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

Department for the evaluation of research units

AERES report on unit:

Institut de la Vision

IdV

Under the supervision of the following institutions and research bodies:

Université Paris 6 - Pierre et Marie Curie

Centre National de la Recherche Scientifique

Institut National de la Santé Et de la Recherche Médicale

January 2013

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

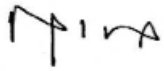
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.

NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1 : Scientific outputs and quality ;
Criterion 2 - C2 : Academic reputation and appeal ;
Criterion 3 - C3 : Interactions with the social, economic and cultural environment ;
Criterion 4 - C4 : Organisation and life of the institution (or of the team) ;
Criterion 5 - C5 : Involvement in training through research ;
Criterion 6 - C6 : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report and its in-house teams received the following grades:

- Grading table of the unit: Institut de la Vision

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

- Grading table of the team: Role of axon guidance molecules

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

- Grading table of the team: Genetic engineering approaches to study retinal development and repair/regeneration

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

- Grading table of the team: Multiligand endocytosis in normal and pathological axial elongation of the eye

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

- Grading table of the team: Neural circuits development

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

● Grading table of the team: Cellular messenger codes for axon guidance

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

● Grading table of the team: Identification of gene defects leading to non-progressive and progressive ocular diseases

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

● Grading table of the team: Rod-derived Cone Viability Signaling for the Treatment of Inherited Retinal Degenerations

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

● Grading table of the team: Retinal information processing – pharmacological and pathology

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

● Grading table of the team: Vision and Natural Computation

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

● Grading table of the team: Neurophysiology and optogenetic applications in the retina

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

● Grading table of the team: Mitochondrial dysfunction and ocular diseases

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

- Grading table of the team: Chemokines and physiopathology of the eye anterior segment

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

- Grading table of the team: Physiology of the retinal pigment epithelium and associated diseases

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

- Grading table of the team: Inflammation in neuronal degeneration and vascular remodeling

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

- Grading table of the team: Gene therapies and animal models for neurodegenerative diseases

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

- Grading table of the team: Development of corneal innervation and re-innervation after corneal surgery

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

Evaluation report

Unit name:	Institut de la Vision
Unit acronym:	IdV
Label requested:	UMR CNRS and INSERM
Present no.:	U592
Name of Director (2012-2013):	Mr José-Alain SAHEL
Name of Project Leader (2014-2018):	Mr José-Alain SAHEL

Expert committee members

Chair:	Mr Stephen E MOSS, UCL Institute of Ophthalmology, UK
Experts:	Mr Alberto AURICCHIO, TIGEM, Telethon Institute of Genetics and Medicine, Italy
	Mr Carlos BELMONTE, Institute of Neurosciences of Alicante, Spain
	Ms Valérie CASTELLANI, Centre de génétique et de physiologie moléculaire et cellulaire de Lyon
	Ms Benedicte DURAND, Centre de génétique et de physiologie moléculaire et cellulaire de Lyon, (representative of CNU)
	Ms Catherine FAIVRE-SARRAILH, Centre de Recherche en Neurobiologie et Neurophysiologie de Marseille, (representative of CNRS)
	Ms Christina FASSER, Retina suisse, Zurich, Switzerland
	Mr Henry KENNEDY, Stem Cell and Brain Research Institute, Lyon
	Mr Francis MUNIER, Retinoblastoma clinics of Lausanne, Switzeland
	Ms Isabelle RANCHON-COLE, Inserm - Equipe Biophysique Neurosensorielle, (representative of CSS)
	Mr Heinz WÄSSLE, Max-Planck-Institute for Brain Research, Frankfurt, Germany

Scientific delegate representing the AERES:

Mr Jacques HAIECH

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

Mr Etienne HIRSH, INSERM

Mr Paul INDELICATO, Paris 6

Mr Bernard POULAIN, CNRS

1 • Introduction

History and geographical location of the unit

The Institute emerged when Mr José-Alain SAHEL moved from Strasbourg to Paris in 2002. The Center for Clinical Investigation was created in 2005.

The unit was created in 2009 as a unit managed by University P. and M. Curie-Paris 6, INSERM and CNRS (U592). The unit suffered from a fire that destroyed most of the building in february 2009.

The Institute is in a building located in hospital XV-XX, 17 rue Moreau - 75012 Paris.

Management team

The unit is directed by Mr José-Alain SAHEL. The Institute is built around 4 departments, Department of development headed by Mr Alain CHEDOTAL (Team S1 to S5), department of genetics headed by Mr Thierry LÉVEILLARD (Team 6 and 7), department of visual information headed by Mr Serge PICAUD (Team 8,9 and 10) and department of therapeutics headed by Mr Florian SENNLAUB (Team 11 to 16).

A common project has been built for the Institute through interactions between the different team leaders and under the supervision of the director, recognized as a charismatic and energetic personality.

Technological platforms have been set up and are open also to the startups housed in the incubators.

AERES nomenclature

SVE1_LS4 Physiology, physiopathology, medical systems biology

SVE1_LS5 Neurobiology

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	13	13	13
N2: Permanent researchers from Institutions and similar positions	19	19	19
N3: Other permanent staff (without research duties)	5	5	
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	3	3	3
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	35	36	36
N6: Other contractual staff (without research duties)	38	38	
TOTAL N1 to N6	113	114	71

Percentage of producers	***100%***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	26	
Theses defended	42	
Postdoctoral students having spent at least 12 months in the unit*	21	
Number of Research Supervisor Qualifications (HDR) taken	33	
Qualified research supervisors (with an HDR) or similar positions	12	17

2 • Assessment of the unit

Strengths and opportunities

The *Institut de la Vision* has developed with remarkable speed to become a world-leading centre for eye research. The research strengths embodied in its scientific teams are complemented by a close working relationship with the Hôpital XV-XX, and a vigorous and productive partnership with the neighbouring Bio-incubator. The triangulation of Institute, Hospital and Industry is unique in eye research and provides both strength and opportunities for future scientific advances and ultimately the delivery of sight-saving therapies for patients with visual impairment. The success of the *Institut* derives in large part from strong and inspiring leadership that is both strategically astute, and capable of working effectively with multiple partners. Indeed the *Institut* is regarded as a model or flagship by CNRS and INSERM, an example of how a modern research Institute can meet its scientific, econoic and societal obligations.

The *Institut* has notable strengths in its research Teams, many of which publish their work in the highest impact journals, and whose leaders have won numerous prizes and international markers of esteem. To build on the solid foundations created by the established groups, the *Institut* has wisely invested for the future by recruiting some outstanding young investigators. These new Teams bring dynamism and energy, and contribute to the multidisciplinarity of the *Institut* by the introduction of innovative and cutting-edge technologies. A planned appointment in visual psychophysics will further strengthen and build capacity in low vision sciences and visual rehabilitation.

In times of economic uncertainty the *Institut* has developed a measure of financial strength by not becoming overly dependent on a limited number of funding sources. For example, the Fondation Voir et Entendre provides one unconventional source of funds, and investments in the Bio-incubator are an important source of both direct and indirect support, such as the Fovea-Sanofi projects that help drive the *Institut*'s mission to deliver novel therapeutics and early phase clinical trials. The start-ups that have emerged from the *Institut* help to maintain the therapeutic pipeline and strengthen the position of the *Institut* as a leading centre for investment, innovation and translational research.

The emphasis on translational research also strengthens the *Institut* by bringing clinicians into the laboratory together with their access to patients and patient samples. The close relationship between hospital and *Institut* ensures that basic scientists, instead of being remote from the clinic, have a heightened awareness of patient needs that in turn stimulates prioritisation of individual research goals. At an overarching level, the interaction between clinicians and scientists maintains the cycle of clinical need driving research direction, that in time will lead to new and better therapies and eventual patient benefits.

Weaknesses and threats

The *Institut de la Vision* is a relatively young Unit that has evolved quickly to become a global leader in its field. It has no significant weaknesses. However, in common with many research Institutes it faces threats. The instability of the financial situation, both nationally and across Europe, means that Governmental budget allocations to the major funders such as CNRS and INSERM face on-going uncertainty. Linked to this, having a large number of staff on temporary contracts means that the *Institut* faces the threat of losing key skills and know-how if those individuals are lost.

The *Institut* is now almost full in terms of its ability to house individual research teams. During the growth period of the last few years it has been possible to prioritise recruitments in important emerging areas such as optogenetics, but physical constraints may make it difficult or impossible to develop research programmes in new domains or 'hot topics' as they emerge in the years ahead. Even for the Teams currently in place pressures on space will grow, particularly as the newly recruited Teams increase in size.

Space limitations have already had an impact on the ability of the *Institut* to house all the rodents it needs for its work. Breeding stocks have now been moved off-site and although it is too early too say whether this will be an effective solution, it creates the threat of reduced efficiency in the management of animal experiments. The lack of capacity to accommodate species other than rodents (for example lagomorphs) also poses a minor threat to the ability of certain Teams to conduct all the work they would like to.

Finally, there is no doubt that the extraordinary success of the *Institut* in achieving its current position is due in large part to the vision and determination of the Director. However, dependence on the leadership of one individual creates a fragility that could leave the *Institut* exposed, and it is not obvious that any of the current Team leaders has the necessary experience and skills to take on this central role.

Recommendations

The *Institut de la* Vision has undergone a phase of rapid growth in the last few years and at least one further significant staff appointment is envisaged in the immediate future. The committee believes that the coming period should therefore be one of stabilisation and consolidation, during which special attention should focus on the nurturing and development of the emerging Teams. In practical terms this might mean restricting administrative load or teaching responsibilities from those Team leaders, prioritising the allocation of resources to the emerging Teams, and supporting collaborative grant applications with senior team leaders.

The *Institut* benefits from excellent working relationships with its partner organisations, including the Université Pierre et Marie Curie, the Hôpital XV-XX, CNRS and INSERM. These relationships deliver significant mutual benefits but cannot be taken for granted. The *Institut* director and senior staff should continue to take a pro-active role in sustaining the support of these Institutions.

The *Institut* currently has a good balance between basic and translational research and this needs to be maintained. As translational research can frequently access funding sources that lie beyond the reach of basic science, such as industry/pharma and clinical budgets, this may occasionally mean making strategic decisions to use central funds to bolster the basic science groups in order to maintain the balance.

The *Institut* has done well in attracting funding from private sources and we recommend that, with continuing uncertainty over future national and international science budgets, there should be a greater focus on fundraising. This might come from a variety of sources, and could include private well-wishers, patients who wish to express their support, philanthropists and the business world. Income from these sources will provide a buffer against the vagaries of political decision-making, and help sustain the strategic autonomy of the *Institut*.

As part of the consolidation phase we recommend that the *Institut* stays up to date with new technologies with appropriate investment wherever and whenever possible, providing there is a suitable fit with the research strategy. For example, there are currently exciting developments around the use of adaptic optics for imaging the live mouse retina that could clearly benefit the work of several of the groups at the *Institut*.

Finally, we recommend that technical staff have more regular meetings (perhaps annual) with Team leaders that could take the form of appraisals, with feedback and advice as to personal development, career track and so on. The *Institut* is encouraged to support the attendance of technical staff on specific training courses where it is deemed mutually beneficial.

3 • Detailed assessments

Assessment of scientific quality and outputs

In the field of ophthalmology the *Institut* is at the leading edge in terms of the impact and scientific quality of its outputs. The Teams have made significant progress in a relatively short time in advancing knowledge in this field, with particularly impressive breakthroughs in defining new disease genes, generating new therapeutic tools and strategies, and moving into clinical trials. The editorial media they choose for the publication of their studies reflects the importance of the work, which often means the most prestigious and reputable scientific journals.

Assessment of the unit's academic reputation and appeal

The *Institut de la Vision* has an outstanding academic reputation. The reputation of any scientific Institution may be viewed as the product of the reputations of its most successful researchers. The lead investigators at the IdV regularly publish their research in the highest impact peer-reviewed journals, and have responsibilities outside the *Institut* on journal editorial boards and funding agency review panels that testify to their esteem and international profiles. And the appeal of the *Institut* is evident in the fact that it recently received 200 applicants for two group leader positions. So far the *Institut* has established its reputation mostly on 'home grown' talent, but with time it is likely that the numbers of overseas PhD students, post-docs and team leaders will steadily increase. Unsurprisingly the *Institut* has become a model, or flagship, in the eyes of its supporting organisations

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

The *Institut* is in no way an inward-looking organisation, and has important interactions with the outside environment. The two most prominent interactions are with the Hôpital XV-XX and the Bio-incubator. Through its interactions with the hospital the *Institut* takes its research outputs directly to the public, and in particular to people with low vision or eye disease who are clearly excited about the research judging by their willingness to participate (in significant numbers) in clinical trials. In addition to delivering societal benefits through improvements in health provision, the *Institut* also makes an important contribution to the wealth of the nation through the spin-out companies it has created, and by hosting a range of small biotech and pharma companies in the Bio-incubator. The level of activity in this area is a consequence of the generation of new intellectual property and patent filings, which themselves are positive indicators of enterprise and knowledge transfer.

Assessment of the unit's organisation and life

The *Institut* is divided into four Departments, each with its own head and clear sense of identity. Regular meetings between the Department heads and their teams, and also between the four Departments, create a strong sense of cohesion and engender an excellent team spirit. The research efforts of the individual teams are underpinned by a number of platform technologies, that are in effect pooled resources that facilitate and support the work of all. All of the Team leaders have responsibilities at *Institut* level, in areas such as postgraduate education, health and safety, and management of the communal facilities.

Assessment of the unit's involvement in training through research

The *Institut* has an excellent record in student guidance and supervision, particularly at PhD level, and there are plans to introduce a new Masters degree course in Vision. The PhD students are associated with four different doctoral schools, namely School 158, Cerveau-Cognition-Comportement; School 387, Interface de la Chimie, de la Physique et de l'Informatique avec la Biologie; School 391, Sciences Mécaniques, Acoustique, Electronique et Robotique; and School 394, Physiologie et Physiopathologie. The *Institut* is also active in training clinicians in research.

Assessment of the five-year plan and strategy

The five-year plan pulls together the individual goals of each Team in an ambitious and synergistic framework. Taken as a whole, the strategic plans of the *Institut* are clearly mapped out, well-designed, realistic, and most important, achievable. The objectives for this period are bold and original, and even if they are only partly successful this will mean new therapies for patients with visual impairment, new technologies for researchers and investigators across many scientific disciplines, and new intellectual property, patents, commercialisation of research and wealth generation. Delivery of the five-year plan will require the pro-active cooperation of various academic and non-academic partners, and it is clear that the Hôpital XV-XX, Université Pierre et Marie Curie, INSERM and CNRS are all fully supportive of the *Institut* and its goals. The *Institut* has mapped its path ahead with the clear intention of exploiting its strengths, whilst at the same time showing awareness of any minor weaknesses and threats. For these reasons, and because of the excellent track records of the Team leaders, the five-year plan is feasible and should be attractive to funders.

4 • Team-by-team analysis

Team 1 : Role of axon guidance molecules

Name of team leader: Mr Alain CHEDOTAL

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent EPST or EPIC researchers and similar positions	3	3	3
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	7	7	7
N6: Other contractual staff (without research duties)	5	5	
TOTAL N1 to N6	18	18	11

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	5	
Qualified research supervisors (with an HDR) or similar positions	5	5

• Detailed assessments

Assessment of scientific quality and outputs

The group has studied the development of neuronal networks in the vertebrate brain, focusing specially on the mechanisms controlling neuronal migration and axonal guidance and made seminal contributions to the field of neural development in the last years. Several of the scientific questions addressed by this team are general in developmental neurobiology, rather than specific to the retina. The team has 5 different Aims. Two of them are devoted to general neurobiological problems: Development and Function of Brain Commissures (Aim 1) and Neural crest and head development (Aim 5). The other aims are more directly related to eye problems: Aim 2 intends to analyze the development of the various retinal layers in mammals, using molecular techniques and genetically modified mice to identify the role of Semaphorin6A and and PlexinA4, and silencing the genes in different subsets of retinal neurons. Aim 3 will study the role of oligodendrocytes in myelination and remyelination in the CNS but in the optic nerve in particular, during development and in pathological conditions. Aim 4 will be devoted to the analysis of axon guidance molecules, and in particular, Robo and Slit proteins, in angiogenesis, using in vitro and in vivo approaches. This is a broad and ambitious project, that uses a modern and multidisciplinary approach and addresses fundamental questions of brain development, extending some of them to the particular case of the retina. The project is original and highly interesting, and moves at the cutting-edge of modern developmental neurobiology. Nonetheless, the objectives are affordable and realistic, considering the high quality of the research team.

The permanent members of the team have an uncontested international reputation. In addition to the leader of the team, who is a researcher at the peak of his career, two senior members are recognized internationally among the main figures of modern developmental neurosciences. Their presence in the team will undoubtly provide wisdom and perspective to the junior staff. The team 1 has made important publications, often in collaboration with leading international teams and making major contributions. These papers have been published in Development 2010, Plos Biol 2010, J. Neurosci 2008, PLos biol 2008, J. Neurosci 2008, Nat Neurosci 2008, J. Neurosci 2012, in Glia 2012; plus collaborative roles in Nat Neurosci, PNAS (twice) and Neuron (both 2011), and a review with Mehlen Nat Rev Cancer 2011. Conclusion: Since 2007 team 1 has played the lead role in over 8 major publications in top ranking journals.

Assessment of the team's academic reputation and appeal

Awards and Distinctions. One of the senior members has received numerous distinctions since 2007 (Grand Prize of Neuroscience SfN, Prix d'Honneur de l'INSERM, Grand Croix de l'Ordre National de La Legion d'Honneur. The other one has been elected Foreign Member of the "Real Academia de Ciencias Exactas, Fisicas y Naturales" of Spain.

Attractiveness for students. Team 1 presents excellent record of student first author signing top papers J. Neurosci, Plos Biol (X2), Development (X2), Nat Neurosci (Students: 5 master, 5 PhD, 9 Post docs).

Recruitment. Two scientists have recently joined the team 1 and an young researcher has been recruited.

Quality of journals in which the team publishes. Outstanding

Organization of meetings. Team leader organized an EMBO workshop 2008 and in the fall 2013, Cold Spring Harbor Meeting Sept 2012, Member of the scientific committee of the Brain and Mind exhibit Cité des Sciences Paris (until 2024).

Editorial activity of the team members. Team leader is on the Editorial board of Plos One, associate editor of Journal of Neuroscience, Faculty 1000. One team member is on the Editorial board of PNAS.

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

Knowledge transfer. Team 1 has deposited a US Patent 2008 on the use of Semaphorin6A for promoting myelination and oligodendrocyte differentiation. This patent was filled with an investigator at Biotechnology company (Boston USA) with whom Team 1 has developed novel organotypic culture models for the study of myelination and remyelination.

Existence of joint productions with non-academic partners. Team 1 has published with BiogenIdec (Bernard et al., Role of transmembrane semaphoring Sema6A in oligodendrocyte differenteiation and mylination. Glia 2012), these results suggesting that Sema6A is a positive regulator of myelination are potentially important from both a medical and industrial perspective.

Choice of partners. Team 1 has been able to adopt a strategic position in the field, this is reflected by interactions and publications with several highly influential and internationally powerful groups. Strong interactions exist within the *Institut*.

Impact of this partnership. As we shall see, the partnerships alluded to above will provide a strong base for the development of future research orientations.

Assessment of the team's organisation and life

The team is composed of 3 senior scientists (1 DR1 and 2DRE), 2 tenured researchers (CR1 and MCU), 1 post-doc, 2 PhD students, 1 IE and 1 IR. The critical mass and the experience of the staff guarantees optimal advancement of the proposed projects. Given that the PI has a high load of research administration work, the role of the two younger tenured researchers is important. The team could also accept more Post docs and PhD students since the project is ambitious and has a high profile internationally. What is not very clear from the proposal is 'who is doing what' and more junior staff could allow better implication of researchers in specific tasks. From the document it is difficult to assess the frequency of the scientific meetings within the team.

Assessment of the team's involvement in training through research

The team has supervised 5 master students, 8 PhDs and 11 Post docs. This group is in a position to attract many students. The involvement in high-level teaching of team leader and one of the senior scientist is impressive. One assistant professor has a high teaching load which may partially explain a small science production (1 paper in 5 years although a seemingly important one of the team and as first author equal contribution).

Assessment of the five-year plan and strategy

The future research project of team 1 is to investigate the function of axon guidance molecules in the developing and adult organism and to explore the therapeutic potential of their manipulation. This extremely ambitious program has a high potential for success given the teams' expertise in *in vivo* mouse models of axon guidance molecules in cerebellar and visual systems coupled with tight partnerships that the team has developed at both the national and international level. The implementation of this research project will fully exploit the high clinical expertise of the *Institut de la Vision* and promises insights into deep fundamental issues in neuroscience coupled with exploration of novel therapeutic approaches to important medical issues in retinal pathology and neo-angiogenesis. Altogether, the experience of the team represents a serious guarantee of the success of the projected studies.

Conclusion

● Strengths and opportunities:

Strengths. Team leader has correctly listed his team's strength (expertise, international and national partnerships, core facilities, new research perspectives, publication record). We would add to that outstanding and highly complementary senior scientists which gives a richness to the research projects, which is rare. We would add here that the research strategy that is outlined in the report is in itself a strength. The combination of fundamental research but with clear clinical medical articulations as outlined for example in the project looking at the role of axonal guidance molecules in angiogenesis and investigation of Slit as a possible anti-angiogenic molecule, is an important factor which will help this group weather the storm of funding difficulties experienced in the research community in Europe.

Opportunities. The presence of two senior scientists has allowed team 1 to strengthen and broaden his research projects (for example in looking at the migration of precerebellar neurons and the future development of the chick model for manipulating gene expression in vivo). We wonder if recruitment of young researchers here could not more explicitly exploit the opportunities presented by the presence of these two senior scientists? We are sure that the team 1 has thought of this, but in the same way that the earlier recruitment of one of the senior scientist broadened the research scope of the team, could not the team also take more advantage of the recent recruitment of the second senior scientist? For example looking at the role of slits on the motility and patterning of neural crest cells? Finally, the location of the team in such an efficient and rich environment as presented by the *Institut de la Vision* is an inestimable strength and opportunity.

● Weaknesses and threats:

Weaknesses. The weaknesses listed by team 1 are valid. We find it extremely surprising that there is no permanent technical staff and we would suggest that this is a very high priority for the *Institut* to obtain an technical support for this team in the near future. The recent recruitment of a young scientist is a very good thing. Overall there is perhaps a small problem in the scientific productivity of one junior faculty. Reinforcement there would be appropriate.

Threats. Team 1's list of threats is a familiar tale of woe. The mention of bureaucracy makes us wonder what is the secretarial support for the team? Our experience is that the French bureaucracy is such that strong secretarial support is an imperative. For example it would be advisable that team 1 has a personal assistant. Does he? The difficulty to find funds that is mentioned is of course a major problem for a French team. Although past grants of the team 1 were listed as an opportunity, the team should endeavour to obtain an ERC grant. Further, if the senior members were to obtain ERC grants on a regular and alternative basis many of the threats and weaknesses would be resolved.

● Recommendations:

- Recruitment of a Technician;

- Recruitment of a personal assistant for the team leader;

- Recruitment of junior researchers;

- Apply for and obtain an ERC grant;

- Possibly exploit better the team's expertise in neural crest cell patterning.

Team 2 :

Genetic engineering approaches to study retinal development and repair/regeneration

Name of team leader:

Mr Olivier GOUREAU

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

This team aims at understanding retinal development and at developing cell therapy for retinal degeneration diseases. In the last period, they approached these questions: 1) by developing transcriptomic analysis of retinal explants in normal conditions and after CTNF treatment that blocks photoreceptor differentiation; 2) through the use of induced pluripotent stem cells (iPSCs) to understand progenitor differentiation and develop cell therapy protocols.

Their first work based on transcriptomic approaches on retinal explants led to the identification of several important factors required for fate determination of either early or late progenitors. The functional dissection of Ptnf1 and Foxn4, two transcription factors identified in the screen, helped to understand how these two proteins regulate retinal cell differentiation. A third one, Bclaf1, was also shown to promote differentiation of amacrine and horizontal cells of the retina.

More recently in 2011, the team has initiated a project to improve iPSC differentiation protocols and to select with high purity photoreceptors or RPE cells from iPSCs. This protocol is based on the development of ingenious novel human fluorescent iPS cell lines that glow different colors depending on cell maturity. These cell lines have been customized for retinal development and the team has already set up a first differentiation protocol to induce these cells into a retinal fate, which constitutes an important preliminary result. The optimisation of cell differentiation protocols is a central aspect of the future project of the team.

Team 2 contributed to 7 publications in the last period (Dev. Biol, J. Neuroscience, J. Mol. Neuroscience, Plos One) .

Assessment of the team's academic reputation and appeal

Team leader is a recognized scientist in the domain of retinal development and differentiation. He has been invited for several oral presentations at international and international meetings in the last period. The Team has been successful in raising important grants (total > €750,000) from the ANR and from the labex Life science.

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

This project has potentially high social and economic impact as retinal degeneration is an important issue in medical genetics and therapies are still not available.

Assessment of the team's organisation and life

The team is composed of two permanent reseachers (PI and one associate professor) and 2 research engineers who are permanent employees of the University. One PhD student has started last year and one more should be starting next year. Only one Postdoc spent 18 months in the team in the last period.

Assessment of the team's involvement in training through research

The team is involved in training through research. Two PhD students defended their PhD in the last period and one postdoc was trained in iPS cell generation. One associate professor in the team is highly involved in teaching at the Master level at UPMC.

Assessment of the five-year plan and strategy

A first important part of the project is centered around: 1) the development of protocols to generate different retinal cell lineages from induced pluripotent stem cells (iPSC); 2) the creation of cellular models for inherited retinal diseases and drug discovery. This first part of the project clearly takes a technical orientation towards translational research by optimization of iPSC differentiation protocols for therapeutic applications and to produce cell models of retinal diseases for two types of genetic defects: mutation in a transcription factor NR2E3 or mutation in the splicing factor PRPF31. The project is well conceived and relies on a network of researchers and clinicians involved in iPSC technology and retinal diseases. It is funded by an ANR grant and by a private research contract from Sanofi-Fovea.

A second part of the project aims at taking advantage of the extraordinary tools developed by the team 4 in the same departement to study *in vivo* retinal progenitor lineages and to evaluate Müller cell capacity to regenerate neurons after injury. This *in vivo* approach appears very promising and will provide important fundamental clues to understand retinal development and regeneration. It is likely that this project will require a reinforcement of the manpower devoted to this part of the project.

Conclusion

● Strengths and opportunities:

- Important grants have been secured for the next two years at least;

- ingenious tools and approaches to adress retinal differentiation;

- established collaborations with researchers and clinicians on iPSCs;

- collaboration with people from inside the *Institut* having complementary knowledge;

- technical support at the *Institut* such as the cell culture plateform.

● Weaknesses and threats:

Weakness :

- Size of the team compared to the objectives.

The leadership of the group is not reflected in the authorship order on publications though there are clear reasons for this.

Threat : - Highly competitive field of research;

- To publish on the project of the team.

● Recommendations:

Team leader is a recognized scientist and has been successful in gathering money to develop his project. It is a very ambitious project. Team leader has to validate his work and his manager position by publishing papers as 1st author or last author. As has already been mentioned,the team has to make sure that he secures the iPSC technology know-how with permanent employees. iPSC technology is relatively new with important applications in research and with potentially therapeutic uses.

Team 3 :

Multiligand endocytosis in normal and pathological axial elongation of the eye

Name of team leader:

Ms Renata KOZYRAKI

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

During the last five years team 3 has moved from the renal physiology to the developmental neuroscience field.

The team 3 has been involved in understanding the function of two multiligand endocytic receptors: Megalin (Lrp2) and Cubulin during development in mouse. These two receptors are known to be required for nutrients delivery and the regulation of several signaling pathways. LRP2 and Cubulin bind multiple ligands and the team leader has shown in previous research works that Cubulin is the receptor for vitamin B12 aborption in the intestine. This work opened important perspectives for the identification in humans of mutations associated with vitamin B12 malabsorption (submitted article). In the last 4 years, the team has created the *cubulin* floxed recombinant mouse strain and used this strain in combination with the *megalin* floxed strain to demonstrate that Cubulin is essential for albumin reabsoption in the renal proximal tubule. This represents the first model of albuminuria. The team 3 has also investigated the function of Cubulin during early stages of anterior neural tube development by inactivating *cubulin* in epiblast cells at early embryonic development. Their observations lead to the conclusion that Cubulin is required for the survival of migrating neural crests cells and to the hypothesis that Cubulin is required for FGF8 signaling by favoring FGF8 uptake by receiving cells. This work is pursued by analyzing FGF8 uptake in *cubulin* deficient mice with an FGF8-GFP transgene. In addition, the team shows in collaboration with a team in Spain that Lrp2 is required for Shh-mediated migration and proliferation of Oligodendrocytes progenitors.

Last team 3 has investigated the function of *Lrp2* in eye formation and shown that *Lrp2* inactivation form E9.5 leads to excessive postnatal axial elongation and abnormally large eyeballs. The understanding of the molecular and cellular mechanisms that underlie these phenotypes in *Lrp2* deficient mice and the possible involvement of mutations in this protein in human syndromes showing similar phenotypes is a major axis of the future research project of the team.

The work developed in the last 4 years helped to understand the developmental function of Cubulin and Megalin and provided the first mouse model of albuminuria. 5 original scientific articles and two reviews were published, but only one article is signed as last author by the team leader (J Am Soc Nephrol, 2010). Only two of these articles are directly related to the team's project, the other 3 appear as collaborations on indirectly related projects.

In parallel, other team members have published 10 articles either on work indirectly related to the team work or coming from previous research experience (Glia, Journal of neurochemistry).

Assessment of the team's academic reputation and appeal

The team has a recognized expertise in multiligand receptor function in animal physiology and development. Team 3 first identified the Cubulin receptor and has a unique knowledge of this family of proteins as proven by important publications in first ranking journals. The team has created a unique and valuable mouse *cubulin* mutant model that allows fine dissection of the complex function of the Cubulin protein during development.

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

Team 3 has developed important collaborations with clinicians working on metabolic or retinal diseases in humans to address the link between human pathologies and Cubulin and Megalin anomalies. Their work opens new avenues for the understanding of human eye pathologies and in particular high myopia for which a patent has been deposited.

Assessment of the team's organisation and life

The team appears to be very small with two researchers and one PhD student and one research engineer. No postdoctoral fellows are directly involved in the project.

Assessment of the team's involvement in training through research

One PhD student was trained in the last period and one has just started his PhD. No postdoctoral fellows directly involved on the project are described. The team plans to recruit several doctoral fellows in the next period.

Assessment of the five-year plan and strategy

The research project of the team is centered around the understanding of the functions of Cubulin and Megalin in retinal development and eye growth. This project is based on *in vivo* approaches by inactivating Lrp2 and Cubulin in the eye field at different stages of eye development. It relies on preliminary observations showing that constitutive inactivation of *Irp2* leads to anophthalmia or microphthalmia, whereas conditional inactivation of *Lrp2* in the anterior neural tubes leads to enlarged eye globes and dramatic myopic shift.

The project is divided in 3 complementary work packages that are very well structured and detailed. The first one focuses on understanding the early function of Lrp2 and Cubulin in eye field induction to understand why deletion of *Irp2* leads to microphthalmia or anophthalmia. It aims at analysing some key signaling pathways in particular the BMP signaling pathway, known to induce similar phenotypes when affected. It also aims at understanding the function of Cubulin in the extraembryonic visceral endoderm by conditional inactivation, as preliminary evidences show that Cubulin is required in this tissue for eye development.

The second work package is to monitor during postnatal development the progression of myopia induced by *Irp2* or *cubulin* depletion in the neural tube using a FoxG1-cre deleter transgene. Using live non-invasive imaging solutions like high resolution imaging, topical endoscopy fundus imaging (TEFI) and Optical coherence tomography, they will measure the variations of optical parameters of the myopic eye. In complement, electroretinograms will be performed to evaluate visual accuity. The anatomical and histological organizations of the different structures of the eye will also be analyzed. Last, this workpackage aims at understanding in which cells and at what stages of eye develoment, *Irp2* and *cubulin* are required i.e. before or after emmetropization (that normally occurs during the two first weeks of postnatal development) or in retinal or RPE cells, by using different Cre-transgenes.

The last work package aims at understanding the molecular pathways downstream of *Irp2* and *cubulin* that are involved in the progression of myopia. High throughput proteomic aproaches on the vitreous body or vitreous/aqueous humor will be performed, completed by transcriptomic approaches of the retinal and ciliary epithelium at various stages of myopia progression by FoxG1-cre induced deletion of the *cubulin* and *Irp2* genes.

This project is very ambitious with simultaneous development of numerous approaches and should give important insights into the function of the endocytic recycling pathway during eye development.

Conclusion

● Strengths and opportunities:

- excellent expertise in multiligand endocytic receptors,

- powerful models to study the in vivo function of these proteins,

- direct implications for the genetic characterization of human eye diseases ond for the understanding of these diseases,

- established collaborations with teams involved in developmental biology or human genetics.

● Weaknesses and threats:

- Only a few scientific publications in specialized journals in the last 4 years for the team leader,

- The aims are ambitious and will require an increase in the size of the team,

- This small team size may also have consequences on the attractivity for PhD students and postdoc,

- No secured long term funding for a project that requires many mouse strains and expensive approaches (transcriptomic analysis),

- no collaboration inside the institute have been mentioned,

- new in the field of eye (moving from renal).

● Recommendations:

The principal investigator should first initially concentrate on completing the previous but still ongoing work that needs to be published in high ranking journals to secure future funding opportunities. Next, the different workpackages should be prioritized to adapt to team size. Special care should be taken to raise funding that will allow the recruitment of PhD students and postdocs around the project.

Team 4 : Neural circuits development

Name of team leader: Mr Jean LIVET

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

Team leader, CR1 INSERM obtained an AVENIR grant in 2007 at the IDV. During his post-doc in Harvard, he has developed a new method named the Brainbow transgenic strategy, which randomly distributes fluorescent proteins of distinct colors in individual cells (Livet et al., Nature, 2007). This method is extremely powerful to study neural circuits and axonal projections or glial and neuronal cell lineages in developing tissues. This work was inspiring to several research groups that developped similar approaches in various organisms. These last years, the team has introduced improvements in the brainbow transgenic technology: new scheme of combinatorial colors, new transgenic lines, electroporation strategy to track neural progenitors in chicken and mouse embryos. The project is ambitious, requires a long time to generate transgenic lines, but it is also of considerable interest for the neuroscience community. One original paper has been submitted for publication (Loulier et al.). One paper in collaboration with K Eggan (Harvard university, USA) about early development in embryos is in press in Curr Biol.

The brainbow labeling requires new developments to optimize imaging in live or thick samples. In collaboration with scientist from Polytechnique and scientist from ENS, team leader reported a method for multicolor imaging by wavelength mixing using multiphoton microscopy (Nature Methods, 2012).

Team leader published prestigious reviews (Curr Opin Neurobiol, 2011; Nat Rev Neurosci, 2008) and protocol articles (3 Cold Sprong Harb Protoc in 2011).

Assessment of the team's academic reputation and appeal

Team leader was invited to 9 international conferences during the 2007-2012 period.

The brainbow technology has a strong impact in the general scientific audience and for the general public.

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

The team 4 participated in many scientific image exhibitions (Palais de la découverte in Paris, MoMA in NY, Ecole Nationale de la Photographie in Arles) and publications in the general press (Biofutur, La recherche).

The team obtained several fundings : Ville de Paris, ANR-JC, Labex, FP7 Marie Curie grants.

Assessment of the team's organisation and life

Not pertinent due to the size of the team

Team leader, CR1 INSERM obtained an AVENIR grant in 2007. One team post-doc in 2009 was recruited CR2 INSERM in 2012. A research engineer INSERM was recruited in 2012. The team also includes 1 PhD student and has funding for 1 post-doc to be recruited.

Since the team is small, lab meetings organized at the level of the department could be certainly fruitful.

Collaborations exist within the *Institut* with team 1, team 2 and team 9.

Assessment of the team's involvement in training through research

There is a PhD student since 2009. The team supervised several students 3 M1, 1M2, 2BTS. The team leader participates on Master and PhD level courses (Pasteur, ENS Cachan Master1, ENP courses).

Assessment of the five-year plan and strategy

In line with the previous work of the team, the Brainbow strategy will be used to explore how cell lineage constrains neural and glial cell position, architecture and connectivity. This question will be explored in the cerebral cortex by the INSERM scientist (together with 1 PhD and 1 Post-doc researcher) using transgenic lines or electroporation of integrative vectors in embryos. It will also be explored in the retina, in collaboration with the team 2. Cutting-edge technics will be used for multiphoton imaging at high resolution and 3D reconstruction using custom-developed software. The detailed description of the spatial distribution, migration and dispersion of individual clones will bring new insights to apprehend whether the brain circuitry may be constrained by lineage. A collaboration with a group at Baylor college, Houston, (USA) will be established for functional correlation using electrophysiological recording on cortical slices. This field of research is certainly highly confronted to international competition.

A second aspect of the project is to determine the equivalence of neighboring neural stem cells. Using the brainbow technology, the project will first track and compare the lineage of adjacent progenitors. Next genetically induced perturbations of proliferation or differentiation will be induced by interacting with specific signalling pathways either globally or within clones to explore the progenitor potentialities and their regulations.

Third, improvement of the Brainbow technology wil be pursued by the team and via national and international collaborations for the widespread diffusion of the method. Collaborations are already established within the *Institut* with the teams of team 1, 2 and 9. The team 4 plays definitely an important role in the IdV.

Conclusion

- Strengths and opportunities:

The strength of this team is the major impact of the Brainbow strategy in the field of developmental neuroscience and the international reputation of the team leader. Several fruitful collaborations have been established including in the IdV and the team benefits from a stimulating research environment. The recruitment of an INSERM scientist allows the stabilization of the AVENIR team in a way that it can focus on the question of lineage and connectivity in the cerebral cortex.

- Weaknesses and threats:

This is a small team facing a domain which is highly competitive. The team needs to publish on its original work though one paper is clearly submitted.

- Recommendations:

The team should find the appropriate balance between ambitious technical developments, collaborations and focusing on his own biological question. This might mean fewer collaborations and prioritisation of his own scientific interests.

Team 5 : Cellular messenger codes for axon guidance

Name of team leader: Mr Xavier NICOL

Workforce

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

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

• Detailed assessments

Assessment of the five-year plan and strategy

Since this team has been created in 2012, the project only could be evaluated.

The team leadeer is a young and talented researcher (35 years) who created an emerging team in 2012. His project is in line with his previous work at INSERM unit 839 showing that the AC1 adenylcyclase participates in the development of retinal projections. Activation of AC1 in the growth cone is required for ephrin-A repellent effect at the basis of the retinal topography and depends on the spontaneous activity of retinal neurons that occurs during development (Nat Neurosci., 2007). He pursued his research on the same topic during his post-doc at the University of California working on the role of cAMP and calcium transients on Netrin-dependent axonal guidance of commissural axon (PNAS 2011). A combination of powerful imaging technics were used including FRET sensors to monitor cAMP pulses and optogenetic tools to photoactivate adenyl cyclase. These technics are currently being implemented in the IdV with the assembly of a dedicated microscope.

The project is aimed at dissecting how cAMP signaling is spatially structured in the filopodia and central part of the growth cones. The role of lipid rafts, focal adhesions and AKAP (A kinase anchoring proteins) will be investigated in the model of Ephrin A-induced retraction of retinal axons. Both in vitro and in utero electroporated retinal axons will be used as model systems.

All the specific aims are clearly described in the project with respect to methodology and expected results: For example, fusion with targeting sequences can be used to direct cAMP FRET sensors to rafts or focal adhesion microdomains. Rescue experiments with AC1 modified for its targeting will be performed in the AC1-/- background. Photoactivable AC will be used for rescue experiments after light stimulation.

The project is based on the development of new tools in collaboration with a group at Cambridge (UK) for AC mutants and another one in Amsterdam for cAMP FRET sensor. The collaboration with a group at INSERM unit 839 will be continued with a PhD student working in the two labs.

Scientific production: The team leader published recent papers in top journals: Nat Neurosci 2007 and PNAS 2011 as first author and PloS one as last author.

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

This is a promising team but it is too early to assess such interactions.

Assessment of the team's organisation and life

This is an novel team created in 2012 by Xavier Nicol, CR1 CNRS who obtained an ANR "retour post-doctorant". A post-doc fellow has been recruited from 2012. An "Ingénieur d'étude" was recruited in 2012. The team also includes part of time a PhD student.

The team obtained fundings : ANR, IDV Labex, Foundation Fyssen grant.

The thematic proximity with tem 1 and team 4 should be beneficial for all teams. Lab meetings organized at the level of the department will be certainly fruitfull.

Conclusion

- Strengths and opportunities:

This is an emerging team that seems to be very promising. It benefits from the appropriate scientific environment from both technical and thematic aspects. The team has a good record of publications and funding.

- Weaknesses and threats:

The team needs to get rapidly its dedicated microscopic equipment.

- Recommendations:

The team leader is well aware that he has to attract and stabilize collaborators.

Team 6 :

Identification of gene defects leading to non-progressive and progressive ocular diseases

Name of team leader:

Ms Isabelle AUDO and Ms Christina ZEITZ

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	1	1
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	2	2
N6: Other contractual staff (without research duties)	4	4	
TOTAL N1 to N6	7	8	4

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

• Detailed assessments

Assessment of scientific quality and outputs

The team 6 works as a single entity with the Department of Genetics. The Team is relatively new, having been initially recruited in 2007 and then established with permanent positions in 2010, and from their publications and outputs in recent years they are clearly two talented young geneticists. Considering their relatively recent appointment, the Team has an impressive track record in terms of productivity with authorships on 23 peer-reviewed papers since 2007(American Journal of human genetics, BMC genetics, Current opinion in neurology,Human Mutation,Nature genetics, New England journal of medecine). Whilst quite a few of these are publications in which team leaders are clearly not lead authors, these papers exemplify a wide number of productive collaborations and their involvement in projects beyond the *Institut de la Vision*.

Assessment of the team's academic reputation and appeal

The team 6 is part of the Foundation Fighting Blindness Centre at the *Institut* which not only provides resource, it also gives the Team an international profile and access to other related groups around the world. One of the team leader is on the Scientific Advisory Board of the FFB and has given invited talks and reviewed grant applications. She also participates in patient groups and public engagement activities, and regularly reviews papers for the major eye journals. The other team leader has a similar range of esteem indicators with regard to reviewing papers and grant applications, and is also a member of several prominent eye societies.

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

The team 6 has filed one patent application in the area of diagnosis and therapy for retinitis pigmentosa, though no details are given as to possible plans for commercialisation, onward licensing or downstream development. The major goal of the research is to identify new loci for retinal disease, which may create further possibilities for the generation of intellectual property.

Assessment of the team's organisation and life

The joint leadership of two scientists appears to work well, indeed synergistically judging by the productivity of the Team. The balance of post-docs, students and technical staff appears suited to the type of work, presumably the high number of technicians reflects the practical nature of high intensity genome sequencing and bioinformatics. There is no indication that any of the Team attends scientific conferences – this can be motivational at an individual level, as well as raising the profile of and contributing to the organisation and life of the Team.

Assessment of the team's involvement in training through research

The Team has two new PhD students and also provides mentorship for one or two post-docs. Mentoring responsibilities are clearly shared between the two leaders, and one of the leader in particular contributes to teaching beyond the *Institut* through contributions to a wide range of Diploma and Masters courses.

Assessment of the five-year plan and strategy

The five-year plan has two major components. The first is to identify new genetic defects in a large cohort of patients with a range of inherited retinal diseases, and the Team has already established important links with various companies and organisations who will be involved in the project. In addition they have either obtained, or are in the process of obtaining all the necessary ethical approvals for the work. Team leaders expect to discover at least three new disease genes in the next five years. It is not clear how they chose this number, but they have thought about how they will then choose a gene to focus on, and the collaborators they will go to in order to pursue functional studies. However, it seems that this could be unpredictable. By contrast, their second axis is devoted to functional studies about previously identified disease genes that are implicated in visual signal transmission The group has already discovered three previously unknown genes involved in CSNB that code for membrane channels (TRPM1) or receptors (GPR179) implicated in signal transduction at the level of ON bipolar cells. Their goal in the next five years is to elucidate the functions of these genes. They propose a range of studies including high-throughput screening for ligand identification, cell biological experiments, and the generation and application of appropriate animal models. Together this constitutes a cohesive programme of basic science that should throw new light on the molecular basis of disease pathology, and may also reveal new ideas for future therapeutic strategies for CSNB. The SWOT analysis provides an objective and accurate assessment of the current position.

Conclusion:

- Strengths and opportunities:

The Team has a good track record in their area of expertise so there is a good chance they they will succeed in achieving their goals. In addition, they have access to large cohorts of patients and an excellent phenotyping centre. The discovery of new genes may create opportunities for new intellectual property or therapeutic strategies.

- Weaknesses and threats:

Team leaders correctly identify the avalanche of genomic data as presenting a challenge in terms of bioinformatics and the extraction of useful information. And there will always be other groups chasing new genes involved in retinal disease, though this should not be a deterrent.

- Recommendations:

The Team must ensure that the bioinformatic and data mining facilities/manpower/resources are available, funded and in place, in order to profit from the hunt for new disease genes. This is an important endeavour and one would hope that he *Institut* would be able to provide some pro-active help in this respect. Assuming the gene hunt is successful, the Team must be careful in choosing which gene to focus on as they embark on functional studies, and they must be ready to file patent applications if the target gene looks druggable.

Team 7 :

Rod-derived Cone Viability Signaling for the Treatment of Inherited Retinal Degenerations

Name of team leader:

Mr Thierry LEVEILLARD

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	4	4
N6: Other contractual staff (without research duties)	3	3	
TOTAL N1 to N6	10	10	5

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

• Detailed assessments

Assessment of scientific quality and outputs

Team 7 has originally identified RdCVF and has demonstrated that it protects cones from degeneration in rodent models of retinal degeneration. He proposes to gain additional insights into RDCVF following aspects: therapeutic effect, receptor and signaling, role in CNS neurodegeneration, role in AMD.

In the commitee's opinion the soundest section is on the anti-apoptotic effect and some details have been given on the plan to move this into the clinic in the next future.

Team 7 aims at elucidating RdCVF upstream and downstream signaling. The most crucial part is on the receptor identification. Team leader has shown interaction between RdCVF and Basignin-2, and he is analyzing BSG2 expression in the retina to test that BSG2 expression pattern is compatible with RdCVF protection on cones but not on rods and is using a decoy BSG2 to block RdCVF activity.

In the part related to RdCVF2 and 2L, Team leader is testing RdCVF2/2L expression in the CNS to better elucidate its interaction with TAU in the cortex where the tauopathy occurs.

Assessment of the team's academic reputation and appeal

Team leader is internationally known in the field of inherited retinal diseases, mostly for his work related to RdCVF. In the last 5 years (2007-12) team 7 has published 8 original articles as last author (from PubMed), including 2 in Human Mol Genet. Six patents have been issued.

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

The *Institut de la Vision* is an ideal environment for the development of a project like the one proposed and for potential future translation of these studies to the clinic.

Assessment of the team's organisation and life

The unit includes 1 researcher, 3 engineers, 3 technicians 4 post-docs, 3 PhD students and 1 undergrad student. The size of the team appears appropriate to study the various aspects of RDCVF activity proposed.

Assessment of the team's involvement in training through research

The Unit includes 3 PhD students and one undergrad. This is a reasonable training through research for the team leader and the researcher working under him.

Assessment of the five-year plan and strategy

The overall plan is quite ambitious as it proposes to study 4 different aspects related to RdCVF, however the results obtained so far by the team 7 are extremely encouraging on each of these aspects.

Conclusion

● Strengths and opportunities:

- Long-standing project on a growth factor originally identified by the PI,

- High therapeutic potential,

- Fast translation to the clinic for testing in patients with retinal diseases.

● Weaknesses and threats:

- Lack of a well-characterized mechanism of action but the team is working very actively on it and some of the RdCVF signalling is being elucidated,

- Focus on AMD and CNS seems wide.

● Recommendations:

Focus on the translational aspects on the retina and the identification of RdCVF receptor/signalling. Extension of the research into the areas of Alzheimer's diseases should be conducted in collaboration with other groups.

Team 8 : Retinal information processing – pharmacological and pathology

Name of team leader: Mr Serge PICAUD

Workforce

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

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

Team 8 is focusing on understanding retinal information processing under normal and pathological conditions. To achieve this goal, the team has put together an ambitious translational research program aimed at bridging basic retinal processing and their implications for prosthetic or optogenetic rehabilitation of visually impaired patients. The scientific quality of the program is very promising. Thanks to various collaborations, the Team has managed to create the necessary technological platform to address the proposed aims. Specifically the *ex vivo* and *in vivo* systems implemented in the laboratory are ready to go, including human retinal explants in culture. In terms of publication records, the team is credited by numerous papers in class A journals .

Assessment of the team's academic reputation and appeal

The citation index of the team is impressing with at least 4 papers quoted by more than 100 citations. In addition, team leader has worked impressively in attracting new investigators working in complementary areas, and has established a strong Department that has available technologies that are at the cutting edge of the restoration of vision in blind people which are optogenetics and retinal implants. Clinical trials are already successfully established, and new evaluation tools elaborated.

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

The team is interacting with two start-up companies. Also the team filed two patents on a 3D prosthetic implant design, and the use of asynchronous visual sensor as visual encoders for rehabilitation strategies. Companies interested in licensing taurine.

Assessment of the team's organisation and life

The way in which this group has developed, grown and nucleated a Department provides an exemplar for emerging groups.

Assessment of the team's involvement in training through research

The team is presently training 3 PhD students. Two more students are working in the team.

Assessment of the five-year plan and strategy

As stated in the self-evaluation document, the team has pursued 3 main axes of research aimed at generating novel strategies for neuroprotection and visual rehabilitation.

Current work focusses on interface between retinal prosthesis and retina, problems of glial reactivity. Optogenetic project – on to primate studies, using AAV delivery of ChR2 is proposed.

Conclusion

- Strengths and opportunities:

As already mentioned, the team has put together an outstanding arsenal of techniques with most of them already validated on animal models and even human postmortem retinal explants. They also established collaborations with leading researchers (e.g. a group in Basel) and are building a strong network with startup companies.

- Weaknesses and threats:

No obvious weaknesses.

- Recommendations:

Considering the wide scope of their ambitious research program, we would recommend to increase the manpower to achieve the proposed aims within a reasonable time frame.

Team 9 : Vision and Natural Computation

Name of team leader: Mr Ryad BENOSMAN

Workforce

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

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6	
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions		

• Detailed assessments

Assessment of scientific quality and outputs

To provide fundamental novel means of sensing and processing visual information for various artificial vision applications, research in team 9 falls into 4 inter-related areas. One area is dedicated to the establishment of new benchmarks in terms of redundancy suppression/data compression, dynamic range, temporal resolution and power efficiency at the sensor hardware level as well as increased throughput and processing performance at the system/application level. The second area is going to focus on the applications of the developed technology in the fields of medical imaging, retinal prosthetics. The third area concerns the neuromorphic asynchronous event-based sensors. Team 9 plans to demonstrate that these sensors are the key pieces of any neuromorphic real world computation by entering Human Brain Project and Robot Companion. Finally, the fourth area will focus on research about physicals models of retina and retinal defects in Very Large Scale Integration (VSLI) silicon.

The projects planned by team 9 are of great scientific interest and are very ambitious. It is clear that the team leader is competent. This together with complementary knowledge currently present in the team, the *Institut* and in collaborating groups outside the *Institut* should bring success to at least some of the aims. The combination of theoretical framework development and immediate implementation within the same research institute should allow a fast technology transfer.

Assessment of the team's academic reputation and appeal

Team leader is internationally recognized for his research. The team has been productive with, since January 2007, 31 papers, 15 reviews and 17 conferences with 8 papers in 2012 (Journal of neural engineering, Neural networks,Plos one). The scientific goal is to merge biological and computational vision into a unique computational paradigm using event based acquisition. Team leader has contributed to a start-up. He is associate editor of International Conference in robotics and Automation and international Conference on robotics and system, and of Simulation of Artificial Behavior. He is a member of review committee of several scientific journals.

The team was at first composed of 3 "Maitres de Conférences". It has recently been joined by a researcher and there are 7 PhD students. They have several international collaborations: Instituto de Microelectronica de Sevilla, Computational Sensory Motor Lab at Johns Hopkins University, SINAPSE at the National University of Singapore). Two post-doctoral researchers are going to join the team as well as a one-year sabbatical from Johns-Hopkins University.

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

The combination of theoretical framework development and immediate implementation within the same research institute should allow a fast technology transfer. Visual processing study, visual rehabilitation project and retinal-processing inspired detector are of high interest to solve problems link to vision impairment. This project should give the opportunity to improve medical care and medical imaging application as well as robotics for ambient assisted living. In addition, the research developed by Team 9 can have a wide range of possible applications such as the autonomous flying robot as mentioned in the project.

Assessment of the team's organisation and life

The organization and life of the team is not clearly defined. Collaboration with the team 8 has already leaded to publications (2011, and 2 in 2012) on artificial retina.

Assessment of the team's involvement in training through research

The team is involved in training through research with 7 PhD students. The team is highly active in several training programs and teaching with UPMC with members being involved in various courses and PhD programs.

Assessment of the five-year plan and strategy

In the implementation of the project, 2 specific aims are developed. For the first one the team will study the processes underlying biological sensory and data processing systems. From the acquired knowledge, they will implement and design novel morphometric vision sensors. They want to develop a combination of biomimetic sensors with programmable/event-based focal-plane processing and improve the data transmission by solving the wiring problem. The second specific aim is computation and modeling of the visual system in order to develop artificial vision system and to investigate new methodologies of light codification for new advanced electrode array designs.

The projects are very ambitious. Although the PI is competent in the field, concerns are because of the large number of projects of an extremely ambitious nature. Will all of these programs really be run in parallel given the number of permanent full time-equivalent researchers constituting the team.

Conclusion

- Strengths and opportunities:

  - International collaborations and scientific network;

  - A new field in expansion;

  - Proximity to clinical and industrial entities;

  - Attractiveness of the institute.

- Weaknesses and threats:

  No obvious weaknesses.

- Recommendations:

The team should stay focused within the scope and strategic objectives of the *Institut* and on the specific project.

Team 10 : Neurophysiology and optogenetic applications in the retina

Name of team leader: Mr Jens DUEBEL

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

The aim of the team is to optimize optogenetic treatment strategies. The technology involves genetically engineering cells other than photoreceptors to respond to light by adding microbial opsin genes such as channelrhodopsins or halorhodopsin that are sensitive to light. These proteins sit in the photoreceptor cell membrane and are activated by light, controlling the flow of ions into or out of the cell. When light strikes the cell, the channels can open or close, either stimulating or suppressing the electrical activity of the cell. The team is planning on introducing these genes with an AAV delivery tool to bipolar cells or ganglion cells. In addition, this technology will be used to better understand the neurocircuitry in the retina.

Optogenetics is a highly innovative treatment approach to restore light-sensitivity to a retina that has suffered significant degeneration. It offers the ability to bypass damaged photoreceptors.

Since his arrival in the institute en 2009, he published three main papers in Cell, Science and Nature Methods.

Assessment of the team's academic reputation and appeal

Team leader had been selected by the SAB among 87 applicants. He has been invited speaker to several scientific conferences mainly in Germany (also Swiztherland, Hungary and Japan).

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

Collaboration with 2 teams in Germany;

He is involved in 2 patents.

Assessment of the team's organisation and life

The team is composed of 1 leader and 1 engineer. However, it is mentioned that there is the financial possibility to recruit post-doctoral and graduate students to perform the experiments.

Assessment of the team's involvement in training through research

No training through research is on course.

Assessment of the five-year plan and strategy

In the implementation of the project two specific aims are developed using optogenetic approaches to restore vision and to investigate neuronal circuits in the retina. For the first part of the project, preliminary data show by patch-clamp recordings that the team successfully restores light detection in mice or human photoreceptors by optogenetics using Channelrhodopsin-2 and halorhodopsin. Team leader wants now to investigate the neurotransmission from genetically modified photoreceptors to the inner retina by patch-clamp recordings. In addition, team leader is going to work with a new microbial opsin targeting specific cone cells to improve light detection in order to restore color vision. He also plans on targeting inner bipolar cell and ganglion cells to restore visual function in a retina lacking photoreceptors. In the second part of the project, team leader is going to focus on the vGluT3 amacrine cell type that has been suggested to be a dual transmitter neuron. By using optogenetics with two-photon imaging and patch-clamp recording, these cells function in the neuronal transmission circuit will be investigated.

Conclusion

- Strengths and opportunities:

  - ERC grant for 5 years;

  - AAV vector production;facility at the *Institut;*

  - Collaboration with expert in optogenetics from Germany;

  - Viral delivery tools expertise at the *Institut;*

  - Proximity of industrial and private entities;

  - Access to human samples.

- Weaknesses and threats:

Weaknesses : - number of researchers in the team is too small. Although the number of scientific publications is very limited (6 publications since 2004) they have been published in high impact factor journal (Science, Neuron, Cell). However, there is only one paper signed as first author and he is encouraged to demonstrate leadership in his future published outputs.

Threats : - Management of the technical aspects such as patch-clamp recordings, AAV delivery. To develop a competitive team.

- Recommendations:

There is no doubt about the interest of the research project: working on ways to restore vision by making other cells of the retina, which are spared by the disease, sensitive to light might be one key to bring back vision. However, team leader has planned a very ambitious program for only one researcher making the project rely maybe too much on its collaborations. He should accelerate the development of his group with the recruitment of post-doctoral and PhD students.

Team 11 : Mitochondrial dysfunction and ocular diseases

Name of team leader: Ms Marisol CORRAL-DEBRINSKI

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

Team leader is an experienced scientist with an excellent track-record in mitochondrial physiology and mitochondrial diseases. She trained originally in a group at the Perelman School of Medicine, University of Pennsylvania (USA), with whom she still collaborates, and joined the *Institut de la Vision* in 2004. Her outputs in the last few years are typical of a scientist developing their own laboratory (and having to suffer the major inconvenience caused by the fire of 2009), with a solid number of publications in reasonably good journals (J.B.C, J. Mol. Biol, Plos One). She has also co-authored several papers with her collaborators, in particular a group at INSERM unit 676, suggesting that her interaction with this Paris group has special significance. Looking ahead, the big project on the horizon concerns the clinical trial for LHON and if this is successful it will certainly elevate team 11 in terms of high impact papers.

Assessment of the team's academic reputation and appeal

There is not yet any strong evidence for the involvement of the Team in national and international projects, but there are clearly some important collaborations, and these can only be good for the reputation of the Team and the prospect of recruiting talented post-docs, PhD students and technical staff. Team leader also regularly gives talks at major international scientific conferences, she reviews papers for several high impact journals and reviews grant applications for some of the major national funding agencies. These are all markers of esteem and provide evidence of team leader's growing reputation.

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

The Team has developed an AAV-based vector for the the treatment of LHON, and a patent has been applied for in relation to this, though it is not clear exactly whether the patent relates to the actual gene therapy vector, or the method of treating a mitochondrial disease. The team leader refers to her hopes that if a Phase I/IIa trial is successful then the further development of this therapeutic approach may be picked up by a pharmaceutical company, though there are no indications as to whether any companies are actually interested or have been approached. Nevertheless, this shows good awareness of the need to pursue and hopefully commercialise the Team's research outputs.

Assessment of the team's organisation and life

The Team appears to have a good critical mass and an appropriate balance of staff when comparing the numbers of post-docs, technicians etc. And it is a good sign that all of her staff, including technicians, have attended international scientific conferences – this suggests that she adopts a supportive role in terms of the career development of those in her Team. The team leader contributes to the life of the *Institut* in her role on the Scientific Board of the Animal Facility.

Assessment of the team's involvement in training through research

The experience of the team leader should provide her with good mentoring skills, so it is a little suprising that there is only one PhD student who is apparently her first. However, she teaches on three different Masters courses, in Paris, Toulouse and Grenoble, so her training skills are clearly in demand.

Assessment of the five-year plan and strategy

The five-year plan has three major objectives. The first of these, and the most important, is a clinical trial of gene therapy for LHON. The Team also intends to develop new animal models and conduct further investigations into other mitochondrial diseases, with major studies already under way using the *Hq* mouse, and finally they aim to develop innovative treatments for a wide range of eye diseases, using gene therapy to address problems of mitochondrial dysfunction. Overall this is an ambitious five year plan. For example, with regard to the third aim, in a five year strategic plan most invesigators would consider it a success to generate *one* innovative therapy for *one* eye disease. It seems highly unlikely that the Team will do more than this, given their heavy commitment to LHON, and their basic science work on elucidating pathological mechanisms in mitochondrial disease. The Phase I/IIa trial for LHON is rightly the priority as this will be a landmark study if it is successful. However it is not clear whether the trial is fully funded and if so, what is the source of the funding. Funding is in place. Preclinical safety and toxicology studies are apparently in progress, so one must assume that funds are in place for the trial. The SWOT analysis appears to provide an objective view of the current position of the Team, but work will need to be done to create a relationship with a pharmaceutical company in order to take the LHON gene therapy forward. The major threats are several other groups also pursuing a gene therapy approach for LHON and it will be important for the Team to be at the forefront of these efforts. Taken together the five-year plan contains some exciting and important science, but maybe over-ambitious in which case there should be some clear strategic prioritisation in the use of resources.

Conclusion

- Strengths and opportunities:

The Team has a strong position in the field of retinal mitochondrial diseases, it has good collaborators providing active support, and a clinical research environment that should facilitate the successful execution of the LHON Phase I/Ia clinical trial. Together this creates an excellent opportunity for team leader to elevate her profile, and that of the *Institut*, by becoming a world leader in this area.

- Weaknesses and threats:

There is a danger that the ambitious five-year plan will dilute the efforts of the Team, with the inherent risk that projects may stall as a result, and there are questions over the source and extent of the funding available for the LHON trial. Competitors in the LHON field pose a serious threat though no doubt the Team will move as quickly as possible in order to mitigate the risk of being scooped.

- Recommendations:

With regard to the Phase I/IIa trial, and the benefits it would bring not only to the Team but also the *Institut de la Vision*, the continuing pro-active involvement of the *Institut* Director and senior academic and clinical colleagues will be important in ensuring that the trial gets under way in a timely manner.

Team 12 : Chemokines and physiopathology of the eye anterior segment

Name of team leader: Mr Christophe BAUDOUIN/Mr Stéphane MELIK PARSADANIANTZ

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	4	4	4
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	4	4
N6: Other contractual staff (without research duties)	2	2	
TOTAL N1 to N6	13	13	11

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	7	
Qualified research supervisors (with an HDR) or similar positions		

• Detailed assessments

Assessment of scientific quality and outputs

The team is internationally recognized for its work on inflammation and eye diseases, as well as for its findings showing the toxicity of preservatives present in ophtalmic medications. The major results of the past period concern the demonstration of a toxic effect of a common preservative compound found in ophtalmic medications. The group demonstrated that it induces an inflammatory response. This finding prompted the group to investigate the role played by chemokines and it could implicate them as important mediators of the inflammatory process. These data found the research project for the future period. The translational potential of the team´s activity is very high. The fundamental research activity was suggested by the SAB to be strengthened. This recommandation has been taken into account with the recruitment of two academic researchers who are expert in the biology of chemokines. The team is highly productive in terms of the number of publications in medical journals.(Ophthalmology; J Am Path; Cornea). The fundamental research is published in rather good but not outstanding journals (Mol Vis; PLOSone; J Neurochem).

Assessment of the team's academic reputation and appeal

The PI has a good international reputation in his field, particularly for his work on ocular surface diseases and glaucoma. He attracted several students, post-doc and two academic researchers. He participated in the creation of the "Institut de la Vision "and the team is closely connected to the Clinical Investigation Center.

The PI has multiple other contributions, in addition ot his research and clinical activity. He is editor in chief of the French Journal of Ophtalmology since 1999, is very active in writing books for the large public. He has an impressive list of participations at national and international meetings and conferences as invited speaker. He is also vice president of French Glaucoma Society, and member of 7 other societies related to Ophthalmology.

Other team members make also important contributions, for instance by heading INSERM study sessions

For the future period, Mr Christophe BAUDOUIN will share co-direction with Mr Stéphane MELIK PARSADANIANTZ , one of the two academic researchers that joined the team in 2012. The rationale for this decision is reinforcement of the fundamental research activity of the team.

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

The theme of the team has broad implications for society. The team communicates to the large public through the different media (radio, TV, newspapers) and participates in the "semaine du cerveau".

Assessment of the team's organisation and life

The team seems to be very dynamic and trained numerous PhD and Master students (10 over the period). The recent recruitment of two academic researchers will bring novel strength to the team, particularly reinforcing the fundamental research activity of the group. The team combines medical (ophthalmologists) and academic members, in excellent adaptation with the objectives. No information is given about the team´s life, such as lab meeting frequence etc.

Assessment of the team's involvement in training through research

Dynamic implication in training, with several master and PhD students.

Assessment of the five-year plan and strategy

The project follows the research directions of the past period, with a clear and pertinent strategy and experimental program. The group will pursue the investigation of chemokines in glaucoma and dry eye diseases, with several objectives ranging from the characterization of chemokine expression profiles, the identification of their role and mechanisms of action in these pathological contexts, the development of new animal models and novel therapeutic strategies based on chemokine receptor antagonists. The project appears to be well balanced between fundamental and applied sciencific objectives. The team members bring together a solid and complementary expertise. At present it is difficult to assess the competence of the group concerning the fundamental part. Efforts appear to be necessary to increase the visibility of the published data. There is no doubt that the group is expert for the clinical aspect of its activity.

Conclusion

● Strengths and opportunities:

- Very solid group in terms of members, students, relationship with the local environment, medical institutions, and university,

- Strong translational activity,

- Increased ambition for the fundamental research project,

- Critical (and realistic) auto-evaluation on the strength and weakness of the team.

● Weaknesses and threats:

- Difficult to assess the competition in the field (in terms of fundamental research) but the Team should be able to maintain a leading position,

- Too low visibility of the publications.

● Recommendations:

To continue the effort put on the development of ambitious scientific projects, to concentrate onto a few chemokine signaling and go into the details of their mechanism of action, to develop interdisciplinary interactions for integrating questions of immunology, cell biology and neuroscience. It would be advisable that once Team 16 is fully established the two Teams explore and exploit the potential for collaboration.

Team 13 : Physiology of the retinal pigment epithelium and associated diseases

Name of team leader: Ms Emeline NANDROT

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

The team leader is interested in the physiology of the retinal pigment epithelium and its role in maintaining the health of the retina and in the development of disease pathology. The team leader joined the *Institut de la Vision* in 2008 and moved to a permanent position in 2010. The work is of a high scientific quality, with evidence for this clear in a number of high impact publications obtained by the team leader as a post-doc at Fordham university New York. Progress of the team was impeded by the fire in 2009, but it appears to have regained momentum and has several interesting on-going projects, particularly with a focus on the Mer tyrosine kinase and its role in retinal phagocytosis. The outputs in the past five years show the effects for the team leader of having to relocate, starting a new lab, and recovering from the fire of 2009, and mainly comprise middle author positions on solid if unspectacular papers (Advances in experimental medecine and biology,American Journal of human genetics, human mutation, Plos One). This is entirely to be expected and one would hope the next five year period to be accompanied by a real development of research standing and a good number of high impact papers.

Assessment of the team's academic reputation and appeal

Being a young Team there is not yet extensive involvement in international and national projects, although the team leader does have a number of high profile collaborators in France, Italy and the USA, all of whom have expertise and skills that should synergise with those of the Team to enhance its reputation. The productiveness of these collaborations is evident in several joint publications, and these may help the Team to recruit high calibre researchers from elsewhere in France and overseas. The team leader's reputation is also evident in her role as a regular reviewer for all the top eye journals, as an invited author on several scholarly review articles, and in invitations to give talks at international conferences.

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

The Team has yet to make any significant contribution to breakthrough innovations, but their work on retinal phagocytosis and spicing factors in retinal disease has the potential to generate new intellectual property and opportunities for commercialisation. The link with a pharmaceutical company is positive in this context, and the Team is clearly aware of the importance of innovation as their work progresses.

Assessment of the team's organisation and life

The Team has an appropriate heirarchical structure with the team leader providing clear leadership with close collaboration with UK key opinion leader in the field. The team leader has a number of important responsibilities at the *Institut de la Vision*, serving on Lab Council and as Head Health and Safety Officer. It is not clear whether the team has their own specific lab meetings, or how they contribute to *Institut*-wide activities such as the seminar programme of retreats.

Assessment of the team's involvement in training through research

As a young Team it is too early to assess the team leader's success in mentoring PhD students through to completion, far less to view the career progression of those individuals as post-docs and beyond. However, theTeam does have one PhD student, and the team leader contributes to teaching on a Master's course and also acts as mentor to two post-docs and three Master's students.

Assessment of the five-year plan and strategy

The five-year plan has three major objectives, namely to i) elucidate the regulation of MerTK receptor activity during timely retinal phagocytosis, ii) identify new receptors for rod- and cone-specific phagocytosis, and iii) investigate the pathogenesis of Prpf RNA splicing factors in retinitis pigmentosa. The first two of these build on areas of expertise that reflect the core strengths of the Team, and score well in terms of originality and chances of success. The proposed work might be classified as 'basic' rather than translational, which in the context of the *Institut de la Vision* is important as there is a strong emphasis on translational research. A solid foundation in understanding fundamental cellular mechanisms is important, as it often from this kind of work that future translational opportunities emerge. Indeed, the Team proposes to develop studies on pharmacological modulators of MerTK, and one cannot exclude the possibility that such compounds might find some therapeutic application. The search for new receptors, particular for cone phagocytosis, is more speculative but worthwhile given the gaps in our knowledge and the importance of cone renewal in human vision and disease. Finally, the studies on Prpf signify a new direction in RPE cell biology for the Team, which is sensible and strategically important, espcially as this work offers opportunities to move into iPS technology.

The SWOT analysis provides an accurate analysis of the current state of the team and its work, though I would recommend that 'Opportunities' should comprise more than just a list of collaborators. What about iPS technology, acquisition of new technologies, potential for commercialisation etc? And among the weaknesses, it is difficult to believe that a presitigious Institute such as this lacks a film developer for western blotting? One would hope such a deficit could be easily remedied. Despite this, the five-year plan looks feasible, logical and exciting.

Conclusion

- Strengths and opportunities:

The Team has the potential to become one of the leading RPE groups in Europe over the next five years, and it is important for its long-term development and for the reputation and prestige of the *Institut de la Vision* that the Team seizes this opportunity during this period. Another strength is the research environment in which they work, which provides opportunities for collaboration, and access to specialist skills and expertise. Again, these strengths only become meaningful if the Team translate their potential into activity.

- Weaknesses and threats:

The team has a good current level of funding, and we recommend the team leader takes an active role in exploring all available opportunities, both in national and international programmes, and with pharmaceutical and biotech companies. We believe that the current lack of high impact papers from the Team is a weakness, though there are clearly papers either in preparation or submitted. A strong track record of publications in peer-reviewed journals will inevitably consolidate and affirm the international reputation of the Team, and thereby help to drive new resource.

- Recommendations:

The Team needs to stay focused on their strategy, and given the increasing interest in regenerative medicine it may be prudent to invest time and effort into developing skills and know-how in generating RPE cells from iPS and stem cells. This would also ensure a good fit with the translational aspirations of the *Institut*.

Team 14 : Inflammation in neuronal degeneration and vascular remodeling

Name of team leader: Mr Florian SENNLAUB

Workforce

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

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	5	
Qualified research supervisors (with an HDR) or similar positions	3	4

• Detailed assessments

Assessment of scientific quality and outputs

Age-related macular degeneration (AMD) and ischemic proliferative retinopathies (IR: diabetic retinopathy, retinal vein occlusion) are the most common diseases resulting in blindness. Inflammatory reactions causing neuronal degeneration, microvascular degeneration and neo-vascularisation are the major pathological mechanisms in both AMD and IR.

Team 14 concentrates forces on AMD and IR and focuses on the role of monocytes (microglia cells and macrophages), which invade the degenerating parts of the retina. In 2007 members of the team published a study (J. Clin. Invest. 117: 2920-2928) in which they showed that in humans a polymorphism in the chemokine receptor gene CX3CR1 favors the appearance of AMD. In mice, deletion of this receptor and also deletion of the ligand CCL2, together with light damage, lead to progressive photoreceptor loss with an accumulation of microglia cells in the outer retina and Drusen-like structures, all reminiscent of the AMD-pathologies.This prompted the team to investigate in great detail the activation of microglia cells by different chemokines, and to develop inhibitors of CCL2 to block the pathological influence of CCL2 in AMD. The Team could also show that microglia cells and macrophages play an active role in IR and vascular remodeling and studied systematically in chemokine k.o. mouse models the neonatal hyperglycemia, diabetic retinopathy and retinal vein occlusion.

The scientific quality of the studies of Team 14 is excellent. Given the fact that AMD involves complex interactions of genetic and environmental factors, it was important for them to concentrate forces onto a narrow and restricted aspect of this disease. Only the future can show whether the detailed study of the activation of microglia cells and macrophages by chemokines was the “correct avenue”. More recently the Team has also studied further pathways and signals involved both in AMD or IR (Interleukin-1beta, CD 36, Netrin-4, or GPR91). The methods the Team applies are the state of the art at the highest level. The Team takes great advantage of the unique situation at the *Institut de la Vision* to study both animal models and human disease models. The Team developed an outstanding repertoire of optical techniques, such as the application of Adaptive Optics and is able now, to study pathological changes *in vivo* both in the rodent and in the human eye. The team has an outstanding publication record, both in quality and number (Plos Genetics, Science, New England of medecine among them).

Assessment of the team’s academic reputation and appeal

The publications of the team are highly cited: the paper in J.Clin.Invest., mentioned before, received more than 120 citations since its appearance in 2007. Recent reviews (for instance in American Journal of Ophthalmology, 2013) discuss the results of Team 14 in great detail.

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

The team has filed three patents since 2007: One patent relates to the blockade of CCR2, two further patents are involved with the modulation of CD36. All three patents are related to the treatment of AMD.

Assessment of the team’s organisation and life

The team leader has been at the Institut for only one year and he is already Head of Department (by election) so is now taking an active role in the broader direction of Institutional affairs as well as directing and stimulating the life of his own Department.

Assessment of the team’s involvement in training through research

The team has trained 5 PhD students between 2006 and 2013. Two more students started their thesis in 2012. Furthermore, three master students were trained between 2006 and 2013.

Assessment of the five-year plan and strategy

The team lists in the "Evaluation Report" a total of 7 future projects. They are all concentrating on deciphering the role of pathological microglia cells and macrophages in AMD and IR, and the possible therapeutic blockade of their deleterious effects:

1.) Inflammatory Chemokine and chemokine receptor expression;

2.) Chemokine pathways involved in the accumulation of microglia cells and macrophages;

3.) Mechanisms of microglia cell and macrophage accumulation;

4.) Consequences of prolonged presence of microglia cells and macrophages in the inner retina and in the subretinal space;

5.) Microglia cells and macrophages as mediators of neurotoxicity and vascular remodeling;

6.) Inhibition of of microglia and macrophage accumulation in chemokine receptor k.o. animals;

7.) Inhibition of neurotoxic and angiogenic mediators in chemokine receptor k.o. mice.

The projects are a logical continuation of the previous work of Team 14 and are excellent examples of both scientific depth and clinical importance.

Conclusion

- Strengths and opportunities:

As mentioned above, the team has in the *Institut de la Vision* the great advantage to have expertise in both animal models and human diseases. The Team is strong in inflammation, neovascularisation and AMD. It has solid connections to a group at INSERM/UPMC UMRS 945 (Paris) and a group at the university of Montréal (Canada). This network is mutually supportive and the successful cooperation should continue.

- Weaknesses and threats:

Possibility of a drop in continuity of funding as major grants come to an end, but in view of his promising results and standing we view this threat as not serious.

- Recommendations:

The major EU- and ANR-grants of the team expire in 2013 and it is mandatory for the team and the *Institut* to acquire new grants as soon as possible.

Team 15 : Gene therapies and animal models for neurodegenerative diseases

Name of team leader: Ms Deniz DALKARA

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

This is an emerging team formed basically by a junior young investigator initiating her independent research, two junior scientists completing their PhD work and one technician. The expertise of the group is centered on gene delivery with the aim of optimizing the techniques currently under development for gene replacement and gene knockdown therapies, and to apply them to the treatment of Retinitis Pigmentosa and Macular Degeneration. The principal investigator has an excellent training in the use of adeno-associated viral vectors to target cells that she has applied earlier to retinal cells. This first-level technical capacity appears to be a particularly valuable strenght for the team. They intend to apply this methodology to a rather heterogeneous group of questions in retinal pathology, including delivery of neurotrophic factors to prevent retinal cell death and optogenetic tools for restoratrion of light sensitivty. The group appears capable of improving the specificity and accessibility of viral vectors to the retina; for their therapeutical application to particular retinal problems they will necessarily require the collaboration of other groups of the Institute. In this respect, the various possibilites offered by other research teams there represent a distinct advantage both for this group and for other researchers of the Institute, that will have at hand a research group ready to provide them with excellent genetic tools.

Assessment of the team's academic reputation and appeal

This is a very small group based on just a junior scientist with a very good training and expertise in a rather specific but highly promising field. It is too early to evaluate their capacity to translate the knowledge and enthusiasm reflected in the research project of the group into high level scientific and translational research results. However, it is definitely worth to have in an institution like the *Institut de la Vision* researchers with the determination and technical expertise offered by this small group. The part-time incorporation to the team of Drs. SAHEL and another scientist represents a guarantee for the appropriate use of the research possibilities offered by this junior group.

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

The group is in its initial steps, but the leader shows very clear ideas about the possibilities of her work and the need to establish intense collaboration with other international laboratories in her field of interest as well as with other members of the institute. It is too early to judge about other aspects of the team's activities, like international projection, publications, transference, patents etc. although possibilities appear brilliant.

Assessment of the team's organisation and life

No details are provided about the internal organization of this small group in terms of work distribution or development of join activities. Considering the size and the short life of the group, it is probably premature to try to evaluate these aspects.

Assessment of the team's involvement in training through research

The group leader has under her supervision two ingineers and one predoctoral student. It is obvious that these will have to work closely in order to develop the proposed goals and this is going to be the training program of this personnel. No specific plans in this respect are provided.

Assessment of the five-year plan and strategy

As mentioned above, the research plan appears to be primarily the development of better technical tools for gene delivery and how these will be specifically adjusted to solve the particular problems in retinal pathologies. This is partly a technological development program and partly a scientific plan to develop new gene therapies at a pre-clinical stage. Still, considering the focus and expertise of the group it is worth to support this opportunistic strategy approach.

Conclusion

- Strengths and opportunities:

Provision of a cutting-edge technology to the institute and a new and promising young research group with a great potential for growth.

- Weaknesses and threats:

Full dependence on the particular expertise of the group leader, fragility of the group due to its small size and technological challenges. The technology is of interest to the whole Institute, and the Team leader should continue to prioritise the development of her own research programme.

- Recommendations:

Provide support for future growth and for international interchange and collaborations.

Team 16

Development of corneal innervation and re-innervation after corneal surgery

Name of team leader:

Mr Vincent BORDERIE

Workforce

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

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions		3

• Detailed assessments

Assessment of scientific quality and outputs

This is a new research unit composed by two researchers with a long experience in experimental and clinical eye research, aimed at opening a new field of research directed to analyze experimentally the molecular and cellular mechanisms governing the development of normal innnervation and the processes involved in neural regeneration following surgical damage of corneal nerves. The proposal is based on the incorporation of a junior researcher with full dedication to the experimental work and the defined support and involvement of Team 1. This appears to be an excellent combination of complementary technologies and knowledge, in the core of the objectives of the *Institut de la Vision* aimed at developing science of excellence with translational possibilites. The clarification of the mechanisms of peripheral nerve regeneration after injury are of general interest in neurosciene today and particularly in Ophtahlmology, where the clinical consequences of nerve injury after corneal surgery or peripheral nerve damage accompanying viral infections, diabetes or dry eye are of great importance and affect a very large number of patients. The success of this initiative relies fully in its success in obtaining more human resources and solid collaboration with internal and external laboratories.

Assessment of the team's academic reputation and appeal

The international reputation of the two principal researchers of this Unit and of their collaborators from team 1 is very solid, and the combination of their efforts and expertise to develop this reseach plan is appealing and attractive. All of them have participated in multiple research programs in the past, exhibit a very good publication record in their respective fields and possess the expertise and knowledge required to successfully develop the experimental plan presented here.

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

According with the comments made above, the success in social, economic and cultural environment has to be judged on personal basis, because the team has not been yet formed as such. The subject of research has many potential technical and therapeutical applications.

Assessment of the team's organisation and life

There is no specific information on how the very important and necessary interaction between researchers will be implemented. It is advisable that regular interchange of information and seminar activities are planned.

Assessment of the team's involvement in training through research

Although not specifically addressed, it appears reasonable to predict that the research developed by this team may have a very positive effect on the training of junior ophthalmologists associated to the clinical activities of part of the team and favor traslational initiatives between clinicians and researchers.

Assessment of the five-year plan and strategy

The five year plan involves the study of how corneal innervation develops under normal conditions and the role played by axonal guidance molecules, a field in which Team 1 occupies a leading position in the world. The extension of this information to the human cornea after surgery and to corneas following transplantation is an additional important objective, in which the participation of the clinical members of the team is critical. The plan is clearly defined and experimentally feasible.

Conclusion

- Strengths and opportunities:

Experienced researchers in all the methodologies proposed. Combination of very different expertises. Research problem with basis and applied scientific importance.

- Weaknesses and threats:

Lack of junior researchers for direct implementation of the program. Requirement of a defined involvement of the senior researchers in the development of the project

- Recommendations:

Reinforce the research team with junior researchers and technical personnel. Collaboration with groups working in complementary questions (Team 12).

5 • Conduct of the visit

Visit dates:

Start: 28th January 2013 at 8h30

End: 29th January 2013 at 19h30

Visit site:

Institution: Institut de la Vision

Address: 17 rue Moreau - 75012 Paris

Specific premises visited:

The platforms of the *Institut* were visited, namely the imaging platform, the homelab and the incubator.

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

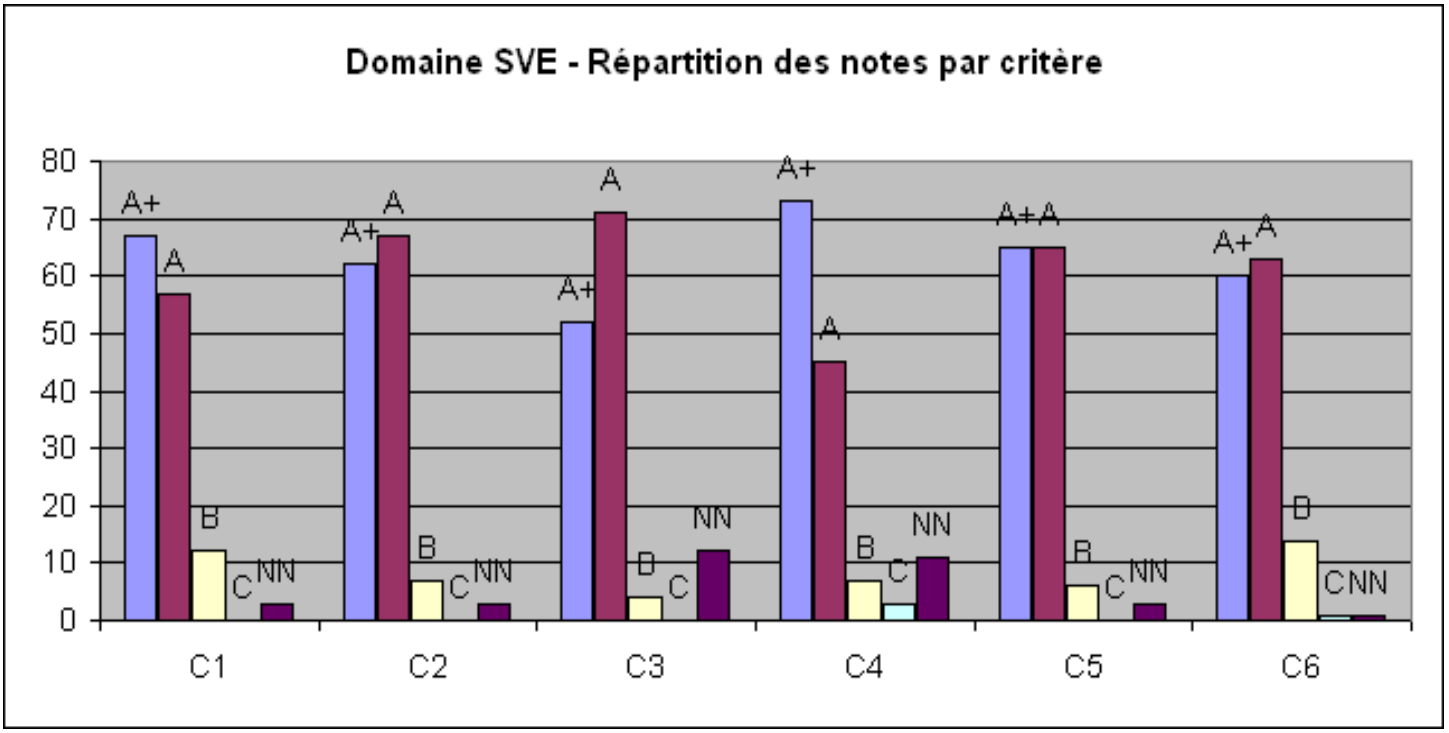
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



7 • Supervising bodies' general comments

Paris le 24 04 2013

Le Président
Didier Houssin
Agence d'évaluation de la recherche
et de l'enseignement supérieur
20 rue Vivienne - 75002 PARIS

M. le Président,

Nous avons pris connaissance avec le plus grand intérêt de votre rapport concernant le projet de l'Institut de la vision, porté par M. Sahel. Nous tenons à remercier l'AERES et le comité pour l'efficacité et la qualité du travail d'analyse qui a été conduit.
Ce rapport a été transmis au directeur du laboratoire qui nous a fait part en retour de ses commentaires que vous trouverez ci-joint. Nous espérons que ces informations vous permettront de bien finaliser l'évaluation du laboratoire.

Restant à votre disposition pour de plus amples informations, je vous prie de croire, M. le Président, à l'expression de mes salutations respectueuses.

Le Vice -Président Recherche et Innovation

Paul Indelicato

Vice-présidence Recherche et Innovation
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Paris, April 18th 2013

We thank the Committee for their accurate and very positive assessment of the activity and the international positioning of our Institute, despite the occurrence of a fire that destroyed our building and delayed our work by approximately one year. As mentioned by the reports, we would like to underline the difficulties the Institut de la Vision is facing to obtain permanent technician-Engineer-Admin positions (13 permanent positions for 71 persons enrolled on a contract basis). Very few permanent technical or administrative positions were obtained despite this poor ratio and the fact that 7 new researchers were recruited (and potentially 2 more since the evaluation according to the CNRS and Inserm ranking) increasing a chronic serious imbalance which may, in the near future, create a negative impact on the quality of the work performed by the research teams as the immense majority of our programs are funded through contracts.
Some inaccuracies are corrected below:

Alain CHEDOTAL-S1: Role of Axon Guidance Molecule
Organization and life

We hold weekly lab meeting together with the teams of Jean Livet and Xavier Nicol.
A. Chedotal also meets with team1 members at least weekly to discuss their project
For the two projects financed by Sanofi, there is a bimonthly meeting where results and milestones are discussed

The Department of Development has a biweekly journal club and a monthly meeting

We appreciate that the committee underlined and was surprised by the lack of permanent technician position in a team of 20 people including 5 academic researchers.
The group leader would like to remind that the same anomaly was noticed when he obtained his first INSERM unit in 2008; The team was ranked first by the INSERM scientific council and in its final report the CSS8 INSERM said that the recruitment of a technician was required.
Not only a position was not opened but the only technician (AI CNRS) who was in the team at that time was not allowed by CNRS to follow the team to the Vision Institute

because it did not yet have then a CNRS affiliation...so the situation is even worse now than in 2008.
The team leader does not understand why INSERM did not support the team although it selected twice (2008 and 2010) publications from the team as Neuroscience highlights for its yearly report.

Olivier GOUREAU-S2: Genetic Engineering approaches to study retinal development & repair/regeneration

We first want to thank the committee for their positive appraisal concerning our projects and the work performed in our group. Team members agree with valuable comments and recommendations pointed out by the AERES committee. Starting up projects like our iPS project is always demanding, but in view of our first results we have good hope to publish rapidly in high impact journal. Concerning the authorship order on old publications, the rational thought has been clearly evoked during the meeting with AERES members. Since another senior researcher was present in our group, it was obvious that this researcher should be the last author in the subject he was in charge of, and the team leader second to last author but still co-corresponding author. As recommended by the committee, we make a lot of effort to obtain a permanent position to secure our iPS know-how in the near future.

Renata KOZYRAKY-S3: Multiligand endocytosis in normal and pathological axial elongation of the eye

We thank the AERES committee for the insightful comments:

1) Concerning the number of publications in specialized journals

During the last four years our team has switched from the renal to the developmental field; given this switch and the size of the team the decrease of the number of publications was predictable.
However the ratio N°of publications/N° of years concerning the team leader (5 original articles and one review article) is less problematical than expected. Since the evaluation, one major publication has been accepted in JBC :
"Cubilin, a high affinity receptor for fibroblast growth factor 8, is required for cell survival in the developing vertebrate head" Olivier Cases, Aitana Perea-Gomez, Diego P. Aguiar, Anders Nykjaer, Sabine Amsellem, Jacqueline Chandellier, Muriel Umbhauer, Silvia Cereghini, Mette Madsen, Jérôme Collignon, Pierre Verroust, Jean-François Riou, Sophie E. Creuzet and Renata Kozyraki.

2) The aims are ambitious and will require an increase in the size of the team

Our aims are ambitious but realizable. We plan to recruit more Phd students as well as a postdoc. To do so we are currently applying for adequate funding.

3) The small team size may have consequences on the attractivity for PhD students/postdoc .

We did not meet any difficulty to find candidates for a PhD; as soon as a funding is available we will be able to recruit a postdoc.

4) No secured long term funding

One of our priorities is to obtain funding for the next five years.

5) No collaborations inside the institute have been mentioned,

We are the only team inside the institute to work on axial elongation and ciliary body function; however our ongoing collaboration with Michel Paques (team S14) is essential for the phenotypical evaluation of several of our mutants. Similarly Serge Picaud (S8) helps us to analyze the retinal function of our mutants. These two collaborations were mentioned in the power-point presentation of the group. On more technical aspects our group has close interactions with Marisol Corral-Debrinsky's group (S11). We feel confident that new collaborations especially with the groups of the Therapeutics Strategies' Department will be developed within the next couple of years.

6) New in the field

Being new in the field is a weakness if one considers that funding is more difficult to obtain and that without funding it is difficult to publish.
However, the currently available funding even if it is not a long term one, will help us to show that "new in the field" may also be synonymous of enriching for the field.

Jean LIVET-S4: Development of Neuronal circuits

Team S4 (J Livet) thanks the evaluation committee for its report which underlines well the assets of our team and the general interest and timeliness of our project on lineage and connectivity. The weaknesses pointed in the report –the small size of the team and the need to focus our work accordingly– are being addressed. These are clearly a consequence of our recent start as an independent team. Our methodological advances now make it possible to recruit new team members on funded projects; these advances also lead the team to refocus its activity on lineage-related scientific objectives. Two articles originating from the laboratory of which one is submitted should be published this year. Our integration within IdV is increasingly reinforcing through projects led in collaboration with other teams (O. Goureau, A. Chédotal, R. Benosman…), and our expertise in genetic engineering opens exciting possibilities for multidisciplinary projects combining physiology and imaging (S. Picaud, J. Duebel).

Minor points: The 2nd EPST researcher of the team was recruited as such only in Oct 2012 and was still a postdoctoral researcher in the team on 30/06/2012. The research engineer mentioned on p22 is currently on a contract that we seek to secure on the long term.

Xavier NICOL-S5E : Cellular Messenger codes for axon guidance

We thank the AERES committee for its encouraging assessments about team 5, and for their helpful recommendations. We are pleased that the committee finds our

team very promising. We would like to mention the complementary measures that have been taken since the visit of the committee at Institut de la vision.

- *"Weakness and threats :*

The team needs to get rapidly its dedicated microscopic equipment"

A FRET-optogenetics microscope is now set up at the institute, and we successfully performed the first FRET experiments at Institut de la Vision.

- *"Recommendations :*

The team leader is well aware that he has to attract and stabilize collaborators."

Actions have been taken to go to the direction pointed by the committee. Internship offers have been posted to hire a master student from Master BIP or BMC from Paris 6 University for the next academic year (2013-2014). In addition to the support we already received from ANR and Institut de la Vision through the Labex "Lifesenses", we applied to the ATIP/AVENIR program and the "Emergences" program from the City of Paris. Both programs include funding for a post-doctoral researcher (3 to 5 years depending on the program).

Isabelle AUDO / Christina ZEITZ-S6: Identification of gene defects leading to non progressive and progressive ocular diseases

The team leaders Isabelle Audo and Christina Zeitz appreciated the effort of the members of the evaluation board and their mainly positive, otherwise fruitful comments and recommendations concerning their team. Please find below only minor comments in respect to the statements and recommendations,

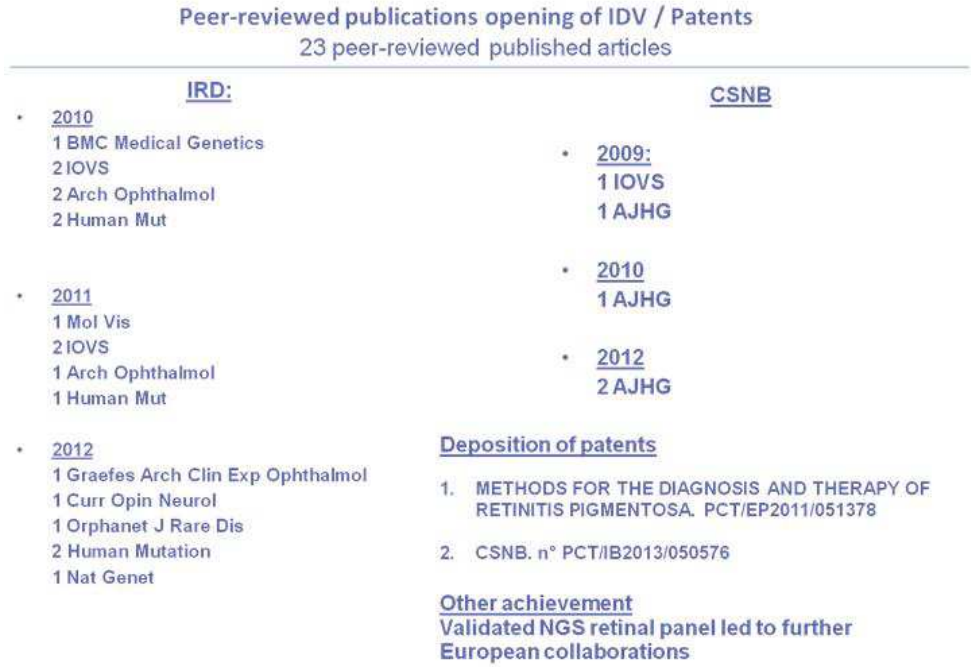
1. In the last table of page 27: actually our group did not have doctoral students as of June 2012. However, in September 2012, two new PhD students joined our group, including one who previously was an assistant engineer in the team. Therefore, doctoral students' number as at 30/06/2012 should be "0" and number as at 01/01/2014 should be 2.

2. Page 28, last sentence of the first paragraph:

"Whilst quite a few of these are publications in which the team leaders are clearly not lead authors, these papers exemplify a wide number of productive collaborations and their involvement in projects beyond the *Institut de la Visison*."

Obviously our report and oral presentation was not clear in this respect and therefore we want to clarify this point:

During the evaluation period (from last AERES evaluation until 25.01.2013) the team leaders published in 23 high impact factor peer-reviewed journals (e.g. 4 AJHG and 5 Human Mutation, etc.; please find copy of oral presentation below). In all but 3 the team leaders are first or last authors.



3. Page 28, last sentence of the before-last paragraph:

"There is no indication that any of the "Team attends scientific conferences-…"

We feel unfortunate that this point was missed and want to make clear that every postdoctoral fellow and PhD student in addition of the team leaders attend national and international scientific conferences (e.g. The Association for Research in Vision and Ophthalmology (ARVO), Société de Génétique Ophtalmologique Francophone (*SGOF*), two associations for which they are also active members).

4. Page 29, under "Weakness and threats"

".. challenge in terms of bioinformatics and the extraction of useful information"

As mentioned during our oral presentation since January 2013 a new postdoctoral fellow expert in bioinformatics and statistic joined our team. In addition our team has access to institutional bioinformatic support.

Again, the team leaders thank the evaluation board and hope this additional points mentioned by us could be adjusted.

Thierry LEVEILLARD-S7: Rod-derived cone viability signaling for the therapy of inherited retinal degenerations

Weaknesses and threats:

Lack of a well-characterized mechanism of action but the team is working very actively on it and some of the RdCVF signalling is being elucidated,

Focus on AMD and CNS seems wide.

1. **The cell surface receptor of RdCVF has been identified and its mode of action characterized. The work is not published but was extensively presented in the document submitted as well as during the presentation of the team.**
2. **The participation of the team as coordinator of EU-JHU, a subcomponent of the meta-consortium AMDGene was recognized in the recent publication "Seven new loci associated with age-related macular degeneration" in Nature Genetics in which Thierry Léveillard is labeled 129 as [129]These authors jointly directed this work.**

Recommendation
Focus on the translational aspects on the retina and the identification of RdCVF receptor/signalling. Extension of the research into the areas of Alzheimer's diseases should be conducted in collaboration with other groups.
Thierry Léveillard is Principal Investigator of a grant from the Plan Alzheimer 2012. This project involves a collaboration with Hamid Meziane from the Mouse clinic (ICS) in Strasbourg and Laurent Pradier from the Therapeutic Strategy Unit Aging Alzheimer/Parkinson indication at Sanofi-Aventis

Serge PICAUD-S8: Retinal information processing – Pharmacological and pathology

Serge Picaud thanks greatly the committee for the very positive evaluation of the team and for underlying his successful effort to attract new teams in the department.

Ryad BENOSMAN / Christoph POSCH S9: Vision and Natural Computation

We would like to thank the committee for the positive and encouraging assessment of our team. There are two remarks/comments we would like to bring forward:

(1) The team is co-directed by Christoph Posch (Research Professor, UPMC) and Ryad Benosman (Associate Professor HDR, UPMC). We would like to kindly ask this fact to be reflected in the final AERES report. (All required details can be found in the documents submitted to AERES or can be supplied on demand).

(2) Concerning the recommendation on required focus on scope and strategic objectives of the Institute (and on the specific project), we would like to add that some current activities that seem to be marginal with respect to the main direction of the Institute are remains from the history of the two teams recently merged (formerly at ISIR/UPMC and AIT). On the other hand, a cautious and gradual expansion of the Institute's scope of Vision into adjacent fields embracing e.g. biologically inspired artificial vision in non-biomedical applications is intentional and was also one of the motivations to establish this team at the Institute.

Jens DUEBEL-S10E: Neurophysiology and Optogenetic Applications in the Retina

Weaknesses : - number of researchers in the team is too small. Although the number of scientific publications is very limited (6 publications since 2004) they have been published in high impact factor journal (Science, Neuron, Cell). However, there is only one paper signed as first author and he is encouraged to demonstrate leadership in his future published outputs.

Two papers are signed as first author (Neuron: first author; Science: shared first author)

Threats : - Management of the technical aspects such as patch-clamp recordings, AAV delivery. To develop a competitive team. Recommendations:
There is no doubt about the interest of the research project: working on ways to restore vision by making other cells of the retina, which are spared by the disease, sensitive to light might be one key to bring back vision. However, team leader has planned a very ambitious program for only one researcher making the project rely maybe too much on its collaborations. He should accelerate the development of his group with the recruitment of post-doctoral and PhD students.
Based on the funding from ERC and Labex, PhD students and post-doctoral fellows are now recruited. Two graduate students have already been hired and the recruitment of two post-docs is currently on going. Within the year 2013 the team size will be expanded at least to five group members:

- **2 graduate students**
- **2 post-doctoral fellows**
- **1 Computer Engineer**

The custom-made two photon microscope is now fully working and preliminary data on non-primate retinal tissue has already been generated.
Since the evaluation by the AERES committee, Dr. Duebel has been ranked second out of two (CNRS commission) and therefore should get a permanent position as from autumn 2013.

Marisol CORRAL-DEBRINSKY-S11: Mitochondrial Dysfunction and ocular diseases

"Assessment of scientific quality and outputs" She trained originally in a group at the Perelman School of Medicine, University of Pennsylvania (USA), with whom she still collaborates, and joined the *Institut de la Vision* in 2004. Her outputs in the last few years are typical of a scientist developing their own laboratory (and having to suffer the major inconvenience caused by the fire of 2009), with a solid number of publications in reasonably good journals (J.B.C, J. Mol. Biol, Plos One).

Precisions and complements: The post-doc training of the team leader has been performed in the Pr. Douglas Wallace laboratory (Emory School of Medicine, Atlanta, USA). Pr. Wallace discovered back in 1988 the first mitochondrial DNA mutation responsible of Leber Hereditary Optic neuropathy (LHON): the G11778A mutation; the one chosen by her for building the gene therapy protocol. She went then to the ENS (Paris) where during 8 years she decipher the molecular blocks in yeast mitochondrial biogenesis which allows today being confident in the gene therapy strategy developed (Mol. Microbiol, EMBO J, MCB, MBC, EMBO reports, Genome Biol.). Once, she joined the institute she developed the molecular tools aimed at protecting visual function in patients suffering from optic atrophies due to mitochondrial dysfunction and with this solely objective in mind she and her team published in prestigious journal each publication legitimating each one of their hypothesis (RNA, BBA-Mol. Cell Res., Am. J. Hum. Genet, Brain).

"Assessment of the team's involvement in training through research": The experience of the team leader should provide her with good mentoring skills, so it is a little surprising that there is only one PhD student who is apparently her first.

Precisions and complements: Since 2004 the team leader directed three PhD students whom defended brightly their thesis in: October 2007 (V. Kaltimbacher), October 2009 (S. Ellouze) and October 2012 (A. Bouaita) which appears at a high standard performance regarding that she is the only permanent position researcher in the team possessing the Research Supervisor Qualifications. For the scholar year 2013-2014 she will train a Master 2 student whom could if the funding is obtained stay for doing his/her thesis research program. However, it is worth mentioning that, within the 2008-2012 period, two Master degree students (second year) were trained successfully in the team for a 9 month-period each one (S. Sghari and J. Ayache).

Conclusion- Weaknesses and threats: "There is a danger that the ambitious five-year plan will dilute the efforts of the Team, with the inherent risk that projects may stall as a result, and there are questions over the source and extent of the funding available for the LHON trial. Competitors in the LHON field pose a serious threat

though no doubt the Team will move as quickly as possible in order to mitigate the risk of being scooped".

Recommendations: "With regard to the Phase I/IIa trial, and the benefits it would bring not only to the Team but also the Institut de la Vision, the continuing pro-active involvement of the Institut Director and senior academic and clinical colleagues will be important in ensuring that the trial gets under way in a timely manner".

Precisions and complements: The Institute Director does know the importance of the Phase I/IIa clinical trial, project and is a highly strong support at the daily basis, mid- and long-term. As mentioned, by the AERES committee in the evaluation: commitment in the LHON project will create the excellent opportunity for team leader to elevate her profile, and that of the *Institut*, by becoming a "world leader in this area". Both Pr. Sahel and Dr. Corral-Debrinski share the principal dedication of "improving by any mean patient's quality of life"; therefore Pr. Sahel fought to be certain that the financial aspect will not impede this goal. For this the French company **GenSight** was created last year: **32 millions of Euros** were raised from four international fund trusts (one American, one European and two Swiss) to guaranty that the LHON project will go until the application for marketing authorization to the European Medicines Agency, hopefully in 20017. With this purpose **GenSight** acquires: (i) the exclusive license for using in ophthalmologic conditions of our patent (EP2006005323 PCT: Importation of mitochondrial proteins by an enhanced allotopic; which encompasses the intellectual property of vectors we will use in the clinical trials); (ii) the non-exclusive license of the patent for using in central nervous system diseases; (iii) a contract for pursuing within the Institute de pre-clinical research for allowing to move ahead with a second gene responsible of LHON (NDA G3460A) ; (iv) the support required for the preparation of the clinical trial (scientific, regulatory and administrative aspects). All of this is performed in harmony and effectiveness with the AFM/Genethon personal who has being and remain a strong support for the project.

Christophe BAUDOUIN- Stéphane MELIK-PARSADANIANTZ -S12: Chemokines and physiopathology of the eye anterior segment

The general comment concerning team 12 is positive and recognizes the strong translational research projects related to original studies on the anterior segments and related pathologies such as dry eye and glaucoma. It should be emphasized that the five-year project not only follows research directions of the past period but also includes an innovative project related to the implication of chemokines in corneal trigeminal pain.

The recruitment in April 2012 of two full-time academic researchers with a strong background and recognition in Neuroscience and chemokine fields, publications listed in annex to the team 12 (*J Neuroscience (IF 7.11), Toxicol Sci (IF 4.65), Glia (IF 4.82), Am J of Physiology (IF 4.75), Endocrinology (IF 4.45),* and reviews*: Nature Review in Neuroscience (30.4), Frontiers in Neuroendocrinology (IF 11.42), Brain*

Research Reviews (IF 10.34), Progress in Neurobiology (8.87), as well as the more recent publications of the group in ophthalmology field *(Mucosal Immunity (IF 6.09), Plos One (IF 4.09*), have been omitted and should be taken into account for the evaluation of the potential of the team in fundamental research.

Emeline NANDROT-S13: Physiology of the retinal pigment epithelium and associated pathologies

Members of Team S13 are grateful to the Committee Members of the "Agence d´Evaluation de la Recherche et de l´Enseignement Supérieur" for their valuable comments and suggestions. We are glad that we convinced the Committee Members that our expertise and projects are promising and that our team has the potential to rise as an European leader in our research field on retinal pigment epithelial (RPE) cells in the future. We agree that starting a new lab in 2008, the fire in 2009 and subsequent relocations in 2009 and 2010 somewhat impacted on our research work. While we certainly do not criticize the Committee's insights, we feel that we need to explain some points raised by the Committee.

Even if the team is new and quite small for the time being (4 people + the PI), the team members are enthusiastic and very dedicated to their projects. We hold weekly lab meetings where the different team members present their ongoing work (sometimes in English). This allows the all team to interact on a deeper level than at the bench, and think about each other's approaches in regards to the global team theme / strategy. Our team members as well participate in IDV scientific seminars and retreats (talks and posters), and present regularly in monthly meetings from the Therapeutics Department that we joined 2 years ago (previously the team was linked to the Genetics Department). As well, we are currently interacting with various PIs at the IDV on different subjects, such the role of outer segments of photoreceptors and proteases in macrophage invasion in the retina during AMD with as Prof. Sennlaub and the role of the Dp70 dystrophin in RPE cells with Dr. Rendon (both Team S14).

We published 8 peer-reviewed papers during the past period, including 3 as first author. As the PI is moving more towards a leading function, we published 1 paper as previous to last author and another one has just been accepted. We currently have 3 axes ongoing, each of them with a potential of publication within the year. Our work is mainly based on animal work and mechanistics, which takes time to generate results. With these various papers and with the trust generated by the ANR grant we obtained for 2013-2016, we will be able to consolidate our funding for the team. Indeed, we plan on applying to a more senior permanent researcher position at CNRS (DR2) and submitting an ERC consolidating grant in the next 2 years.

We have several active collaborations on hot topics. The first one with Prof. Pierce (MEEI, Mass. Eye and Ear Infirmary, Boston, USA) is the study of the role of ubiquitous splicing factors in tissue-specific retinitis pigmentosa cases (Project funded by the NIH). Our expertise in this collaboration is crucial as our recents discoveries make it clear that the phenotype most likely develops first in RPE cells. The second one with Prof. Sahel and Dr. Goureau from Institut de la Vision and Prof. Monville (INSERM/UEVE UMR 861, IStem, Evry, France) on the generation and use of

RPE cells generated from IPSc is promising. Our expertise is required to assess the proper differentiation and function of RPE cells. We are currently submitting an ANR grant proposal on the proof of concept for the RPE cells in human gene therapy and hope to be able to bring it to the clinic in the next few years.
Last, we feel that the IDV is a great place for us to work and develop our projects, especially as the platforms are well-organized and getting state-of-the-art equipments and technologies. For example, the IDV is equipped with various possibilities to image western blots, ranging from manual imaging to digital acquisition of both chemiluminescence and fluorescence signals.

Florian SENNLAUB-Michel PAQUES S14: Inflammation in neuronal degeneration and vascular remodelling

Team 14 would like to thank the Aeres committee for the very encouraging evaluation. We are fully aware of the mentionned « threat » concerning funding and are making every effort to secure knew resources. We would like to point out that Team 14 is directed by Florian Sennlaub and Michel Paques, who was omitted in the report. The number of staff « Permanent professors and similar positions » in the table « Team workforce » should be corrected to 2 / 2 / 2 (Pr Michel Paques and Pr. José Alain Sahel).

Deniz DALKARA-S15E: Gene therapies and animal models for neurodegenerative diseases

We are grateful for the positive comments of the AERES evaluation of Team 15 namely on the excellence of genetic tools provided by this team as well as the potential for the team's contributions being described as possibly brilliant with a great potential for growth. There is one discrepancy between the "Assessment of the scientific quality and outputs" as it states that the team is composed of two junior scientist completing their PhD work and one technician. This statement has been rectified in "Assessment of the team's involvement in training trough research" as 'two engineers and one postdoctoral student' which correctly reflects the team's structure. The recommendations to provide support for future development are being followed as the team continues to receive excellent financial support from the Labex package for the next 3 years as well as new funding recently generated by the team leader (Marie Curie Career integration grant). Furthermore the team leader has recently been ranked 3rd for 5 open positions in the competitive recruitment process for INSERM, which is likely to grant her a tenured position in 2013.

Vincent BORDERIE-S16E: Physiology and cell transplantation in inflammatory

Overall we fully agree with all the comments made by the expert committee and we are grateful for their pertinent suggestions.
Since the committee evaluated the team we have recruited a junior researcher who is currently stating her job in the team. The technical personnel are currently reduced to one engineer but we will aim at recruiting a technician when financial support will

be available from grants or other sources. Of course it implies that first results are available and accepted for publication.
Regular team meetings (twice a month) are scheduled and clinicians meet junior and senior researchers several times a week. This organization should permit “important and necessary interaction between researchers” to be implemented as suggested by the committee.
Collaboration with groups working in complementary questions (Team 12) will be developed through department interactions.