membership testifies to her recognition as an important member of the scientific community.

It is clear that the group has established collaborations with a number of strong international groups who are obviously interested in their important findings. It will be important for the group to consolidate these collaborations and ensure that they benefit from them. The committee would encourage that in the future the group also exploits its visibility by attempting to attract international funding and larger amounts of national funding, and to recruit personnel (post-docs) at the international level.

The committee congratulates the team leader for all she has achieved as an effective Director of the Unit.

- Appreciation on the scientific strategy and the project

The proposed project has a very high potential derived from the significance of the group's findings. The committee would encourage the group to, where possible, focus on the mechanism underlying the phenomena described, as understanding this mechanism will significantly add to the impact of the group's findings. Along these lines, the panel agrees with the team leader that it is wise to put the iPS work on hold for the time being, especially given the group's limited resources and the competitive nature of the iPS field. While the Dnmt2 link could be very important, the committee would suggest that prior to pursuing this potentially interesting observation, the group provides further mechanistic rather than phenomenological confirmation of the role of this factor in methylating RNA.

The proposal is interesting and risky, and may be overextending the group's capacity. Indeed, the team leader has the expertise to carry out some but not all the specific aims. Where she does not have expertise, she appears to have organized scientific collaborations but it is not clear what the eventual benefit of these collaborations will be to her group. For example there are no collaborative grants with other labs to undertake any of these projects.

- Conclusion :

  - Summary:

The achievements of the group over the last 4 years are outstanding. The current research program and proposed future work extend an interesting series of observations. The international impact of this work is very high, but unfortunately it is not at present reflected by the group's current grant support. Overall, the team has greatly contributed to the visibility of the INSERM UMR636 Unit. However, when moving forward, the committee strongly supports a major focus on deciphering the mechanisms regulating the paramutation phenomenon described by the laboratory. These are high impact discoveries that need to be consolidated and capitalized upon by the group.

  - Strengths and opportunities:

(1) Established team leader with an international reputation. (2). Novel observations on an unusual and likely very important but little understood phenomenon. (3) Outstanding genetics and micromanipulation expertise of the group. (4) International visibility for work. (5) Potential to make breakthrough contributions of very high impact.

  - Weaknesses and threats:

(1) Lack of mechanistic understanding of the phenomenon. (2) Minimal description of alternative approaches to specific aims. (3) No international grants. (4) Risk of overambitious projects and as a result spreading research efforts thin for the size of the lab. (5) Collaborations exist, but it is not clear if they are structured to benefit the group.

  - Recommendations:

The team has made extraordinary observations published in outstanding journals. This work is highly original, with the discovery of exciting phenomena. The project has high potential; however, to maintain leadership and prominence, the next step must be focused to address the mechanism underlying the phenomenon that has been discovered.

Team 2 : Organogenesis, kidney diseases and stem cells

Team Leader : SCHEDL Andreas

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	
N7: Number of staff members with a HDR or a similar grade		2

- Appreciation on the results

The team has made several important contributions in characterizing the roles of key transcription factors acting during renal development and physiology. They have created and analyzed murine models for conventional or conditional knockouts of several factors, including Sox8, Sox9, Sox11, Wt1, and Wtx. Some of these models have direct relevance for human genetic diseases, such as Frasier syndrome, for which the team has created a mouse mutant with a targeted Wt1 splice junction mutation mimicking the mutation occurring in humans.

The team leader is an excellent mentor, and has successfully supervised several students and post-docs in the last years. Altogether this work led to 15 research articles over the period of review, some in high impact factor journals. Among these, at least half are primarily the team's work, the others resulting from collaborations with several international teams - including human geneticists and clinicians.

This has been a period of "tool building" for the lab, during which several new mouse models have been generated. Further recent achievements, mainly unpublished (e.g. development of techniques improving the sensitivity of ChIP-Sequencing of small samples, initial lineage analysis of a novel stem/progenitor cell population in the adrenal gland cortex...) also provide a strong basis for the main axes of the new research project. The group is currently poised for a high level of output in the near future.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team and its leader are recognized internationally as one of the reference teams studying molecular and genetic control of renal development and its relevance to kidney disease in humans. The team leader has been invited to write a review article in a high impact factor journal (Nature Rev. Genet.), and is invited for numerous meetings, symposia, and lectures. A network of collaborations with international experts, including clinical researchers, geneticians, and experts in stem cell isolation and transplantation, has been key for the success of this research. Furthermore, the team has a strong international flavor with several foreign post-docs and students. The team leader has been very successful in obtaining funding from various national and international institutions and foundations.

Within the unit, he has shown outstanding leadership ability. He has been generous in his support of the mouse facility from his own budget, and he has also spun off an independent laboratory in the unit (Team 3).

- Appreciation on the scientific strategy and the project

The project is well-balanced and takes advantage of many of the tools the team has created. Whereas some axes of the program are readily feasible considering their expertise, others involving stem cell characterization, isolation, and transplantation/therapy are more risky and uncertain. These represent however cutting edge approaches with a high "up side". Development of these aspects may lead to future applications in human therapy, consistent with the group leader's longstanding interest in research aimed at the mitigation of human disease. Resource allocation (in terms of funding and man-power) is well matched to the research plans in the near future.

- Conclusion :

  - Summary:

The project is ambitious, but probably feasible. The team has demonstrated its capacity to manage several projects involving the study of various gene functions and their relation to disease. Some aspects (Wt1 stem cells) are more risky, but well-balanced by more basic aspects of this research. As the research program is ambitious and involves some technical developments and cutting edge approaches, this dispersion may at some point become limiting with respect to team size, and strategic choices might have to be made.

  - Strengths and opportunities:

(1) Established team leader with an international reputation. (2). Development of outstanding mouse models. (3) Solid combination of skills in mouse genetics and molecular approaches. (4) Strong international group in the laboratory. (5) Links to the clinical community. (6) Potential to make breakthrough contributions of very high impact in the stem cell field.

  - Weaknesses and threats:

(1) It is critical for the team leader to remain aware of other large international groups, so that he maintains his unique niche in the field. So far, he has managed this problem extremely well. (2) Maintenance of a strong mouse facility with manageable costs to the individual laboratories is absolutely critical for the success of this lab.

  - Recommendations:

Publications in the near future should allow the lab to capitalize on its recent discoveries and investments that they have made in generating complex genetic tools. This will also lead to further funding necessary to maintain the capacity of the group.

Team 3: Functional analysis of sex determination in mammals

Team Leader: CHABOISSIER Marie-Christine

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)		
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

Over the last four years the team leader has established her independent career and developed a strong team. The work of the team over this period, and more specifically, those experiments addressing the role of Rspondin, have made a significant contribution to the field and will be important to help uncover the basis of sex reversal disorders and infertility. For this reason their research will have an important impact on human health. The team has uncovered novel interactions within the developing genital ridges and performed some very elegant genetic experiments that have provided novel insights into sex determination and germ cells. This work has resulted in a good number of strong publications (and some are still on their way) and strong national and international collaborations.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The quality of the research has provided the team with international as well as national recognition with invitations to international conferences and long-term collaborations with a number of european and american laboratories. As a result of this, they have attracted excellent funding in collaboration with other teams and have developed a very valuable network of interactions. The committee encourages the team leader to exploit this recognition and interactions by applying for EU funding.

- Appreciation on the scientific strategy and the project

The future proposals are nicely thought out and explained in a clear fashion. They provide a set of experiments that are the natural continuation of the team's past work, and therefore are based on solid data. The proposed experiments are hypothesis driven and thoughtful. They are a good balance between continuing current lines of research and exploring new avenues, and there is every indication that they will provide novel insight into sex determination and fertility. However, the committee considers that there is intense competition in the study of the role of beta-catenin and Wnt signaling and on how meiosis versus mitotic arrest is controlled, and therefore suggests that the team identifies a niche within these competitive areas. For example an interesting avenue to explore would be the expansion of their work on the cellular role of Rspondin. Findings would be of broad interest to the field of development.

- Conclusion :

  - Summary:

The achievements of the team over the last 4 years are very good. The PI has established a strong team and developed a strong research program. The international impact of this work is high and the PI has developed important collaborations to exploit this impact. Moving forward the committee supports strengthening the team niche within the area of sex determination.

Strengths and opportunities:

(1) Established team leader with an international reputation. (2) Has made a significant contribution to the field. (3) Strong research program with good funding. (4) Well established network of collaborations.

  - Weaknesses and threats:

(1) The work on beta-catenin/Wnt signalling and meiotic/mitotic arrest are in very competitive areas. (2) There is still considerable scope to explore the cellular and mechanistic roles of Rspondin. (3) The team leader does not belong to any EU networks.

  - Recommendations:

Strengthening the niche the group is establishing will be essential to ensure strong publications in the future.

Team 4 : Generation of beta cells from alternative pancreatic cell types in vivo

Team Leader : COLLOMBAT Patrick

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)		
N7: Number of staff members with a HDR or a similar grade		1

- Appreciation on the results

The team leader recently has begun his independent group in the Unit, which he joined in 2009. His most recent scientific achievements therefore primarily reflect the work he has performed as a postdoctoral fellow in the Max Planck Institute of Molecular Cell Biology, Gottingen, Germany. This work has been mostly focused on the understanding of pancreas development obtaining sensational and quite unexpected results that have highly impacted the field. His discoveries have great potential impact in the design of cellular therapies for the treatment of diabetes.

The importance of the work is reflected in the production of 9 original articles (5 as first author) and 4 reviews in the last five years, mostly in top journals including Cell, J. Clin. Inv., J Neurosci. and Development. He is a co-author in a patent, and has been invited to present his work at meetings and in seminars, including events designed for the general public.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

As mentioned above, the team leader has recently established his group and it is therefore rather too early to evaluate his trajectory as a group leader. There is however no doubt that he has a great deal of potential. His recent work was not only extremely well received by the scientific community, but this was also echoed in the media. The relevance of the work for the biomedical field enabled him to raise an impressive amount of competitive financial support, especially considering the early stage of his independent scientific career. Notably, he coordinates a major consortium awarded 3.5 mil € from the Juvenile Diabetes Research Foundation (JDRF), from which he has also obtained a personal Career Developmental Award. He has established important collaborations at the national and international level that will certainly foster his position in the field. The potential relevance of his research in diabetes therapy guarantees its socio-economical impact.

- Appreciation on the scientific strategy and the project

The proposed project is a logical continuation of the previous successful work of the team leader, stemming from his postdoc in the Max Planck Institute in Göttingen. It is important to note that this subject will not be pursued by the German group. The proposal aims to better define pancreas morphogenesis with the goal of reprogramming pancreatic cells into insulin producing beta cells, which will be an efficient and patient-specific approach towards the treatment of, and/or cure for, diabetes. To this end the proposal combines mouse genetic approaches with genomics, as well as the use of human foetal pancreatic tissue to extend findings towards rational diabetes therapies. The proposal is very interesting, risky, but certainly worthwhile. The team leader has the expertise to carry out most of the specific aims, and where he does not, he appears to have organized scientific collaborations with groups who can bring in essential expertise to the project. The first goal is based on microarray expression profiling of different mouse models. This usually constitutes a broad approach that even if designed to address a specific question, may change the focus of a project, or lead it into unclear directions. Even so, the team leader seems to have a reasonable plan to validate potentially interesting candidates, and to focus on genes pertaining to his interests. The second aim involves Tet induced ON/OFF expression of Pax4 to look at the transdifferentiation potential of endocrine cells. The transgenic system has been developed and the committee strongly supports the team's focus on this approach. The third goal is to manipulate human pancreatic explants, in collaboration with clinicians. In the longer term this will be necessary for therapeutic purposes, but should probably not be an immediate priority.

- Conclusion :

  - Summary.

The achievements of the team leader during his post-doctoral training have been outstanding. His current research program and proposed future work derives from this very solid foundation. The international impact of his work is very high and is reflected by his current grant support, which is outstanding, even for a junior investigator eligible for start-up opportunities. These high impact discoveries carry significant risk because of the very competitive nature of the field, and because of the financial opportunities and investments resulting from this work. However he seems to be prepared for handling this situation. Overall, he is an excellent recruitment to the Unit.

– Strengths and opportunities:

(1) Young and very promising team leader with excellent experience in the field in which he is building a research program in. (2) Cutting-edge scientific research plan based primarily on basic science, but with excellent translational applications. (3) Research field with socio- economical relevance. (4) Excellent current financial support. (5) Potential to make breakthrough contributions in a very high impact and competitive field.

– Weaknesses and threats:

(1) Strong competition in a very high impact field. (2) Minimal description of alternative approaches to his specific aims. (3) Risk of overambitious projects and as a result spreading research efforts thin for the size of the lab, even though this is quite a large start-up group.

– Recommendations:

The team leader should initially focus his work on the more concrete aspects of the research proposal. For example specific aim 1 may lead him beyond the main goals of his proposed research program. As with most junior investigators, it will be important for him to find his own niche in this very competitive field. Focusing on the ON/OFF mouse seems an initial excellent choice.

Team 5: Patterns and connectivity during brain development in mammals.

Team Leader: STUDER Michèle

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)		
N7: Number of staff members with a HDR or a similar grade		1

- Appreciation on the results

The team was recruited in 2009 and moved to the centre in 2010 from the Telethon Institute (TIGEM) in Naples following an award of an ANR Chair of Excellence grant. Using mouse genetics, the team leader had previously made important contributions to the understanding of hindbrain development. More recently, work has focused on cortical development and the role of the orphan receptor COUP-TFI. The team's major achievements are based on the creation of a new murine model allowing tissue-specific (Cre-mediated) inactivation of COUP-TFI, which in turn has permitted in depth studies of the consequences of targeted loss of function in neocortical cell populations. This demonstrated that COUP-TFI plays a major role in regionalization of the motor and sensory areas during cortical development. Detailed molecular analyses and cell birthdating studies also demonstrated that this factor regulates the balance of early- and late-born neurons, and controls the temporal switch leading to formation of layer V corticospinal motor neurons. The functional relevance of these developmental events was demonstrated by extensive behavioral testing of the conditional mutants. This work represented an important advance in the field since there is little information on how cortical areas are specified.

The importance of the work of this team is reflected in the production of 12 original articles, including two recent manuscripts in press at the time of the site visit. The team leader is the senior author on 5 of these publications. Most of the articles are published in top journals including Nat. Neurosci, Nat Genetics, Genes & Dev, PNAS, J Neurosci and Development. Papers in collaboration with expert international teams also have had a major input from the research program of the team. The team leader has been invited to give seminars and to present work at meetings, and has also been the scientific organiser of two meetings. She acts as referee for Journals and granting agencies. Notably, she has been responsible for the transgenesis service at TIGEM, which underscores her expertise in mouse genetics.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team is well recognised in the field of neural development. They have over ten active scientific collaborations, some with top international experts in neurobiology. These collaborations appear to be on an intellectually equal footing, which underscores the recognized position of the team leader in a very competitive field. She has been invited to international meetings and has collaborated with top national and international scientists in the field of developmental neurobiology and mouse genetics. The team is currently very well supported with major national funds and she has previously been granted funding by international (EU STREP project) agencies. As the team was established quite recently, it is difficult to evaluate its attractiveness with respect to recruitments. At present the team is operating with two post-docs. Recruitment of talented PhD student(s) would be highly beneficial.

- Appreciation on the scientific strategy and the project

The proposed project is a logical continuation of the past, successful work of the group aimed at elucidating the functions of COUP-TFI and II in brain development. The proposal is subdivided in three well connected aims that attempt to address the function of these genes in both progenitor and postmitotic neurons of the cortex, with identification of downstream targets. From a methodological point of view, the proposal takes advantage of the strong background of the team leader in state of the art mouse genetics coupled with up-to-date genomic approaches available through a well established collaboration with a laboratory in Cambridge, UK. The experimental plan is well designed, feasible and realistic, reflecting the maturity of the group leader. The team should have no problem to achieve the proposed goals with the available means and funding.

- Conclusion :

  - Summary.

The team is an excellent recruitment for the Unit. Previous work has led to several important contributions to deciphering the role of key signalling pathways and regulators of hindbrain and forebrain development. Current work on COUP-TFI and the tools that have been created, position the team in a well-defined niche in the field. The track record of publications is excellent, the funding support is strong and valuable network of collaboration with other leaders in the field has been established on an intellectually equal footing. The project is coherent, feasible, and well-designed.

– Strengths and opportunities:

(1) Major strengths are a solid group with a strong tradition and excellent experience of the team leader in the field of the proposed project, (2) A cutting edge scientific plan, (3) Excellent collaborators, and good financial support.

– Weaknesses and threats:

(1) Possible threats may be linked to the fact that cortical development is becoming an increasingly competitive field. (2) Reduced critical mass in neurobiology within the unit and/or the campus may represent a disadvantage in the long run.

– Recommendations:

The committee encourages the team leader to develop the post-natal aspects of her model and to look for opportunities to translate this research towards aspects relevant to human diseases. It is also advisable to carefully address space requirements in the animal facility, given the actual limitations of the infrastructure.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
GÉNÉTIQUE DU DÉVELOPPEMENT NORMAL ET PATHOLOGIQUE.	**A+**	**A+**	**A+**	**A+**	**A+**
GÉNÉTIQUE DE LA DÉTERMINATION DU SEXE ET DE LA FÉCONDITÉ [SCHEDL-CHABOISSIER]	A	A+	Non noté	A	A
GÉNÉTIQUE DU DIABÈTE [SCHEDL-COLLOMBAT]	Non noté	A+	Non noté	A+	A+
CONTROLES ÉPIGÉNÉTIQUES DE L'HÉRÉDITÉ ET DU DÉVELOPPEMENT MÉDIÉS PAR L'ARN [SCHEDL-RASSOULZADEGAN]	A+	A	Non noté	A	A
DÉVELOPPEMENT DU REIN, PATHOLOGIE ET CELLULES SOUCHES [SCHEDL-SCHEDL]	A	A+	Non noté	A+	A+
GÉNÉTIQUE DU DÉVELOPPEMENT DU CORTEX CHEZ LA SOURIS [SCHEDL-STUDER]	A+	A+	Non noté	A+	A+

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
  - **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
  - **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
  - **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
  - **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
  - **SVE1_LS5 Neurosciences**
  - **SVE1_LS6 Immunologie, Infectiologie**
  - **SVE1_LS7 Recherche clinique, Santé publique**
- **SVE2 Ecologie, environnement**
  - **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
  - **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
  - **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

Présidence et
Services Centraux

Université Nice SOPHIA ANTIPOLIS

Nice, le 13 avril 2011

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Ref : Rapport d'évaluation S2UR120001725 - Génétique du Développement Normal et Pathologique. - 0060931E

Monsieur le Directeur,

Faisant suite au travail effectué par le comité de visite de l'AERES et du rapport d'évaluation émis sur l'Unité de Recherche « Génétique du Développement Normal et Pathologique.» portée par l'Université Nice Sophia Antipolis, nous ne désirons apporter aucun correctif factuel ni aucune observation de portée générale au rapport d'évaluation rendu par le comité de visite que nous remercions pour son travail constructif.

Je vous prie de croire, Monsieur le Directeur, en l'expression de mes sentiments distingués

UNIVERSITE DE NICE - SOPHIA ANTIPOLIS
1.1.1996

Pour le Président de l'Université de Nice-Sophia Antipolis et par délégation,
Le 1er Vice-Président

Pierre COULLET

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