Research evaluation

EVALUATION REPORT OF THE UNIT

IdV - Institut de la vision

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Sorbonne Université

Institut national de la santé et de la recherche médicale - Inserm

Centre national de la recherche scientifique - CNRS

EVALUATION CAMPAIGN 2023-2024

GROUP D

Report published on October, 18 2024

High Council for evaluation of research and hihter education

In the name of the expert committee :

Simon Thorpe, Chairman of the committee

For the Hcéres :

Stéphane Le Bouler, acting president

Pursuant to Articles R. 114-15 and R. 114-10 of the French Research Code, evaluation reports drawn up by expert committees are signed by the chairmen of these committees and countersigned by the Chairman of Hcéres.

To make the document easier to read, the names used in this report to designate functions, professions or responsibilities (expert, researcher, teacher-researcher, professor, lecturer, engineer, technician, director, doctoral student, etc.) are used in a generic sense and have a neutral value.

This report is the result of the unit's evaluation by the expert committee, the composition of which is specified below. The appreciations it contains are the expression of the independent and collegial deliberation of this committee. The numbers in this report are the certified exact data extracted from the deposited files by the supervising body on behalf of the unit.

MEMBERS OF THE EXPERT COMMITTEE

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Experts:	Mr David Blum, Inserm - Institut national de la santé et de la recherche médicale Ms Sophie Crespin, Université de Lille Ms Catherine Creuzot-Garcher, Centre hospitalier universitaire de Dijon - CHU Dijon (representative of CNU) Ms Ouria Dkhissi-Benyahya, Inserm - Institut national de la santé et de la recherche médicale Mr Yves Fregnac, Institut des Neurosciences, Paris-Saclay Ms Sarah Guthrie, Centre for Ocular Research & Education (CORE), University of Waterloo, Canada Mr Koen V Haak Tilburg, University / Donders Institute Pays-Bas Ms Sophie Laye, Inrae - Institut national de recherche pour l'agriculture, l'alimentation et l'environnement Mr Guillaume Masson, Centre national de la recherche scientifique - CNRS, Institut des Neurosciences de la Timone, Marseille Ms Emilie Pacary, Institut national de la santé et de la recherche médicale, Bordeaux Mr Alan Stitt, Queen's University Belfast Royaume-Uni - Citoyen britannique, Belfast (Irlande) Ms Muriel Thoby Brisson, Inserm - Institut national de la santé et de la recherche médicale, Bordeaux Mr Cizmar Tomas, Leibniz-IPHT, Allemagne Mr Maciej Wojtkowski, Institute of Physical Chemistry, Pologne Mr Uwe Wolfrum, Johannes Gutenberg University of Mainz, Allemagne Mr Michael J Young, Harvard, États-Unis Ms Elisa Zanier, Mario Negri Institute for Pharmacological Research, Italie

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Mme Saida Guellati-Khelifa, INP
Mr Etienne Hirsch, Inserm
M. Vincent Mouly, Sorbonne Université
M. Bernard Poulain, CNRS

CHARACTERISATION OF THE UNIT

- Name: Institut de la vision
- Acronym: IdV
- Label and number: UMR_S968 Inserm / UM 80 Sorbonne Université / UMR 7210 CNRS
- Composition of the executive team: Serge Picaud and Isabelle Audo (deputy)

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE5 Neurosciences et troubles du système nerveux

THEMES OF THE UNIT

The unit Institut de la Vision (IdV) dedicates its research to understand visual perception and its development, to generate models of ocular diseases useful for deciphering fundamental mechanisms underlying neurodegenerative processes. They develop diagnostic tools, innovative therapies and new strategies to ultimately improve phenotyping and restore vision in human patients. It is composed of eighteen teams, organised in five thematic departments: Development (5 teams), Genetics (2 teams), Visual Information Processing (4 teams), Photonics (3 teams) and Pathophysiology & Therapeutics (4 teams). They are part of four different panels of Hcéres classification: SVE5 (Neuroscience and Nervous System Disorders), SVE7 (Prevention, Diagnosis and Treatment of Human Diseases), ST2 (Physics) and SVE6 (Human Physiology and Physiopathology, Ageing). Of note the existence of a dedicated associated foundation (Fondation Voir et Entendre), that represents an efficient tool for managing and coordinating large national and international grants.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The IdV unit originates from the INSERM Unit 592 created as a University/INSERM team in 1999 in Strasbourg by Pr Sahel. In 2002, the unit moved to Paris to build a genuine translational environment and rapidly several additional teams joined the group. The actual Institute de la Vision building was constructed under a public-private partnership at that time. The real IdV finally opened in 2010, after a delay due to an important fire incident in 2009. In 2009 the IdV became a research centre associated with Sorbonne University (January) and CNRS (September). Since, then several new teams joined the institute while others were either closed or moved in different institutes, resulting in the current set of eighteen teams. Over this period the IdV was repetitively awarded outstanding by the AERES (2008–2013). In 2017 the Hcéres committee recognised IdV as a world-leading centre for research in ophthalmology. In 2019, IdV contributed with others to the IHU project FOReSIGHT. From its origin, the institute was under the responsibility of Pr Sahel who transferred his leadership to Dr Picaud during the Covid period that is effective since the January 1st, 2021. Then Dr Picaud proposed to Isabelle Audo (clinician and researcher PU-PH Sorbonne University) to become his deputy and thus maintain the balance between fundamental and clinical research.

UNIT WORKFORCE: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	13
Maîtres de conférences et assimilés	7
Directeurs de recherche et assimilés	18
Chargés de recherche et assimilés	18
Personnels d'appui à la recherche	31
Sous-total personnels permanents en activité	**87**
Enseignants-chercheurs et chercheurs non permanents et assimilés	12
Personnels d'appui non permanents	48
Post-doctorants	23
Doctorants	84
Sous-total personnels non permanents en activité	**167**
Total personnels	**254**

DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: in physical persons at 31/12/2022. Non-tutorship employers are grouped under the heading 'others'.

Nom de l'employeur	EC	C	PAR
Sorbonne Université	20	1	48
Autres	10	0	40
Inserm	0	27	19
CNRS	0	14	7
Total personnels	**30**	**42**	**114**

GLOBAL ASSESSMENT

The Institute de Vision is a very impressive research centre that has successfully established itself as one of the leading research centres in the world. The current director has done an admirable job of taking over following the departure of the founder of the Institute, and the panel was impressed by the quality of the evaluation document and the presentations, as well as the detailed responses to the numerous questions posed. The Institute has produced an impressive list of more than 1200 publications, with many in top journals, and its researchers have made major contributions in several areas. The Institute has excellent resources, and is very well funded, in particular thanks to income from a private foundation – Fondation Voir et Entendre. It has also made major strides in the development of new therapeutic approaches, with over 60 patents and a very active policy of developing products with industrial partners, including numerous start-ups. Its links to society are globally very strong, thanks to its involvement with many patient associations and links with clinical research. It has been remarkably successful in training students and postdocs, many of whom have gone on to key positions in academia and industry. At the level of individual teams, the institute was also very impressive. The panel evaluated eighteen different teams, and considered that they are all globally excellent to outstanding. There were very few cases where the panel felt there were potential major problems, and most of these could be dealt with relatively simply. That said, there are clearly several issues. The main one concerns the limited space available, and the excessive costs associated with renting the buildings. This is already a considerable constraint that has held back the development of some of the key research teams. In the future it will be important to find solutions.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The previous Hcéres panel made a number of recommendations. In general, the direction of the IdV has taken the recommendations into account.
They recommended increasing the involvement of groups of patients, and this is illustrated by the implication of several team leaders in actions by the Retina Foundation and the Foundation Fighting Blindness (FFB), as well as several research presentations to groups such as Canne blanche, France Choroidérémie, Voir Ensemble and UNADEV.
They noted that elections for representatives for PhD students were too infrequent. Elections now take place every two years. They also noted the lack of support for newly arriving students, and this has also been improved.
They pointed out the limitation on spaces caused by excessive rent costs, and while this is still a serious issue, the IdV is trying to find ways to increase the amount of space available.
They commented on the gender balance among the team leaders, and it is good to see that in the future mandate, eight of a total of sixteen teams will be led by women, although the panel has not yet seen the full details. It is also good to note that the IdV has instituted a coaching scheme for women scientists, as well as dedicating a room to allow women scientists to care for infants on site.
They noted that the mechanisms for evaluating staff members were not firmly established, but there has been significant progress on this point.
At the time, the succession of Jose Sahel as institute director was unclear, but Serge Picaud has now been officially nominated following an international call, and formally took over on the 1st Jan 2021 with a mandate for the next period as well.

B – EVALUATION AREAS

Considering the references defined in the unit's evaluation guidelines, the committee ensures that a distinction is made on the outstanding elements for strengths or weaknesses. Each point is documented by observable facts including the elements from the portfolio. The committee assesses if the unit's results are consistent with its activity profile.

EVALUATION AREA 1: PROFILE, RESOURCES AND ORGANISATION OF THE UNIT

Assessment on the scientific objectives of the unit

The IdV's scientific objectives are clearly defined and very ambitious. The institute conducts cross-disciplinary research in vision, benefiting diagnosis, treatment, prevention, and industrial innovation. It centres on understanding visual perception, exploring neurodegenerative disease pathways, developing vision restoration strategies, and creating advanced diagnostic tools. The IdV comprises eighteen research teams, combining state-of-the-art expertise, connecting with hospitals, and receiving strong support from authorities. They lead national organisations, secure substantial grants, and actively engage in prominent institutions like IHU, ensuring project success.

Assessment on the unit's resources

The IdV has extremely impressive resources at all levels. It has a very large workforce, excellent facilities and financial backing. The research unit's organisation ensures operational efficiency through various entities. It comprises support groups for management, including finance, HR, and general services. Additionally, a communication and fundraising team and an IT team facilitate transfer and communication. The unit excels in economic valorisation and has created twelve start-ups. Eighteen research teams operate under five axes, each supported by twelve core facilities. The Voir et Entendre Foundation aids in funding and managing grants. The unit is part of IHU FOReSIGHT, providing exceptional opportunities for links with clinical work. The IdV has secured funding from various sources, including many highly competitive grants. However, the building's high expenses, dependent on fundraising, are unsustainable. Some smaller teams face challenges, and maintaining technical expertise is crucial. The gender deficit in leadership roles needs attention.

Assessment on the functioning of the unit

The panel was globally very impressed by the functioning of the unit. The Institute excels in complying with regulations and guidelines, boasting a large workforce with effective HR management and intern programs. Promotions and gender balance are strengths, but leadership lacks gender diversity. Despite nine Health & Security officers, the absence of dedicated staff poses a risk. Vulnerable computer systems require immediate attention to safeguard critical data.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The IdV's overarching goal is to conduct translational, cross-disciplinary research in vision, benefiting medical diagnosis and treatments, public prevention, and industrial research, diagnosis, and treatment methods. This goal centres on the understanding of visual perception from development to ageing. Work on diseases is aimed at developing new diagnostic technologies, patient profiling methodologies and innovative strategies to restore vision or treat degenerative vision pathologies. The IdV's uniqueness lies in bringing eighteen research teams together, combining conceptual and technical expertise in a single location, working in direct connection with hospitals to achieve their objectives, and transferring the knowledge into practical application to diagnosis and treatment of patients. The project receives full support from supervisory and governmental authorities and is perfectly embedded in the local and national environment. The IdV leads several key national research and clinical organisations (DIM C-BRAINS, Biocluster Brain and Mind, Labex Lifesenses, RHU LIGHT4DEAF, IHU

FOReSight, Foundation Voir et Entendre) and contributes significantly to others (1 Labex, 1 Equipex, 1 RHU). The IdV's strategy is well supported by internal organisation, including management, research (12 technical platforms, 1 project construction team), industry (12 spin-off companies) and public transfer, communication (1 team), and education (over 160 supervised PhDs). The IdV's success in obtaining national and international grants [10 to 20 M€/year, individual and collective ERC grants: –70% – 230/317 – as PI (the involvement in leading organisations (IHU, Carnot) and the support of local bodies (CPER) for setting up innovative platforms has ensured the realisation of the institute's ambitious projects.

Weaknesses and risks linked to the context

Few weaknesses are associated with the clearly defined scientific objectives, for which the IdV has implemented a sound strategy to achieve their goals. The IdV's primary objective is operationally organised into five departments, each consisting of research teams with shared objectives and complementary expertise. This structure enables the pursuit of the four main questions:

1) Understanding visual perception and development;
2) Investigating neurodegenerative disease pathways and innovative therapies;
3) Developing strategies to restore vision in blind patients;
4) and Creating new diagnostic tools, technologies, and outcome measures for patient profiling.

While four of the departments (Development, Photonics, Information processing, Pathophysiology, and therapeutics) significantly benefit from a substantial number of participants, the Genetic Department has only two teams contributing to this area. The panel regards this as a potential challenge to the ambitious goal of deciphering the mechanisms underlying retinal disorders and developing future therapies.

2/ The unit has resources that are suited to its activity profile and research environment and mobilises them.

Strengths and possibilities linked to the context

The organisation of the research unit comprises several entities to ensure operational efficiency in terms of management, research, transfer, communication, and education. In terms of management, several support groups facilitate the unit's functioning, including financial and administrative management with ten personnel, human resources with two personnel, and general services handled by one person. For transfer and communication, the unit has a communication and fundraising team consisting of four personnel, responsible for project development and fundraising efforts, both at the national and international levels. Additionally, a three-person IT team manages technology-related aspects. The unit boasts substantial economic valorisation through collaborations with industrial partners and the creation of twelve start-ups. Regarding research, the eighteen research teams are organised into five distinct research axes: Developmental Biology, Genetics, Visual Information Processing, Photonics, and Pathophysiology and Therapeutics. The unit has twelve core facilities, encompassing animal facilities, biochemistry, the Biological Resources Centre NEUROSENSCOL, cell culture (cell lines, primary cultures, and iPS), DNA sequencing, flow cytometry, single-cell analysis, high-throughput screening, histology, imaging, phenotyping, and vectorology, each with a dedicated committee. The Voir et Entendre Foundation provides financial support for establishing four new teams and a research infrastructure, such as the E-Zebrafish facility, while managing numerous grants. The unit is a member of the Hospital-University Institute (IHU) FOReSIGHT, providing a strongly medical context on the campus of the National Hospital of Vision. In terms of obtaining funding, the unit has successfully secured various grants, including highly competitive ones in France, Europe, and beyond. These funding sources include Investments for the Future, the Public Investment Bank, the European Research Council, the National Institute of Health, the Foundation Fighting Blindness, among others.

Weaknesses and risks linked to the context

The IdV has been situated in its own building in Paris since 2009. The building's expenses are notably high and primarily depend on fundraising, particularly from the 'Voir et Entendre' Foundation, which strains the foundation itself. These costs are unsustainable since they are not covered by institutional sources and cannot be met through research contracts. While the unit's organisation aids in constructing and acquiring funding and provides access to state-of-the-art technologies through its platforms, some teams face challenges. These smaller teams have only shown modest improvements since the last contract. The team sizes vary significantly, with very small teams being vulnerable due to their size and lack of growth in the previous contract. The IdV has established twelve cutting-edge platforms for characterising cellular and pathological models. Twenty engineers with permanent positions are dedicated to the core facility. However, the demand for technical support is evident from the number of non-permanent IE and IR hires on Grants in recent contract years (88 and 35, respectively). The scientific objectives of the IdV heavily rely on new technical development and implementation, requiring highly qualified personnel. The low ratio of permanent researchers to technicians (0.5) poses a significant challenge in achieving the IdV's goals for the next contract. Ensuring the continuity of developed technical skills is essential for maintaining technological expertise, transferring knowledge to IdV

teams, and pursuing new cutting-edge developments. It is important to note a deficit in women holding department or team leader positions, with the exception of Departments 2 and 5.

3/ The unit's practices comply with the rules and directives laid down by its supervisory bodies in terms of human resources management, safety, environment, ethical protocols and protection of data and scientific heritage.

Strengths and possibilities linked to the context

Overall, the unit operates in compliance with regulations and guidelines set by its supervisory bodies, encompassing human resource management, safety, environmental practices, ethical protocols, data handling, and the preservation of scientific heritage. The IdV's staff count is notably high (933 people between 2017 and 2022). To address the potential challenges arising from this diverse and sizable workforce and to maintain a crucial connection between supervising bodies and staff, a permanent human resources manager has been overseeing staff recruitment since 2019. Furthermore, a dedicated manager handles administrative aspects related to hosting interns, leading to a substantial increase, with approximately 100 trainees annually across all levels. Additionally, the leadership of the Institute de la Vision has been remarkably proactive in promoting its members. In this regard, out of a total of 35 promotions that occurred between 2017 and 2022, twenty individuals received promotions during this period. IdV demonstrates a strong commitment to implement gender-neutral management and equitable hiring practices. At the unit level, a balanced gender representation is maintained (46% male and 54% female members and 51% male and 49% female students).

Weaknesses and risks linked to the context

Despite gender equity at the level of the IdV, only 5 women were occupying team leader positions at the beginning of the previous mandate (2019-2024) out of 18 teams but this has been corrected in the coming mandate (2025-2029) : 8 teams are proposed with woman team leaders out of 16 teams. While the institution boasts nine Health & Security officers, a noticeable gap emerges in the form of dedicated H&S staff. This absence of dedicated personnel is particularly striking given the substantial size of the institute and the high number of employees it accommodates. One of the primary areas of concern pertains to the robustness and security of the computer systems in place. The current infrastructure, as observed, does not meet the expected standards of resilience and security. This vulnerability in the computer system poses a potential risk to the confidentiality and integrity of sensitive data, which is of paramount importance in a research institution of this magnitude. Immediate attention should be given to enhancing the robustness and security of the computer systems, aligning them with the evolving standards and ensuring the integrity of critical data.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The visibility and attractiveness of the unit are outstanding. IdV is a highly renowned unit at the top of ophthalmology research in the world, thanks in part to the large range of approaches available. They cover developmental neuroscience, genetics, photonics and both translational & clinical research in a rich core facility environment. This enables an ecosystem that motivates excellent researchers to perform excellent transversal research. IdV has been very successful in recruiting new group leaders with four new teams. The number of permanent staff increased from 64 to 86 between 2017 and 2022. Despite the departures of 9 researchers for diverse reasons, IdV has attracted 27 new research staff. Regarding engineers, technicians and administrative staff, sixteen new staff joined IdV. Likewise, the number of PhD students significantly increased during the period. IdV members are involved in several editorial boards and scientific societies. They are also very active in organising meetings and scientific committees and have received several scientific prizes and awards. Finally, the scientific visibility and attractiveness can be measured by a high rate of success, as coordinator, to various and prestigious funding schemes (IHU, Labex, RHU, ERC, 14 EU, 1 HFSP) as well as>60 ANR-FRM-INCa-PHRC-Charities grants. The number of publications in high-profile journals also attests the international recognition of the expertise of the unit.

1/ The unit has an attractive scientific reputation and is part of the European research area.

2/ The unit is attractive because for the quality of its staff support policy.

3/ The unit is attractive through its success in competitive calls for projects.

4/ The unit is attractive for the quality of its major equipment and technical skills.

Strengths and possibilities linked to the context for the four references above

1/ The unit has an attractive scientific reputation and contributes to the construction of the European research area.

IdV is an internationally renowned unit, at the top of research in ophthalmology. The organisation by departments dealing with different but complementary fields from development to photonics means that state-of-the art expertise is present in a single institute. This allows the development of high value translational projects that set the ground for the institute's international visibility and scientific reputation. IdV is therefore highly visible nationally and internationally as particularly attested:

- by the numerous invitations to write reviews (114 among which: *Nature Reviews Neuroscience, PNAS, Curr Opin Neurobiol, Optics and photonics news, CMLS, Neuron, Brain Behav Immun, Trends Neurosci, Nature Methods, EMBO J, OSA Optics and Photonics, Biomedical Optics Express*…);
- by invitations to speak at national and international meetings: FENS, European Society of Human Genetics, Conference on Restoration of Vision, Human Cell Atlas, FENS, EMBO, IBRO, ARVO, NECTAR, ISER, IEEE, Society for Neuroscience, EVER, IOVS, Gordon, International Symposium on Uveitis, Annual Macula Society Meeting, ARVO, ISER, FENS, Retinal Degeneration Meeting…);
- by organising meetings (as chair or members of organising committees) among which: FENS Forum, EMBO YIP, Optogen, European Dry Eye Society Congress, European Society of Retina Specialists, European retina Meeting … (69 overall);
- by the involvement to an important number of French and international scientific committees (French Academy of Science, EMBO, SAB Fighting Blindness and many responsibilities in various scientific associations);
- by a remarkable number of publications in peer-reviewed journals (more than 50% as first, last and/or corresponding author) with some having attracted an unusual degree of attention (154 publications in the excellent journals over 1051 publications);
- by the several prizes and honors obtained at national and international levels (Inserm, Cnrs, Académie de Médecine, légion d'honneur, ordre national du mérite, Unesco women in science, Falling Walls Foundation, Duke University, ARVO, OPTICA, Fondation de l'oeil, SATT, Jean Valade…);
- by the recruitment of a large number of students (>170) and post-docs (>90). IdV has been successful in obtaining European and international funding, notably a European H2020-MSCA-ITN (IT-DED3) and MSCA grants to support training through research (doctoral and postdoctoral levels);
- by hosting seven visiting researchers from USA (Arizona State University, Oregon Health & Science University, University of Florida), Israel (Hadassah Hebrew University Medical Center), Italy (Università degli studi di Milano) and France (ENS, Université de Lille);
- by significant actions at the level of lay audience.

2/ The unit is attractive for the quality of its staff hosting policy.

During the last five years, IdV has successfully recruited or consolidated new teams and tenured staff, including the integration of four top-level new teams (Del Bene, Charpak, Emiliani & Tessier). Thanks to the Labex Lifesenses and IHU Foresight, all these new team leaders were granted 'seeding' funds for two years to launch their activities. Despite the recruitment constraints imposed by IdV institutions, the IdV's recruitment policy has been remarkably successful. Indeed, despite the departures of nine researchers for diverse reasons (1 DR1, 2 CR, 2 PU and 4 MCU), IdV attracted 27 new research staff. Sixteen of these were due to mobility, but no less than eleven are newly recruited researchers: 1 DR2, 6 CRCN, two PU, two MC. A further nine researchers were also promoted. Regarding engineers, technicians and administrative staff, despite departure of nine people, sixteen new staff joined IdV (3 mobilities with 13 recruitments and 12 promotions). Particular attention is paid to the quality of hosting upon the arrival of new PhD students and post-docs: a computer and office space is dedicated in shared rooms, private appointment by HR and various guides are provided (Welcome Book, Inside rules, Newcomer Booklet…), including bench based training by staff. New lab members work upon arrival with an experienced team member who coaches them for several weeks.

3/ The unit is attractive because of the recognition gained through its success in competitive calls for projects.

The overall amount of funding obtained by IdV is particularly impressive (136 M€). IdV has been successful in obtaining major European and international funding, including the H2020-MSCA-ITN (IT-DED3) training network. Among these grants, international funding by FFB, DARPA, Brain initiative and NIH represents 29% of the total. IdV also obtained a remarkable number of ERC: six ERCs were obtained before 2017 but still running (3 starting, 2 consolidator, 1 advanced, 1 synergy) but there are a further seven new ERC grants (1 starting, 2 consolidator, 1 advanced, 2 synergy). Other EU competitive grants include H2020, Horizon Europe and IMI projects. 14.8 M€ have been obtained through collaborations with private partnerships. Sixty-one percent of the funding has been obtained through national calls. Some of these are relatively classic (such as ANR, FRM and charities, with over 60 projects worth 35.9M€. But others, including LabEx and PIA are highly competitive (representing>47M€). Among the latter, IdV is coordinator of the LabEx Lifesenses, RHU Light4Deaf and IHU Foresight. IHU Foresight strongly connects IdV with the Hospital National de la Vision into a major care hub, allowing an efficient transfer preclinical studies to clinical practice.

4/ The unit is attractive for the quality of its major equipment and technological skills.

IdV researchers and clinicians benefit from several equipment clusters: Preclinical exploration platform (iPS, zebrafish facility, preclinical ophthalmology facility for rodents and non-human primates – at MirCEN); Cellular exploration platform (Imaging, Histology, FACS, Vectorology…); Molecular exploration platform (Biochemistry, sequencing, biological resource centre); and Rehabilitation platform (virtual reality, artificial street, driving simulator, low-vision centre). The IHU FOReSIGHT has supported the implementation and launch of the three most recent platforms (iPS, Single Cell, zebrafish facility) while completing the required investment contribution by grants from Région Ile de France. These facilities are accessible to all teams but also to industrial collaborators. A significant number of engineers and technicians (20) are dedicated to the core facilities. Most have permanent positions which is an asset to maintain high quality technical support in the various domains covered by IdV. Each platform is supervised by a scientific manager from one of the IdV's research teams. The coordination and financial aspects of the platforms are supervised by the general secretary. Each core facility cost is calculated for the different type of users (IdV members, academic, industrial). The revenue generated is reinvested into new equipment, replacement or maintenance.

Weaknesses and risks linked to the context for the four references above

Overall, no major significant weaknesses have been identified. Regarding recruitment, one weakness is the consequence of the limited levels of recruitment imposed by CNRS, Inserm and other IdV-related institutions. Related to funding, it could be very useful to try and integrate additional EU training networks. Regarding equipment, it will be a challenge to maintain, service and upgrade technical facilities not just for maintenance costs but also for maintaining adequate tenured technical staff. To upgrade facilities, space will be a concern, as for the entire institute.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

Globally, the scientific production of the IdV was found to be excellent to outstanding. The institute published more than 1,200 peer-reviewed papers during the reporting period, with many published in research field-weighted top ranked journals among which: Nature Reviews Neuroscience, PNAS, Curr Opin Neurobiol, Nature Methods, Optics and Photonics news, CMLS, Neuron, Brain Behav Immun… More than half of the original articles are signed in major position by at least one researcher of the institute. PhD students and Post Docs are well represented in the list of publications. The unit has been making efforts to comply with the need to respect fundamental principles of research integrity, ethics, and open science, with nearly 75% of the publications Open Access.

1/ The scientific production of the unit meets quality criteria.

2/ The unit's scientific production is proportionate to its research potential and properly shared out between its personnel.

3/ The scientific production of the unit complies with the principles of research integrity, ethics and open science. It complies with the directives applicable in this field.

Strengths and possibilities linked to the context for the three references above

The publishing record of the IdV is outstanding. According to the IdV self-evaluation documentation, IdV members published more than 1,200 peer-reviewed publications in the reporting period, including around 910 original articles and 300 review articles and other publications. An annual ratio of 2.5 articles per team per year is reached, but there are some teams that have a publication rate of 26 per year. In addition, it should be emphasised that around 90 of the IdV publications are signed by several teams – in one case four different teams were involved, which also underpins the excellent scientific collaboration at the IdV. The number of papers with IdV members as first author reached 381 during the 2017–2022 period and 43 in 2022. There is a fair contribution of Post Docs and PhD students (34% and 14% participation, respectively, in original publications and reviews) to the publication record. The main thematic field of the IdV's publications is clinical Medecine-Ophthalmology (523 articles, 46%) with excellent visibility (20% of them are ranked in excellent journals). An excellent visibility was also observed in the fields of Biochemistry & Molecular Biology (103 articles with 10.6% in the top 10%) and for the Medicine, Research & Experimental (25.9%). In their self-evaluation, the high quality of publications in high-ranking journals from 2017 to 2022 was also highlighted. Unfortunately, this measure procedure is not in line with the commitments agreed by Declaration on Research Assessment (*DORA*) since issues like the field-weighted of scientific publications is not considered. Nevertheless, an evaluation of the publishing record of IdV members in research field-weighted top journals reveals that about 60 articles are published in outstanding-, 225 in excellent-, 165 in very good – , and 160 in good journals. If the citation frequency and year of citation are also considered, 25 papers are listed among the top 1%, 66 among the top 5% and 68 among the top 10% publications published in the period of evaluation. All in all, on this basis, publication output (quality and quantity) is an indicator of research productivity the IdV is in an excellent position. In addition, the unit filed in a total of 61 national and international patents, which were submitted by fifteen teams. These range from one to nine patents per team. Unfortunately, no information on patent applications was provided by the other six teams. Number of patents and licenses translated to commercial products is not given. The unit has been making efforts to comply with the need to respect fundamental principles of research integrity, ethics, and open science. Internal quality control of data collection and verification of results and careful maintenance of laboratory records is given. Internal procedures of editing and reviewing manuscripts are established and a member of the scientific communication team helps the process. Author contributions and journal submission are discussed collegially and approved by the PIs in order to avoid predatory journals or conferences. The IdV adheres to the open-science policy by choosing open access publication options whenever possible with depositing published articles in the open HAL archives (73% of the total number of publications). The ethical principles of research on humans and with human sources as well as work with animals and the respective ethical authorisations are strictly adhered to at the IdV in accordance with the guidelines and directives of the relevant committees. For animal experiments, the SBEA, an animal welfare structure ensures the respect of the 3Rs rule, the training in animal experimentation and ethics. Clinical protocols in Humans are approved by CPP and ANSM.

Weaknesses and risks linked to the context for the three references above

According to the IdV self-evaluation report the IdV still ranks the impact of publications on the journal's impact factors (IFs), a measure which is not in line with the commitments agreed by Declaration on Research Assessment (*DORA*) as *requested by Hcéres*. For ranking of publications, the field-weighted of scientific journals and the citation frequency of the actual publications should be considered. Although the publication record of the IdV is overall remarkable and the proportion of original articles in top journals is roughly the same in all departments, there are clear differences in scientific output between the teams. These differences cannot be attributed to the number of team members or the composition of the team. A practice for identifying suitable distribution media and the fair authorship order is mentioned in the self-evaluation, but is not explained in detail. High publication rates and high publication pressure lead to increased scientific misconduct. The self-evaluation only mentions in general terms that care is taken to ensure the integrity of research, but no measures or procedural guidelines for scientists are referred to. Furthermore, there is no independent contact person for IdV members to deal with issues of scientific misconduct, predatory journal and no independent committee to assess such cases mentioned. In the self-assessment it is not mention whether Idv has the policy to provide raw data from original articles upon request from the corresponding author. This seems to depend on the editorial policy of the journal in which the publication is published.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

Assessment on the inclusion of the unit's research in society

Institut de la Vision excels in scientific communication, connecting researchers, institutions, and the public. Their strong engagement includes seminars, workshops, and media contributions. They stand out in developing products for the socio-economic world, filing over 60 patents, and creating successful start-ups. Proactive public outreach through teaching programs and events demonstrates a commitment to knowledge-sharing. However, the unit acknowledges limited visibility and calls for a strategy to improve it. Some teams need increased involvement in public knowledge dissemination.

1/ The unit stands out for the quality and the amount of its interactions with the non-academic world.

2/ The unit develops products for the cultural, economic and social world.

3/ The unit shares its knowledge with the general public and takes part in debates in society.

Strengths and possibilities linked to the context for the three references above

Institut de la Vision excels in scientific communication. They connect researchers, institutions, and the public, organising seminars, workshops, and courses. They are in close contact with national and international patient foundations for eye diseases. They host scientific events, offer educational programs, and maintain an informative website. Their active engagement extends to press releases, TV, and radio, along with initiatives for rare eye diseases. The Institute actively contributes to knowledge dissemination and community engagement.
The Institute de la Vision actively engages in nonacademic interactions to promote its scientific research and knowledge. They achieve this through scientific seminars featuring international experts and their own researchers, workshops on innovative eye disease imaging, and various scientific events fostering collaborations. Moreover, the institution welcomes local and international delegations to establish partnerships. Internal scientific events further encourage knowledge sharing and collaboration. These activities highlight their strong commitment to bridging the gap between science and the broader community, enhancing research in the field of vision and eye diseases. The Institute de la Vision distinguishes itself through its proactive nonacademic interactions, developing products for the socio-economic world, and sharing knowledge with the general public. It focuses on accelerating technology transfer, fostering innovation adoption, and partnering with private companies. With an aggressive intellectual property policy, the institute has filed over 60 patents. It has also been instrumental in creating several successful companies in the field of vision research (12 start-ups). Additionally, the institute actively engages with the public through teaching programs, annual open-day visits, and events like 'La Semaine du Cerveau.' Their strong media presence includes press releases, interviews, and a web-TV program. They organise conferences for patients with rare eye diseases and collaborate with major patient organisations. The institute's website keeps the public informed about the latest scientific discoveries and fundraising activities.

Weaknesses and risks linked to the context for the three references above

The IdV acknowledges that the unit currently has limited visibility among the general public. A clear strategy to enhance this visibility in the near future should be articulated. Additionally, there are few teams that have not been actively engaged in sharing their knowledge with the general public, and should increase their participation in such outreach activities.

ANALYSIS OF THE UNIT'S TRAJECTORY

The Institute de la Vision, established in 2008, is a globally renowned and dynamic unit conducting exceptional international and translational research in the field of ophthalmology. In the recent period, the Institute's research has produced significant outcomes, resulting in the advancement of cutting-edge techniques in photonics, treatment methodologies, and therapeutics for ophthalmic diseases. Some of these innovations have been successfully transferred to the industrial sector. The recruitment in the last years of new researchers and the creation of several teams with competencies and skills in visual system development, photonic and molecular microscopy, mathematical modelling or development of novel diagnostic tools strengthen the unit's capabilities in achieving its research, training, outreach, and transfer to industries and therapy objectives. The IdV has continued to significantly perform over the past period with a remarkable number of publications in prestigious journals (Science, Neuron, Nature human behaviour, Nature Neuroscience, Immunity, Nature Methods, Cell…). The excellence of the unit is also highlighted by the number and quality of national and international funding for an overall amount>80 M€. From IdV creation until now, the institute has been successful in growing and attracting young and senior researchers/clinicians. The basic and multidisciplinary research performed in the IdV take advantage of the beneficial and unique environment and the support of the academic institutions. The unit has been efficient to develop diagnostic tools for eye pathologies with technology transfer to the industry and the emergence of several start-ups through the partnership with the Carnot Institute and the Fondation Voir et Entendre. The project, which aims to comprehend vision, model ocular disorders and novel therapeutics, and define new diagnostic tools, is a continuation of the previous contract's activities for the next five years. Some teams have been closed in accordance with the institutions involved (INSERM, Université de la Sorbonne, CNRS, Hôpital de la vision). The departmental structure will be reorganised for the upcoming contract in accordance with the retirement or departure of researchers and the team's reorganisation. In order to advance omics and artificial intelligence methodologies and strengthen cellular biology, genetics, and clinical interactions, the IdV also seeks to attract new teams and hire supporting personnel with the adequate expertise. In terms of its organisation, the IdV is efficiently, democratically and transparently managed by a steering, ethical and a platform committee that comprise members of the departments and representatives of the support staff. It complies with rules regarding scientific integrity, gender parity, and ethical concerns.

RECOMMENDATIONS TO THE UNIT

Recommendations regarding the Evaluation Area 1: Profile, Resources and Organisation of the Unit

The IdV has superb science and excellent team leaders. Scientific expertise, enthusiasm and productivity are exceptionally high across teams. Scientific enthusiasm is high across leaders. We have some recommendations that could improve its performance even further.
The IdV has developed a superb research environment over the last ten years and now needs to turn to define its next long-term (10 years) strategy. This could be the opportunity to forge a new generation of leaders around a shared vision mixing both basic and clinical sciences. This ten-year project needs to be built together with the institutions and the rapidly growing environment for brain research in Paris.

Addressing structural, scientific and administrative issues

1. Mitigate the Director's workload by delegating some of his responsibilities, administrative tasks and organisational management, whilst fully respecting the Director's expertise and ultimate responsibility for the IdV. This could be done preferably by hiring a high-level administrative director. Consider mechanisms for how structural and political issues can be addressed in parallel with the ensemble of governing bodies and the team leaders.

2. Develop a more integrated plan and consolidate a common agenda, that is inclusive of the views and expertise of all the constituting teams, and implement better communication between all the teams and grades/functions of different personnel. Issues of control of growth and financial sustainability, as well as issues of mutual interest, should be at the heart of the agenda.

3. Improve strategic decision-making and management by setting up a committee of team leaders and others, to draw on the huge expertise and support of the team leaders. The group should discuss institutional matters and update on strategy and developments, including seeking opinions and input on new hirings and research direction, as well as space issues, and other administrative matters. In order to be inclusive, it would be desirable to have representation from all staff groups at these meetings, including at least one representative from the technical staff and one representative from the researchers.

4. Create a sustainable funding model, in view of the challenges of the current economic model for IdV, by ideally separating out the funds required for the rents from finding funds supporting science.

5. Develop a space plan and, if necessary, create a small steering group to manage this. Presently, there are major issues of space available for all teams which may have serious consequences if not addressed. Space for offices, think-tank discussions and seminars/conferences is too compressed; a new space plan also needs to include provision for future spaces for new research groups.

6. Create a program of scientific animation and seminars for the institute that incorporates external and internal speakers to share their work. Ensure that all members of the Institute play a role in the program design and invite speakers of interest. Such a program would be the foundation of a 'unit' spirit which fosters relationships beyond the scale of a department or a team. Provide a small budget for seminars that can be accessed.

7. Improve the level of internal collaboration which is low for some teams. Reinforce the internal networks for interaction and prioritise applications for collaborative grants.

8. Consider the creation of a platform of photonic imaging in view of the remarkable spectrum of expertise developed at IdV, to provide administrative support for the management of translational applications and encourage the internal sharing of technological tools across teams.

9. Address the administrative difficulties that impede scientific progress and create dissension should be addressed. This includes remedying severe delays in contractualisation (up to one year, leading to a loss of talented personnel's) and discrepancies in hiring salaries, streamlining processes around purchasing, etc., and management of finances.

10. Address issues in IT support by engaging with the governing institutional bodies to improve cybersecurity, big data storage and internet stability. Improve routes for data management and information flux are far from optimal.

11. Consider creation of an administrative post to manage health and safety.

People and inclusion

1. **Ensure that the voices of staff are heard** through representation of groups on committees/groups and efficient feedback of opinions and views to the team leaders and Director, and membership of the IdV steering committee as in point (3) above. Ensure gender balance as well as diversity of individuals are represented within the administrative structures and the staff overall.

2. **Introduce a protocol for welcoming new people** and induction process (students, postdoc et al., especially those from abroad). Offer internal information and emails in English as well as French for non-native speakers.

3. **Implement a structured approach to mentoring** of researchers and PhD students, involving allocation of a mentor when they join the Institute, allowing a pathway for them to gain professional and career advice, mentoring for grant applications and a way to raise concerns separate from their interaction with their team leader. Undertake yearly appraisals to record progress and set goals.

4. **Implement a clear and transparent strategy for applications by researchers for tenured positions**, and advertisements of such positions with equal opportunities.

The Director is encouraged to draw on the huge expertise and support of the team leaders, through regular meetings to discuss institution matters and update on strategy and developments. This would include seeking opinions and input on new hirings and research directions. In order to be inclusive and foster a positive culture, it would be desirable to have representation from all staff groups at these meetings, including at least one representative from the technical staff and one representative from the researchers.

The functioning of the mandatory and consulting councils (Conseil de Laboratoire, comité ITA/Biatss) shall be clarified and improved. IdV should clarify the roles of the different governing councils, how management decisions (staff ranking, promotions…) are made and explained to the whole Institution. The updating of the 'Règlement Intérieur' will be a good opportunity to do so. Moreover, annual budget lines should be clearly identified to key internal actions (scientific animation, training…) in line with (re)attributing collective missions to identified volunteers.

Researchers (and technical staff) would also benefit from a more structured approach to mentoring, which could involve allocation of a mentor when they join the Institute, allowing a pathway for them to gain professional and career advice and raise concerns separate from their interaction with their team leader, as well as a yearly appraisal to record progress and set goals.

In view of the remarkable spectrum of expertise developed at IdV, the panel recommends the creation of a platform of photonic imaging, to provide an administrative support for the management of translational applications and encourage the internal sharing of technological tools across teams.

Some of the problems mentioned by the personnel seem easy to overcome. The deficit in IT personnel should be solved by the governing institutional bodies. The hundreds of thousands of euros needed for cybersecurity, big data storage and internet stability should be provided without delay, in view of the global finances of this wealthy institute.

Recommendations regarding the Evaluation Area 2: Attractiveness

The IdV is already a very attractive place to do research, and has a vibrant and international community of students and postdocs. Nevertheless, it is clear that attractiveness could be further improved by increasing the number of group activities and research seminars which have yet to recover fully following the COVID pandemic. The institute has also been successful in attracting researchers from outside, but this has been limited by space constraints, particularly in the case of teams that have links to the hospital. It is vital that clinical research groups be provided with the space needed to fully develop their research programs.
Another area that could be improved concerns the interactions with the 'Institut de l'Audition', which is literally just rounded the corner from the IdV. There is a great deal of overlap in the research themes of the two institutes, and the attractiveness of the site could easily be augmented by increasing both scientific and social exchanges between the two sites.

Recommendations regarding Evaluation Area 3: Scientific Production

The Institute's publication strategy has clearly been very successful, with a very impressive list of high-quality outputs. The proportion of articles published in Open Access journals has been improving but could be even better. The institute can reasonably aim to reach 100% of open access journals in the forthcoming period.

Recommendations regarding Evaluation Area 4: Contribution of Research Activities to Society

The Institute's commitment to developing translational research strategies that can be of therapeutic value has been successful and should be strongly encouraged in the future. Activities related to the lay public could be improved, and would be particularly useful in generating additional research income via the 'Fondation Voir et Entendre'.

TEAM-BY-TEAM OR THEME ASSESSMENT

Team 1: DEVELOPMENT, EVOLUTION AND FUNCTION OF COMMISSURAL SYSTEMS

Name of the supervisor: ALAIN CHEDOTAL

THEMES OF THE TEAM

The team is studying the cellular and molecular mechanisms controlling the early development of neural networks and their connectivity in a variety of systems and several animal models (rodents, fishes, human), with a specific focus on commissural axons and on visual centres. They combine mouse genetics, cell biology and biochemistry with *in vivo* loss-of-function studies and cutting-edge 3D imaging technologies. The team is also working on continuing improving tissue clearing methods and 3D imaging methods to further develop applications, notably in human embryology in order to build the first developmental human cell atlas. Research focuses on basic developmental neurobiology, with putative medical applications in some pathological contexts, e.g. drug discovery in corneal disease.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

- The previous report suggested that the team focuses mainly on axon guidance. However, even if the visual system is not the exclusive system of interest in the team, it remains the focus for a significant part of the research developed by the group (attested by the track record), fully justifying the presence of the group at the IdV.
- A question was raised about most PhD students being supervised by the team leaders, however all three team members with HDRs now supervise students. It would be desirable to have adjunct supervisors, and although it is stated that mentorship involves more team members, it would be good to have more information about these arrangements. It was also mentioned that some co-supervisors were situated remotely, and this should be addressed. Efforts should also be made to render this visible in terms of publication.
- Some other comments were linked to a possible departure of the team leader that is not relevant as it did not occur.
- The question about diversity of the research themes was commented upon, and does need some clarification, also in regard to how applied research (e.g. corneal disease and therapies) is integrated and liaison between basic and clinical researchers occurs.
- With regard to the criterion around scientific strategy, it would be useful to get more clarity on how scientific leadership of different projects is managed within the team.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**7**
Enseignants-chercheurs et chercheurs non permanents et assimilés	4
Personnels d'appui non permanents	1
Post-doctorants	1
Doctorants	10
Sous-total personnels non permanents en activité	**16**
Total personnels	**23**

EVALUATION

Overall assessment of the team

Overall, the panel considers that this team is excellent to outstanding. It focuses on neural development, including commissural connections and eye development. The committee considers that the team is making outstanding contributions to several fields. These include key conceptual advances, pioneering 3D anatomical imaging and Human Developmental Cell Atlas with international visibility, and an emerging pipeline of translational work to address corneal disease. The team has excellent productivity, attractiveness and resources. The reliance on the team leader requires more delegation and team involvement; the group needs more long-term grant support.

Strengths and possibilities linked to the context

The team is internationally recognised for its work on early development of neural circuits, with an emphasis on commissural connections within the brain and human eye development. For instance, their work prompted a complete rethink the role of Netrin for commissural axon guidance (Nature 2017); in the field of neuro-evolution, they demonstrated that bilateral visual projections precede the emergence of binocular vision in tetrapods (Science, 2021). The team is also internationally recognised for pioneering tissue clearing methods applicable to different species, including human tissues, giving 3D high resolution anatomical insights. Together with an international consortium the team is involved in the establishment of the first human developmental cell atlas (HuDeca). Basic science-clinical collaborations are giving the opportunity to use transgenic lines to investigate corneal innervation in health and disease. The PI is world-leading in his field, as evidenced by an impressive number of invitations to conferences and international meetings (46 invitations over the evaluated period). Moreover, he has been awarded several prizes and was elected to EMBO and the French Academy of Science. The team has an impressive list of publications since 2017, with a significant number of papers in high impact journals, including one in Cell, 4 in Nature, one in Science, five in Neuron, two in Nature Neuroscience Reviews and one in Nature Neuroscience. Overall, the team has a high degree of productivity with 133 publications including 46 original scientific papers, fifteen of which have been co-authored by one or several PhD students, 18/46 have first authorship of one team member and 21/46 as last author. There are fourteen reviews over the evaluated period, with a significant contribution by clinicians (73 clinical articles), with senior clinician authors (Sorbonne). The team's ability to raise funds was excellent/outstanding over the past period with recurrent national and international grants (~1000 k€), involvement in French consortia (HuDeCa, IHU, Cell-ID) and several large international networks (Wellcome Trust HDBI, CIFAR Multiscale Human, NIH) as well as some financial support from collaborations with industry (for ~700 K€) or foundations (~400k€, FRM; Unadev, Genespoir). The team has trained fifteen PhD students (6 foreigners) and several post-doctoral fellows. Four PhD students defended during the evaluated period. All students have conducted successful post-docs and several hold permanent positions (France or Spain).
Three team members (including the team leader) have defended their HDR, improving the future capability of the team to host and train PhD students. The team has ambitious plans for the future, building on synergies between neuroscientists and clinicians to investigate corneal nerve development, neuro-immune interactions and using molecular and anatomical techniques to map human eye development at the single cell level.

Weaknesses and risks linked to the context

Although the overall performance of the team is excellent, there are some weaknesses and risks. There is a strong reliance within the structure of the unit on the team leader for promotion of reputation, including conference communications and for obtaining grant funding. The team leader is also overwhelmed by administrative tasks and other responsibilities in and outside the lab (scientific director of 3 core facilities at IdV, member of several scientific boards). It would be desirable to delegate these responsibilities more to the other team members, including leadership, in order to contribute to their professional development. The other team members should therefore improve their participation in the activities. Further clarification is needed on how the team contribute to strategy development, as there appear to be one postdoc and 2 permanent researchers (Alexandra Rebsam (CR INSERM) and Yorick Gitton (CR CNRS), but a larger number of doctoral students and technicians, and two clinical Professors with affiliations elsewhere.

- What plans are there to create 'lieutenants' to contribute more to activities?
- How is the development of independence by postdocs and gaining experience of grant applications/student supervision/senior authorship ensured?
- How are the PhD students supervised, and the load spread?
- Are the clinician team members fully integrated into the team's activities?

The team's plans also appear to involve predominant development of translational directions, anatomical and 'Omics' technologies. The difficulties of obtaining grants for basic research are alluded to. There is also a limited number of collaborations inside IdV and with clinical groups.

- What are the plans for obtaining long-term grant support?
- How will the team organisation underpin the change in strategic direction and field, given the level of ambition?

Sixty percent of the technical staff are not permanent, inducing a constant turnover with the risk of losing skills and knowledge, especially where sophisticated techniques are involved.

- What are the plans to lobby for more permanent posts and where are the impediments?

Finally, despite a high number of PhD students in the team, only four of them defended during the examined period.

Analysis of the team's trajectory

The future projects build logically on the previous track record, but provide very ambitious prospective, moving forward on two main fronts; corneal nerve development, diseases and treatments, and high resolution anatomical and molecular studies of the eye and other systems, including the pelvic ganglia. Based on the information provided, this seems to signal a more translational and applied research program, with less focus on basic developmental neuroscience (e.g. commissure formation).

Studies are oriented towards the investigation of the development and plasticity of corneal nerves, together with their interactions with immune cells in different mouse models of corneal diseases. First, the team proposes to describe the remodelling of corneal nerves after eye opening using live microscopy performed on several transgenic mouse lines. They will also study the interaction between regenerative axons and macrophages in two pathological contexts (diabetic corneal neuropathy and neurotrophic keratitis). Second, the group plans to continue investigating the 3D organisation of several organs and systems in transparent human embryos and foetuses using the cutting-edge approaches they have pioneered (whole mount immunostaining, clearing tissue and 3D imaging). Some of the work will focus on the development and characterisation of the pelvic ganglia, which is relatively unexplored, though the main emphasis will be on the developing human eye. The final goal is to establish the first Human Developmental Cell Atlas (HuDeca) with an unprecedented cellular resolution, across different developmental stages of the eye. Anatomical data using light sheet imaging will be combined with single cell and spatial transcriptomics to build a picture of the eye and the retina in particular, with adjunct work on retinal ganglion cell projections. The HuDeca atlas will be useful for general knowledge, better understanding of various eye diseases of developmental origin and also help the search for therapies. The proposed work will expand the knowledge on human eye development and explore the problem of poor vision in albino individuals or new areas like corneal diseases and innervation.

The proposed research programme is highly impressive, utilising both the excellent technical platforms of IdV and several international consortia and networks. Funding and solid collaborations should help to ensure success of the programme. The data generated will be of great importance to both the basic neuroscience and clinical communities, as well as eventually for healthcare practice. Given the scale of the ambition, the programme will require very careful management, and will hopefully allow a case to be made for more permanent positions within the team.

RECOMMENDATIONS TO THE TEAM

The team would benefit from an increase in the involvement of permanent researchers in participating more significantly in obtaining funding, training students and giving conferences at national and international meetings. To maintain the inclusion of technical staff as authors in publications is an excellent way for their crucial work to be recognised and will help for their career. This should be continued. It is recommended to secure the financial support over a longer period by obtaining long-term grants.

Team 2: RETINAL DEVELOPMENT AND REPAIR: USE OF PLURIPOTENT STEM CELLS

Name of the supervisor: OLIVIER GOUREAU

THEMES OF THE TEAM

The team's research focuses on unravelling the mechanisms involved in both the development and pathophysiology of the human retina and on the advancement of new therapeutic approaches for patients with visual impairment. To achieve this, the team utilises innovative 2D and 3D cell models obtained from human pluripotent stem cells, including retinal organoids.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

During the previous evaluation, concerns emerged regarding project dispersion, the distinctiveness of this team compared to others in the same field, its capacity to add values from its findings and secure long-term fundings, and the deficit of trainee scientists. In the competitive field of iPSC, the team has managed to gain international recognition for its innovative models. These advancements fostered collaborations, yielded several publications in reputable journals, initiated a clinical trial, and resulted in five patents. Over the last term, the team bolstered its workforce with the recruitment of five engineers, supervision of six PhD students (four defended, two ongoing), and two postdoctoral researchers. An additional HDR in 2023 will strengthen the training of scientists. Long-term funding capacity has been improved through grants within the IHU FOReSIGHT framework and private partnerships. However, projects remain broad.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**5**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	4
Post-doctorants	1
Doctorants	2
Sous-total personnels non permanents en activité	**7**
Total personnels	**12**

EVALUATION

Overall assessment of the team

The team has developed unique innovative organoid cell tools and acquired a worldwide renowned expertise in the field of iPSC and organoid technologies. The scientific production of the team is excellent to outstanding and its capacity to obtain funding from various sources is particularly remarkable. Valorisation has also been excellent during the last mandate. The time of the team devoted to teaching is significant. Overall, the panel considers that the team is excellent to outstanding, and it is strongly encouraged to seek further long-term funding, along with expanding permanent staff for sustained scientific project feasibility.

Strengths and possibilities linked to the context

This team is one of the pioneering teams in iPSC-based organoid technology in the field of vision research and has acquired a leader position by developing new organoid cell tools and by acquiring expertise in the fields of

iPSC. The work of the team has been recognised with the 'prix de l'oeil' from Fondation de France awarded to the group leader. Given the size of the team, the scientific production has been excellent to outstanding in the last mandate with 29 original articles, four reviews and three book chapters (with a member of the team being the first or last author in 11 articles, 2 reviews and 3 chapters) in specialised and multidisciplinary reputable journals (Science Trans. Med, Biomaterials, Nat Commun, PNAS, Cell Stem Cell, J. Clin Invest). Scientific production highlights numerous active collaborations. All PhD students who left the team between 2017 and 2022 signed at least one publication as first author, with an average of 2.5 publications per postdoc/PhD student. The capacity to obtain funding has been outstanding (25 funded projects, 4.6 M€ between 2017–2022). This funding has been obtained from various sources (academy, foundations, patient associations, industry). The team has been also involved in different French scientific networks and in two PIA applications which has allowed the acquisition of new equipment and instruments and the recruitment of engineers. The attractiveness of the team is attested by 21 communications at conferences (with 14 invitations of the group leader to give seminars at international meetings), several collaborations established with external and internal teams, the funding of 25 projects and the establishment of a new 'human iPS cells – organoid' platform at the Institut de la Vision. The capacity to train students is very good with the host of two post-docs, six PhD students, 7 Master2 and five Master1. This capacity for training will be increased in the future thanks to an additional HDR in 2023. The team is also deeply involved in teaching students by contributing to Master programs in different universities. The level of innovation and translational research are all excellent with one ongoing clinical trial, four patents and the co-foundation of the company Tenpoint Therapeutics. The team also shares knowledge actively with general public through patient's association (organisation and participation to regular meetings, member of the scientific council of the association Retina France), articles in general journals, debates.

Weaknesses and risks linked to the context

Overall, there are no major weaknesses. However, it was noted that communications in conferences almost exclusively rely on the team leader, so the other team members should improve their participation.
The proportion of permanent staff is quite low, which might affect the transmission of the wide battery of skills, techniques and knowledge for the future. This is particularly crucial given that the projects rely on highly skilled techniques and involve lengthy protocols.
While successful in securing funding, the team has acquired limited European/international resources, and the obtained grants (for 2–3 years) do not provide long-term visibility.

Analysis of the team's trajectory

The future projects of the team align with their previous studies. Firstly, the team proposes to further explore the potential of iPSC-derived photoreceptor precursors for transplantation and restoration of vision, using different models (rats, non-human primates) and multiple approaches based on optogenetic, genome editing and bioengineering. Secondly, the team plans to generate organoids from patient iPSCs (carrying different mutations in *Rhodopsin* gene) to model certain forms of Inherited Retinal Diseases (IRDs) such as Retinitis Pigmentosa. The goals of these experiments are to identify the molecular and cellular mechanism(s) responsible for the disease and to develop new cell models compatible with High-Throughput Screening and drug discovery. In parallel, the team also aims to improve their retinal organoid technology by covering their organoids with a layer of Retinal Pigment Epithelium (RPE) to get closer to an adult outer retina. Thirdly, the team will use their different iPSCs-based retinal models (made for the generation of large numbers of multipotent RPC cells, mature RPE, photoreceptors or Müller glial cells) for drug screening.
The project is ambitious and aligns well with the expertise of the team. The technological developments proposed by the team are innovative and should open new avenues for understanding the development of the human retina and advancing therapies for visual impairments. The financial support is robust for the next few years to support the development of the various projects. However, projects are broad and seem disproportionate compared to the number of permanent staff in the team.

RECOMMENDATIONS TO THE TEAM

The team needs to develop more focused projects to avoid dispersion and to remain competitive. The team is strongly encouraged to further secure long-term funding by applying to European/international grants and recruit permanent staff to develop their diverse ambitious projects. As the group leader will reach the age limit at the end of the next term, another recommendation concerns the future of the team, which should be prepared sufficiently in advance.

Team 3: DEVELOPMENT AND FUNCTION OF THE VERTEBRATE VISUAL SYSTEM

Name of the supervisor: FILIPPO DEL BENE

THEMES OF THE TEAM

The main interest of the group is to better understand neural circuit formation and activity at the cellular and molecular levels in the visual system, using zebrafish larva as a model system. Their interdisciplinary investigations employ cutting-edge techniques (in vivo imaging, genome engineering…). Their specific interests lie in unravelling intracellular and extracellular regulation of neuronal development in the visual system. They are also particularly focused on the role of commissural inhibitory interneurons in binocular visual information integration. The team is also devoted to developing CRISPR/Cas9-based genetic tools for precise genome editing in zebrafish, enabling the creation of new models for basic research and gene therapy approaches for various human diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team appears to have considered the recommendations of the previous report. For example, in order to improve interactions with clinicians and geneticists, the group has established promising intramural and international collaborations, notably in the context of an EIC pathfinder grant coordinated by the team leader and that involves several European labs as well as a company. The team has also been awarded with an ERC-synergy grant that will increase its international collaborative network.
The recent recruitment of a former post-doctoral fellow as a permanent INSERM researcher not only adds stability but also strengthens the team's expertise and workforce.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**3**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	3
Doctorants	3
Sous-total personnels non permanents en activité	**8**
Total personnels	**11**

EVALUATION

Overall assessment of the team

Although quite small, this team has made several notable scientific and technical contributions. The scientific production of the team is outstanding as well as training. Financially robust, it demonstrates excellent attractiveness, evidenced by international recruitment and collaborations. Overall, this team, internationally recognised, is very active, dynamic and productive. Overall, the committee considers that the team is outstanding but raises a concern about potential project dispersion. Integrating additional permanent staff would be beneficial, especially given the ambitious proposed projects.

Strengths and possibilities linked to the context

The team is nationally and internationally recognised for its work on the visual system with a specific interest in better understanding its development and functional properties as well as evolutionary adaptations. Notably, the team provided the evidence for an attractive gradient of Reelin that is involved in establishing synaptic lamination in the vertebrate visual system (Neuron 2018) and, in a more evolutionary aspect, they demonstrated the existence of ipsilateral retinal projections in ancestral fishes, challenging one of the most established dogmas in the field of developmental neurobiology (Science 2021). The team has also devoted considerable effort to developing new tools to manipulate with an unprecedented precision the genome of the zebrafish in order to be able to introduce human disease-causing mutations in zebrafish as animal models for human pathologies (Nat Comm 2022, eLife 2021). The worldwide recognition of the group leader is attested by several international/national collaborations established with scientists and clinicians, several prizes and nominations (EMBO member, FSER, Fondation Del Duca, ERC). The scientific production is impressive given the group size, i.e. 28 articles between 2017 and 2022 with 16/28 articles signed first or/and last authors. The research performed in the group is excellent and fuels a track record of a high quality: one Science, one Nature Methods, one Neuron, two Nature Communication, etc. Also, 3/3 review articles (Curr Opin Neurobiol, Front Cell Dev Biol, Methods) and one book chapter are signed first and last authors, including by PhD students. Over the past period, the team capacity to raise funds has been outstanding with national, European and international grants for a total amount around 8M€, including one ERC-synergy grant, 6 ANR (1 as a coordinator), one EIC Horizon Pathfinder (coordinator), one NIH, two FRM, two IHU internal projects. Consequently, funding is secured for the next several years. The reputation of the team is underscored by an impressive number of invitations for talks at European and international meetings that involve all team members (46 conferences) and the organisation of three international meetings since 2017. The attractiveness and capacity to train students are of a high quality with the hosting of 4 post-docs (2 from abroad) and 6 PhD students (4 from abroad) all supported by competitive fellowships (FRM and international programs). Six PhD and one HDR defence occurred during the examined period. In addition, all post-docs and PhD students have produced at least one first author publication, with an average of 3.5 paper per team member. The team is actively involved in teaching in international and national courses (European training network, classes for Master students) and implicated in several scientific outreaches towards general public (DECLICS program, semaine du cerveau, Fête de la science,..).

Weaknesses and risks linked to the context

The group seems undersized given the very ambitious nature of the proposed project and the increasing administrative load on the group leader. The development of novel tools to manipulate the zebrafish genome is undoubtedly very attractive for direct collaborators and other research groups in the field but raises the risk of being involved in too many projects. The team leader should pay attention to this risk in order to avoid dispersion. The technical staff is predominantly non-permanent, leading to a continual turnover and the potential loss of skills and knowledge.

Analysis of the team's trajectory

The future projects of the team are in direct continuity with past research and deal with the investigation of the role of 1) redox signalling in retina development and neurogenesis; 2) GFI1ab in the establishment of a specific retinal ganglion cell population; 3) commissural neurons in visual integration in the optic tectum and 4) axonal transport and tubulin post-translational modifications in the development and correct function of retinal ganglion cells. Concurrently, in a collaborative project Horizon Pathfinder they aim to advance new genetic approaches applicable to both basic research and gene therapy.
Overall, the proposed project is very ambitious and might be oversized in comparison with the number of permanent researchers presently composing the team. However, the team has obtained an impressive amount of funding that should allow hiring people to significantly increase manpower.

RECOMMENDATIONS TO THE TEAM

Given the ambitious project proposed, the group should exploit any opportunities to recruit additional permanent researchers/technical staff to strengthen the workforce and potentially incorporate new expertise.
The team leader should be cautious not be overwhelmed by managing too many diverse projects

Team 4: NEUROGENESIS AND CIRCUIT DEVELOPMENT

Name of the supervisor: JEAN LIVET

THEMES OF THE TEAM

The team is interested in deciphering how neural stem cells are generated during early development and later how their lineage impacts functional circuit formation. Key questions concern whether neural progenitors from the same clone form part of the same circuit. To achieve its goals, the team has invested a lot of effort in developing genetic and optical techniques for multiplex lineage tracing, circuit mapping and large-volume 3D imaging, with a specific focus on retina and cortex, using mainly mice but with some work on the chick. There is a strong emphasis on technology development, asking some fundamental questions about neural development, and the aspiration to study how lineage relationships are altered in disease states.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

One weakness identified in the previous report was a lack of permanent researchers (one previous permanent researcher has left and only the team leader is permanent). The team leader argues that this has been temporarily solved with the recruitment of a researcher with long-term ERC funding. However, the team leader has been lobbying the Sorbonne University since 2018 to obtain an MCU position affiliated to the group. The lack of permanent posts created concerns for the feasibility of achieving goals across the broad range of projects. The team leader makes a good case for that the projects are related and synergistic. Nevertheless, the workload and management remain an issue. Another reservation was the lack of senior author publications. During the evaluated period, the productivity significantly increased with the publication of several papers (16 peer reviewed articles), some which were very high impact, with five senior author publications by the team as a whole (3 by the team leader). Some of the technological discoveries of the group have had a lot of impact.
Economic impact was also mentioned as an issue, however, during the assessed period the team improved 1) its external interactions, with one patent application and several public communications, and 2) its involvement in training. The issue of lack of own imaging system was also addressed by the acquisition of a multichannel imaging system fully devoted to the team.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**2**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	1
Doctorants	5
Sous-total personnels non permanents en activité	**8**
Total personnels	**10**

EVALUATION

Overall assessment of the team

The scientific objectives of the team focus on the early mechanisms of lineage and connectivity in the retina and cortex, using several unique lineage tracing, genetic manipulation and imaging approaches. The committee considers that the team is technologically world-leading, is developing highly innovative tools with potential of broad impact and shows excellent scientific production and funding (<3M€). One issue remains the challenge of maintaining a broad program with a small team, and the need to ask scientific questions that offer the potential for conceptually significant advances. Overall, the panel considers that this is an excellent team.

Strengths and possibilities linked to the context

The group shows a high level of technical innovation in the development and application of sophisticated imaging techniques to trace, map and identify the connections of single neurons, as well as to manipulate them genetically. They have developed precious tools which can be used by the community broadly and have applications beyond development. The team leader is renowned for developing labelling and imaging approaches with an excellent track record. International recognition of the team is attested by the significant number of invitations at national and international meetings (n=17). Between 2017 and 2022 the team had very good productivity, and published sixteen original papers and one review, including high-impact papers (e.g. Neuron – 2 –, Nat Comm – 2 –, Plos Biol – 1 –, Plos Comput Biol – 1 –; 50% of team members in first and/or last position). Key findings included establishing how astrocyte precursors colonise the cortex during the prenatal developmental period (Nat Comm, 2019), revealing principles by which the same progenitor can generate two astrocyte subtypes. They also developed a new strategy (named iOn for integration-coupled On genetic switch) to accelerate and simplify genetic engineering in culture systems and model organisms (Neuron, 2020) and an advanced large-scale microscopy approach allowing bi- and tri-dimensional multicolour imaging (Nat Comm, 2019). The development of state-of-the-art approaches to label and image specific neurons are of primary importance for all groups interested in ontogenesis and circuit formation. Their national and international funding is also excellent and long-term thanks mainly to ERC grants (ERC consolidator and ERC Synergy; total of 5.8 M€ since 2017). The team shows an excellent capacity to train PhD and postdoc fellows with three theses defended (with 2 thesis prizes) over the examined period with more to come (n=3) and six post-docs present in the team between 2017 and 2022. Moreover, the work of PhD students and post-docs is generally included in high-level publications (in average 3 per PhD and 2 per Post-docs). All past PhD and post-docs have obtained positions in academia or industry and two emerged as independent researchers, testifying to the excellent training.
The team's ambitious plans involve mapping the lineage and architecture of the retina and the cortex to decipher the rules of stem cell dispersion and connectivity, as well as further technological development. There are many possibilities here, of collaborations inside the institute as well as broad collaboration and applications externally.

Weaknesses and risks linked to the context

As highlighted by the previous report, the team's productivity and progress clearly suffer from the low number of permanent researchers in the group. This has been mitigated by long-term ERC funding, but it would be useful to know whether further recruitment is a prospect.
The team leader has a world-leading reputation in producing sophisticated tools for cell labelling and genetic manipulation, and is an asset to the IdV. It will be important that in tandem with the creation of ever-more sophisticated technologies, there is clarity as to how the experiments proposed will contribute to an increased conceptual understanding. Given the power of the technical approaches, there are difficult decisions to be made here about the scientific direction with careful prioritisation around the high number of collaborations relating to work in a wide variety of cellular types (neuronal, ependymal or glial cells), structures (cortex, retina, cerebellum, motor circuit), and regions of interest (central nervous system, peripheral organs, animal models).
In the context of the future program it appears that the majority of the work is on cortical development, whereas work on the retina focuses on the chick rather than the mouse. This is due to the fact that the MAGIC Markers and iOn schemes, relying on electroporated genome-integrating vectors, are easily applicable to the chicken embryo, and this model facilitates access to the early embryonic stages at which NPCs proliferate. Also, key results obtained in the chick are replicated in mice. There is much potential here for the group to team up their expertise with the groups working on stem cells and organoids, and this could be more clearly articulated.
Overall, the field of lineage studies in the brain is a very competitive one, with rapid technological development (e.g. use of somatic cell mutations to track cells), and the positioning of the group within this competitive context will be key for its future success.

Analysis of the team's trajectory

The proposed projects are in direct continuity and follow logically from previous work. The team will use a multidisciplinary approach based on the unique methodologies they have developed in the past contract to examine in situ the organisation of entire CNS regions at a single cell resolution level while following the developmental history of individual neural cells through a multiplex clonal strategy. Within the framework of the ERC Synergy grant, previous approaches using lineage tracing and 3D imaging on astrocytes will be reiterated on neurons in the retina (as a direct follow-up of the past work) but also in two new brain regions: the neocortex and the hippocampus. Models proposing clonal relationships between small groups of pyramidal cells will be tested, for example. Genetic manipulation of cells is mentioned as a possibility. There is great strength in these approaches, which are proposed to model the pyramidal cell ensembles and to apply computational modelling to understand patterns of dispersion and later circuit formation.
With the support of another ERC grant (Proof of concept program 2020), the team also projects to continue developing genetic tools for stem-cell studies not only for fundamental science but also for numerous biotechnological and biomedical applications. The goal is, on the one hand, to optimise the present methodologies using iOn vectors and, on the other hand, to expand the range of applications in neurodevelopmental studies and more directly applied purposes (with possible related patents).
The team members have made a huge contribution to the field, and have a good strategy, including relevant collaborations to enlarge its ability to map the development and circuit formation of the cortex. The future program of work is exciting and timely, and has the potential for further patent development and technology transfer.

RECOMMENDATIONS TO THE TEAM

The team should seriously take into consideration all opportunities for recruiting more permanent researchers, hopefully with the help of the Sorbonne University.
After having invested a lot of time (previous assessment period) in developing original state-of-the-art labelling and imaging techniques, the team leader should pay attention to developing a clear niche in a competitive field, and in applying these advanced methodologies to address scientific questions that will end in conceptual innovations. The potential to synergies with other groups working on the eye and eye development could be explored more, including working on the mammalian eye and organoids. Potential synergies in some of the proposed approaches within IdV for eye diseases could also be considered.

Team 5: MECHANISMS OF SENSORY MAP DEVELOPMENT

Name of the supervisor: XAVIER NICOL

THEMES OF THE TEAM

This team is interested in uncovering the intrinsic mechanisms driving the development of neural networks (neuronal migration, axon guidance and pruning), mainly in the visual system. In particular, the team focuses on the contribution of secondary messenger pathways (cAMP, GMPc, Calcium) in different sub-cellular compartments but also, more recently, into the role of cytoskeleton remodelling in these developmental processes. The research axis of the team is important to understand the mechanisms that guide axons and shape connectivity in the visual system.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Several concerns were raised during the previous evaluation in particular the weakness of the scientific production, a limited interaction with the non-academic world, the size of the team in relation to the feasibility of the ambitious project and the lack of PhD students. All these concerns have been efficiently overcome.
First, the last five years researchers of the team published twelve original articles, seven as last author and two as first author, in excellent journals such as Cell reports (3 times) and J Cell biol (2 times). A paper has been just published with the PI as last author in Nature Communications. The team also published five reviews during this period.
Second, the team significantly increased interactions with the non-academic world with two patents granted about the original tools developed the last years (sponges inhibiting Ca2+ or cGMP signalling), connection with patient associations (Unadev, ASL-HSP) as well as lay audience events.
Third, the team currently includes twelve members and will reach fifteen at the end of 2023, leading to an increase of the scientific production for the last years. In addition, three PhD students have defended the last few years, four are currently members of the team and two will join in October 2023.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	3
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	4
Post-doctorants	2
Doctorants	4
Sous-total personnels non permanents en activité	10
Total personnels	13

EVALUATION

Overall assessment of the team

Globally, this is an excellent to outstanding team. Using state-of-the art and original in-house developed tools, the team performed an impressive in-depth characterisation of the role of second messengers at cellular sub-compartment levels as well as of the cytoskeleton remodelling in the development of the visual system both in vitro and in vivo. The committee considers that the team is on an excellent dynamic curve and carries out exciting research projects coupled with excellent to outstanding publications. The team members have an excellent academic supervising activity and outreach activities with a significant (and voluntary) time devoted to teaching.

Strengths and possibilities linked to the context

This is an excellent young team that developed a project aimed at deciphering the mechanisms driving the connectivity during the development of the visual system with a particular attention towards the role of second messengers such as cAMP, cGMP, calcium as well as the role of the cytoskeleton remodelling, in particular of microtubule-severing enzymes. These are innovative and competitive lines of research that perfectly complement other thematic developed at the institute. To achieve this goal, the team developed innovative and invaluable tools (2 patents) allowing the analysis of the role of these second messengers at the subcellular level, notably at lipid rafts, combined to new high-resolution imaging and FRET devices applied to in vitro, zebrafish and mouse models including computational modelling. This technical development, that allows the manipulation of subcellular second messenger signals to understand how they control the development of neuronal networks between the retina and the brain will have more broad impact, in particular with the identification of potential therapeutic targets for other developmental processes in order to restore functional connectivity in a pathological context. The project is ambitious but feasible. The committee considers that the scientific production has been largely improved the last years and is currently excellent or outstanding. The team has proven its attractiveness in recent years. First, for such a small team, they published a significant number of excellent (Cell Reports, J Cell biol) to outstanding (Nature Communications) papers. The level of innovation is excellent with two patents and large distribution of their innovative tools in the community through Addgene repository. The attractiveness of the team is also attested by the significant number of grants obtained as PI or partner from ANR, IHU, foundations (FRM, UNADEV) and patient organisations including EU funding though a Marie-Curie Doctoral Network for an overall amount exceeding 3M€. Since 1997, the team attracted three post-docs and three PhD from abroad thanks to an EU MSCA network. The team also shared knowledge through scientific meetings or invited seminars but also to general audience through patient associations or more general events such as Brain Awareness Week. It is also worth mentioning that Xavier Nicol, who is a full-time researcher, has been strongly involved in teaching activities at Ecole Polytechnique for several years (60 h/years) as well as instructor to the renowned Cajal program of FENS (3 weeks/year). He is also responsible for the biochemistry platform of the institute.

Weaknesses and risks linked to the context

Overall, there are no major weaknesses. However, the committee considers that the interface with other teams of the institute should be further developed, for instance, with geneticists or other developmental teams. Another question relies on the long-term relevance of the research axis investigating the role of spastin in motor circuit development and degeneration in the IdV environment focused on the visual system. PhD publications as first author can be improved. Another concern is the lack of space that can slow down the development of new imaging tools.

Analysis of the team's trajectory

The trajectory of the team is in direct line with previous work, aimed at understanding the developmental events that shape the visual system. The team aims to go deeper in the understanding of subcellular control of second messenger signals by axon repellents, guidance of growth cones as well as their role at contact points of the RGC axons. Another point of interest relies on the link between the cytoskeleton remodelling and the subcellular second messenger signals in neuronal circuit wiring. In order to provide a general view how these messengers specifically control signalling events downstream of axon guidance molecules, the team aims to develop computational modelling of axon guidance by these second messengers in collaboration with INRIA. Finally, the team will investigate the role of microtubule-severing enzymes more particularly how cytoskeleton rearrangements they control affects the development of the visual system.

RECOMMENDATIONS TO THE TEAM

This young team is on an excellent dynamic curve with outstanding promise that nicely translated by the development of innovative tools to challenge original scientific questions. The contribution to teaching should be acknowledged. The co-direction of the team by two leaders sharing complementary expertises in cell biology is an asset to achieve the project envisioned. A potential area for improvement will be to increase the number of PhD publications as a first author. The committee encourages the team to develop further collaborations within the institute and translate their original toolsets for translational applications at both the local and the european levels. Interactions with other teams of the institute that could be developed include work with geneticists, but it is clear that translational application will arise from the recent findings notably in pathologies associated with an excess of Ca2+ and/or cGMP such as Retinitis Pigmentosa.

Team 6: IDENTIFICATION OF GENE DEFECTS LEADING TO NON-PROGRESSIVE AND PROGRESSIVE OCULAR DISEASES

Name of the supervisor: ISABELLE AUDO AND CHRISTINA ZEITZ

THEMES OF THE TEAM

The main field of interest of this team is improving the identification pathogenic gene defects in inherited retinal disorders (IRD). This research starts from the very well characterised and phenotyped cohorts affected by IRD. Genetic analyses have been performed to identify potential candidate gene defects. The functional effect of the variants that are characterised in the initial step are studied through in vivo and in vitro methods. This is the mandatory initial step to diagnose patients but also to target potential therapies as many patients can obtain a genetic diagnosis. An important publication record was mentioned with more than 120 publications during this five-year period with a very good rank rate journal.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Consideration of the recommendations of the previous report-T6
Last evaluation underlines the high quality of this research team but pointed out that genetic unit remains small and needs to NGS sequencing based elsewhere. The limited size of genetic team was underlined especially the need for a real bioinformatics core. A bioinformatician has been hired recently, although non-permanent. Moreover, recruitment of post-doctoral fellows with their personal funding were recommended but remains an issue due to both difficulties to recruit candidates and space to welcome them.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**6**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	1
Post-doctorants	1
Doctorants	3
Sous-total personnels non permanents en activité	**7**
Total personnels	**13**

EVALUATION

Overall assessment of the team

This is an excellent to outstanding team. It has excellent expertise in medical and basic research in IRD. For the population, it can lead to a higher proportion of genetic diagnosis for IRD and potential therapeutic options. Both team leaders are well-recognised international experts in the field of IRD. An important publication record was mentioned with more than 120 publications during this five-year period. Moreover, this team was attractive with more than twenty publications from five PhD students. The team raised many funding from both national and international grants. They disseminate their work at internal seminars, patient organisations, national and international conferences such as Euretina, ISER, EVER, and ARVO.

Strengths and possibilities linked to the context

The team's productivity has been extremely impressive with a total of 133 publications, of which 15% are in the top 10% in terms of citation rate. Funding has also been excellent, with over 4.8M€ in grants.
The proximity with the national centre of rare disease at the Quinze-Vingts hospital with a large cohort of IRD patients with more than 8000 index cases with 800 new patients included each year with about 500 representing rod-cone or cone-rod dystrophies is a fantastic opportunity and has been very well valorised with identification of 45–70% of gene defect in IRD patients. The team has developed a new generation sequencing panel to rapidly diagnose more than 250 genes implicated in IRD. The research is not only descriptive. Retinal signalling studies performed both in vivo and in vitro has been developed. A collaboration with other teams in the Institut de la Vision has been initiated with new techniques like pluripotent stem cells and retinal organoid methods, Crispr/Cas 9 based zebrafish. The team has been successful to obtain many national and international funding with a recent EU funding to better understand the genetic basis of myopia and the link to IRDs.

Weaknesses and risks linked to the context

Weaknesses identified in last report has pointed out that genetic unit remains small and needs to use NGS sequencing based elsewhere. Team has hired a new bioinformatician (who is not permanent) and have tried to develop a close collaboration with the bioinformatician core recently developed in IdV. The development of a stronger genetic unit is strongly encouraged but they need both space and permanent positions. In addition to the NGS sequencing of patient samples, omics methods, for example for phenotype analyses of IRD models, must be implemented to a greater extent, which requires further bioinformatic support. Moreover, the fact that four people only are permanent in the team can induce a high rate of turn over needs to be considered. The fact that Isabelle the team leader is the main clinician (with one fellow) and is deputy director of the IdV can also decrease her involvement in the team by lack of time.
The team mentioned that are willing to work on myopia considering that syndromic myopia associated with IRD can be a good approach for genes involved in myopia development. Indeed, one of the team leaders has been an expert in that field and got an EU grant to work on that field. However, the diversity of the research project from IRD to myopia and finally AMD seems quite wide. A more targeted field of research with excellent level of publications is a guarantee to attract post doc necessary to strengthen this small team. The fact to add AMD as another project initiated by team#7 also need to be questioned.

Analysis of the team's trajectory

The trajectory of the team is in line with the previous works on IRD, interested in the analysis of mutation prevalence of a rod cone dystrophy cohort. The close relationship between clinician and researcher will raise a better understanding in genotype/phenotype correlation interesting for both diagnosis and potential therapeutic approach. It is a great and very efficient collaboration. The team aims to increase the rate of genetic diagnosis of IRD. They are willing to develop good collaboration with other IdV team like Team S2 (for iPSC-derived 3D retinal organoids and 2D cultures of RPE cells) and Team S3 to investigate candidate genes in zebrafish models. The expertise in CSNB, especially with a mouse model are going deeper in the identification of molecule involved in signalling cascade. These experiments aim to deliver new genes underlying different IRDs with both in vivo and in vitro results and can lead to therapeutic options.
Myopia linked to CSNB will be proposed as a model to study mechanisms linked to myopia development in patient and animal models. Finally, the arrival of new members led to the development of research about the implication of metabolic dysfunction on the pathogenesis of age-related macular degeneration.

RECOMMENDATIONS TO THE TEAM

The team is emblematic of translational research with a clinician and a fundamental scientist leading this team. The main field of interest of this team is to better understand inherited retinal disorders (IRD). They really succeed with an increased rate of gene defect in IRD. An important publication record was mentioned with more than 120 publications during this five-year period and five PhD students. However, this team remains quite small with 4 permanent people only and a high turnover rate. A stronger genetic platform should be developed. The development and further expansion of omics approaches requires further bioinformatic support. As pointed out in last report, there is a high risk to develop less focused research with project on myopia and AMD. IRD remains the field of excellence of this team, has been very successful and is the opportunity to attract postdoc fellows. The arrival of a new member can be considered as a great opportunity but can increase the risk of diversity of research

Team 7: METABOLIC AND REDOX SIGNALLING OF THE NUCLEOREDOXIN-LIKE-1 GENE FOR THE TREATMENT OF ROD-CONE DYSTROPHIES

Name of the supervisor: THIERRY LEVEILLARD (Deceased)

THEMES OF THE TEAM

This project is based on the identification of the cone viability factor (RdCVF) and almost two decades of intensive basic and translational research to understand why cones degenerate after rods. The deep understanding of the function of the two protein products of the NXNL1 gene, RdCVF and thioredoxin RdCVFL, gained through continuous research led to the concept of metabolic and redox signalling in the retina and was rewarded by a clinical trial for the treatment of IRDs to be conducted with the company SparingVision from 2023. During the reporting period, it was shown that a dysfunction of this novel metabolic and redox signalling pathway plays a role in age-related macular degeneration (AMD) and Alzheimer's disease (AD).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Several concerns were raised during the last evaluation, in particular the weak level of interactions with patient or other public organisations, the relatively low number of PhD positions and the problem of attracting highly qualified researchers to the team, as well as the fear that a stronger focus on Alzheimer's could divert attention from the IdV's main objectives of finding treatment options for patients with IRD. These concerns have been allayed.
1) the team is in constant contact with the American Foundation Fighting Blindness (FFB) and the French patient organisation IRRP and also publishes in the CNRS annual report. 2) Three doctorates were completed during the reporting period. 3) two American researchers joined the team during the reporting period. 4) A clinical trial for the treatment of IRD, which is being conducted with SparingVision, has been prepared, which matches the IdV's central missions.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**3**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	1
Post-doctorants	0
Doctorants	1
Sous-total personnels non permanents en activité	**4**
Total personnels	**7**

EVALUATION

Overall assessment of the team

As the previous team leader had reached the age limit for renewing his own team at the time of the report, the plan was to close the team in 2025 and transfer the group and parts of research questions under the leadership of two new researchers (Team 6). Due to the tragic, unexpected death of the team leader in June this year, this transfer must now take place earlier and without his assistance.
Despite these problems, the panel considered that the research activity of the team has been of an excellent standard.

Strengths and possibilities linked to the context

The team worked continuously on the research questions arising from the preliminary work, applying appropriate tools at a high level.

Weaknesses and risks linked to the context

The team leader's expertise as a supervisor will be missing and cannot be compensated for by the new team of supervisors. The research projects of the supervisors leading Team 6 are already very heterogeneous. None of these projects are related to the proposed project, which is planned to be continued. As can be seen from the description in Team 6, a project on AMD initiated by the PI entitled 'Does retinal metabolic dysfunction contribute to the pathogenesis of age-related macular degeneration (AMD)?' was planned to be continued. In this project the general objective is to investigate the extent to which aerobic glycolysis is essential for photoreceptor function and whether deficits in lactate efflux from the outer retina could be an important aspect of AMD. It can be assumed that the methodology established in Team 7 can be continued by the experienced team members in the project. However, it remains to be seen whether the new team of supervisors, who cannot match the PI's expertise in the field, will be able to lead the project at a high level.

Analysis of the team's trajectory

The team continually worked characterisation of the molecular functions and translational potential of the cone viability factor (RdCVF) since its identification. The deep understanding of the function of the two protein products of the NXNL1 gene, RdCVF and thioredoxin RdCVFL, gained through continuous research led to the concept of metabolic and redox signalling in the retina and was rewarded by a clinical trial for the treatment of IRDs to be conducted with the company SparingVision from 2023. In recent years, besides the preparation of the clinical trial the team extended the research on *NXNL1*/RdCVF its evaluations on the role its retinal cell signalling in the development of age-related macular degeneration (AMD). Further, they study the signalling of its paralogue RdCVF2 in glucose metabolism and the putative role of *NXNL2*/RdCVF2 in sporadic Alzheimer's disease (AD).

RECOMMENDATIONS TO THE TEAM

It is suggested that the PhD students carry out their work under the guidance of experienced postdocs and the tandem of the team leader. The necessary scientific support should also be provided for the clinical study that has been started using the tools that are available in the team. If possible, experienced post-docs from ongoing projects should develop their own independent projects to continue the very important research.

Team 8: VISUAL INFORMATION PROCESSING: NEURONAL CODING AND VISION RESTORATION

Name of the supervisor: OLIVIER MARRE

THEMES OF THE TEAM

The team focuses on retina physiology and pathophysiology with two main approaches: (i) a basic research stream investigates neural coding of complex scenes in the mammalian retina, combining both computational modelling and state-of-the-art experimental (optogenetics, imaging, electrophysiology) approaches and (ii) vision restoration by stimulating retinal neuronal networks with two complementary but independent strategies: retinal electrical prostheses and gene therapy to make retinal neurons light-sensitive. The team combines several preclinical models (rodents, non-human primates) for both in vivo and in vitro/ex vivo studies. Finally, the team has engineered several technological activities in both neuroinformatic (spike sorting software) and brain imaging (optogenetics, US functional imaging).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Balance and interactions between the two research objectives (neural coding, retinal restoration) were interrogated in the previous report, in particular regarding the long-term efforts and resources that must be dedicated to the vision restoration projects. The team's answer is that vision restoration research has led to important, high-impact publications (Nat Med, Nat Biomed Eng). Moreover, the team has attracted and recruited several young researchers in the past years and obtained highly competitive funding.

The other main concerns were about 1) the workload of the previous team leader who was also IdV Director and 2) the lack of women at leading scientist positions. The first aspect was solved with a researcher taking full leadership of the Team. The criticism about parity was not yet addressed, the team claiming rightly that it has not been able to attract female scientists and offer them the possibility to apply for INSERM/CNRS positions.

The last point questioned the strategy regarding non-human primate (NHP) research. Several high-impact publications have been done (PNAS, Nat Biomed Eng) on functional brain imaging and retinal stimulation in the macaque monkeys. Facilities have been build-up at the nearby MIRCEN site, outside Paris and animal resources are secured. The team is also currently looking for alternative NHP models (lemur, marmosets) for the neural coding activities. Still the workforce in permanent researchers/engineers supporting NHP activities remains rather limited in view of the difficulty and ambition of the task.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	9
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	6
Post-doctorants	2
Doctorants	11
Sous-total personnels non permanents en activité	20
Total personnels	29

EVALUATION

Overall assessment of the team

The team has made several outstanding scientific contributions regarding the mapping of single cell receptive fields and population dynamics using natural images. Combining state-of-the-art mass recording of retinal ganglion cells and optogenetic neural circuit dissection, the team has unveiled the diversity and versatility of neural coding in the retina. The visual restoration pilar has produced high-impact results investigating the potential of different functional stimulation strategies that can be used to restore vision in retinal degenerative diseases: retinal prostheses and gene therapy. These important results open the door for clinical studies. The team is highly dynamic as evidenced by the recruitment of young permanent researchers and the awarding of highly competitive national and international (ERC) grants. The future research plans are well structured around these objectives. Overall, the panel considers that this is an outstanding team.

Strengths and possibilities linked to the context

· *Scientific quality and productivity*. The team has produced excellent to outstanding science over the 2027-2022 period, with publications in leading disciplinary (neurosciences, ophthalmology) and interdisciplinary (basic and clinical sciences) journals. The number and quality of publications (80) is remarkably high, given the size of the team. This production is well distributed between the two main research objectives, although the work dedicated to retinal pathophysiology and visual restoration is much more diversified, due to the wide spectrum of collaborations. The outstanding work of the team is more fundamentally oriented. The neural coding subgroup (4 researchers) has established new functional approaches of ganglion cell properties regarding coding of natural scenes and information processing. They developed state-of-the-art tools and models to simulate population dynamics (synchronisation, emergent coding) and build generative models of natural scenes retinal coding. At a more theoretical level, the team made important contributions regarding efficient coding and metrics of decoding. This fundamental research led to high-impact articles (e.g. Nature Comm 2022; PNAS 2018; PLOS Comp Biol 2021). The outcomes of the visual restoration subgroup are impressive regarding the basic physiology and physiopathology of the outer segment of the retina and the development of functional restoration strategies. The production (about ¾ of the total team production) is in general of high quality with two main proof-of-concepts in NHP models: (i) the efficiency of retinal electrical-stimulation prostheses and (ii) the promises of gene therapy for make surviving retinal cells light-sensitive in order to bypass the degenerated photoreceptors. These results have been published in top-level journals (Nat Med, Nat Biomed Eng, PNAS) and attracted a lot of media coverage. Several other projects, such as in vivo functional brain imaging using ultrasound technologies and ex vivo 2photon imaging, have also produced promising results and high-impact articles (PNAS). *Innovation and technologies.* The team devotes a large effort to the development and testing of new technological approaches, for both basic science (spike sorting software, holographic stimulation, functional US imaging) and applied, medical sciences (design of retinal prostheses, molecular engineering of vectors and optogenetic proteins). These efforts have generated six patents, several research grant/contracts and high-impact publications (PNAS, Nat Comm). The team managed to recruit three young researchers (1 INSERM, 1 CNRS, 1 SU) over the period. The recruitment scheme is, however, unbalanced between the two research axes. The reputation of the team is demonstrated by the national (3 ANR JCJC), international (ERC Consolidator, ERC Synergy) grants. One researcher is now the recipient of an Essilor Chair. The team has a strong scientific visibility through its publications and PhD/PD training (10 PhD completed over the period) but is less visible in high-profile international conferences or prizes and its presence in international Journal/Society boards. This may be due to the youth of the principal investigators. Nevertheless, the team has benefited from the worldwide impact and visibility of the last director of the IdV. With ten PhDs completed (for 4 permanent researchers/academics) and currently training twelve doctoral fellows, the team is strongly involved in training, although the number of post-docs was relatively limited (3 at the end of 2023).

Weaknesses and risks linked to the context

Basic sciences: The team has gained the reputation of a world-class research group in the field of neural coding in the retina. It perfectly mixes computational and empirical/electrophysiological approaches. The approaches are not so much driven by perceptual implications since most of the scientific questions and protocols are designed based on information theory and receptive field mapping approaches rather than natural/naturalistic approaches. This approach is also grounded on strong international collaborations. The transfer of what is learned about efficient coding in retina to the definition of optimal electrical/optogenetics stimulation for visual restoration remains to be strengthened.

Clinical implications: Regarding preclinical studies on either retinal prostheses or gene therapy, it is not clear how translational strategy to clinical patients is organised. Preclinical works appear as proof-of-concept (in particular in NHP) but with limited, mostly case-report clinical outcomes so far. In particular, the report does not document the rest of the human clinical cohort which led to the breakthrough of 2021. Are the initial hopes confirmed? In the future, international collaborations are set to overcome the obstacles that can be seen ahead: there are indeed more and more possible technological/research tracks for visual restoration (retinal, central visual system stimulation) and functional exploration. Promising efforts have been launched in parallel, thanks to a dense network of highly qualified collaborators at IdV or outside, but the definition of the priorities and endpoints should be better clarified.
Innovation: How the spiking circus software compare with other solutions in terms of quality but also diffusion. It is unclear what will be the strategy for maintaining/developing this software after the closing of team#17 at IdV and the leave its members (in particular the main author of the software).
Technical support: The situation seems to be clearly at risk given (i) the number of different scientific/technological projects (ii) the level of job insecurity (CDD) among technical staff and (iii) the distance of the PNH facilities and limited technical permanent resources.

Analysis of the team's trajectory

The team proposes a research plan for the incoming term that is structured around the same two streams: (i) basic science approach of neural coding and visual processing and (ii) visual restoration through functional stimulation at either retinal or central levels with different technologies (retinal implants, fUS, gene therapy). These two streams remain, at least in their presentation, rather independent. A new research theme is myopia and eye growth that attempts to bridge the gap between basic physiological work and eye disease. We would have expected that, in the written document, it would have been explained in greater details how the highly ambitious workplan will be distributed among the permanent staff and which human resources will be allocated to each component.
The projects on neural coding are well structured and grounded on previous work by the team. They will extend the perturbation approaches (natural scenes + noise pattern) to map receptive fields and population dynamics to dynamical scenes. The objective is to build and test a Gaussian process model of the nonlinear properties of ganglion cells, when stimulated with natural scenes. Variability of these neural dynamics will be probed by varying the properties of the (added) structured noise patterns. By combining these two approaches, the team aims at building generative models of natural scenes encoding by the retina and test their efficiency. At circuit level, they will use sophisticated techniques on molecular engineering of amacrine cells and holographic optogenetics to apply light stimulation patterns at cellular resolution throughout the intermediate layers of the retina. This project is highly ambitious but grounded on the team's expertise and benefiting of the new collaboration engaged with team#18 at IdV. The combination of new tools, well-defined empirical approaches and computational modelling is very strong and clearly world-class. It is conducted by a group of young investigators and has the potential to become key players in this field.

The projects on visual restauration are very ambitious and will pursue three different strategies: retinal prostheses, gene therapy and central visual system (LGN, V1) opto/sonogenetic stimulations. In collaboration with Team #15, they aim at improving the design of viral vectors for retinal gene therapy and move towards clinical trials. The second goal is to optimise the image encoder to vision restoration, using behavioural approaches with retinal prosthetic implants and gene therapy in blind patients. Finally, the team aims at exploring several new central visual system targets and technologies (optogenetics, ultrasound) in preclinical (rodents, NHP) models. All these projects are highly innovative and ambitious.

RECOMMENDATIONS TO THE TEAM

The team has presented highly innovative and ambitious research goals in both basic and applied sciences, focusing on retinal and central visual processing with state-of-the-art molecular, electrophysiology and imaging technologies. There is a clear common vision and interest to maintain these two research objectives (retinal circuits and computation, vision restoration) strongly linked. There is a strong and young leadership of the team leader who has embarked several young researchers recently. The team shall, however, consider the following recommendations.
First, it is important to build stronger bridges between the two research lines. Computational models of retinal information processing can be better linked to the complementary objective of optimising visual information encoder for retinal stimulation. These intertwined theoretical and experimental challenges could be useful to unite the young researchers around a common functional perspective, linking retinal processing and visual perception/behaviour. It may also drive interesting approaches on the statistics of natural scenes and their retinal encoding, moving further along naturalistic, non-stationary inputs and not only natural images perturbations.
Second, the team intends to develop a variety of approaches in non-human primate models for investigating visual function/dysfunctions are different levels neural integration along the early visual pathways. This is extremely an valuable and important endeavour but it shall grounded on a more solid strategy around three

main questions: (a) selecting the right models (macaque, lemur, marmoset) through national/international collaborations that can fit the two team's objectives, (b) attracting/recruiting a permanent researcher with a strong background/project in primate visual neurophysiology and (c) extending ex vivo approaches in retinal neural coding to NHP retina, as different features seem to be encoded in rodent vs NHP retinal circuits.
Third, there is a risk that the technological challenges for central visual system stimulations are too broad, in particular when considering NHP studies. Running in parallel 2/3 photon microscopy for reading/writing neural activities and sonogenetic US stimulation in NHP will require a humongous amount of resources and expertise. The risk is that the team will continue to produce state-of-the art proof of concepts but not being able to fully exploit these technological advances for the understanding of visual processing and its restoration. It may be important to make choices on a mid-term perspective.

Team 9: VISION AND NATURAL COMPUTATION

Name of the supervisor: RYAD BENOSMAN

THEMES OF THE TEAM

N/A

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

N/A

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	0
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	0
Sous-total personnels non permanents en activité	1
Total personnels	1

EVALUATION

Overall assessment of the team

The team was closed after the departure of its team leader. It has not produced a scientific report for the evaluated period, and was not evaluated by the panel.

Strengths and possibilities linked to the context

N/A

Weaknesses and risks linked to the context

N/A

Analysis of the team's trajectory

N/A

RECOMMENDATIONS TO THE TEAM

N/A

Team 10: NEUROPHYSIOLOGY AND OPTOGENETIC APPLICATIONS IN THE RETINA

Name of the supervisor: JENS DUEBEL

THEMES OF THE TEAM

The team of Jens Duebel was closed for personal reasons of the team leader (2019) with a move to Germany. No information has been provided as to the functioning of the team prior to its closure.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

N/A

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**0**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	0
Sous-total personnels non permanents en activité	0
Total personnels	0

EVALUATION

Overall assessment of the team

N/A

Strengths and possibilities linked to the context

N/A

Weaknesses and risks linked to the context

N/A

Analysis of the team's trajectory

N/A

RECOMMENDATIONS TO THE TEAM

N/A

Team 11: IMAGING OF SENSORY PROCESSING AND NEUROVASCULAR COUPLING

Name of the supervisor: SERGE CHARPAK

THEMES OF THE TEAM

This team focuses on investigations into neurovascular coupling (NVC) and brain oxygenation, as well as technical developments to measure blood flow and comparison of microscopic versus mesoscopic brain imaging. The focus of this team is not directly related to the mission of the IdV, but they have recently started to work on applications in the visual system and their expertise and biological knowledge is considered uniquely valuable to the unit and other teams.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Several concerns were raised during the previous evaluation: (1) evidence of public outreach and commercialisation is scant; (2) there should be some consideration given to expanding PhD student numbers; (3) gender balance and the loss of a key research engineer; (4) space issues and problems regarding relocating equipment and staff. Except for gender balance and the appointment of one additional PhD student, these weaknesses have persisted.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**4**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	2
Doctorants	2
Sous-total personnels non permanents en activité	**4**
Total personnel	**8**

EVALUATION

The overall assessment of the team

An overall academically outstanding research team focusing on basic research into neurovascular coupling and associated technology development. Importantly, the team plans to close in 2025 and integrate into S18. Despite efforts to increase focus on the visual system, there remain some concerns regarding the team's embedding in the IdV's global strategy but this issue will likely be remedied by integrating the team into S18.

Strengths and possibilities linked to the context

The team's strengths are linked to their academic excellence and technological innovation, with a focus on quality rather than quantity. The group is small (N=6) but reasonably productive and internationally competitive with outstanding scientific contributions that are consistently published in some of the fields most reputable journals. The team leader is also an exceptionally internationally recognised expert in the field as evidenced by e.g. review articles and editorials in highly prominent journals, invited lectures and highly competitive funding in

the past. Past team members have excellent academic prospects. The approach taken to measure oxygen in the brain is innovative, using advanced technologies including, two-photon phosphorescence lifetime microscopy (2PLM) to measure PO2 in vivo, custom-built two- and three-photon microscopes, and functional ultrasound.

Weaknesses and risks linked to the context

Most of the concerns raised during the previous evaluation have not been addressed. In addition, the production during the evaluation period lacks a clear synergy with the mission of the IdV. This improves a bit in the team's future projects (listed under the self-evaluation of S18), but this could be increased by focusing on e.g. neurovascular disorders of the retina or other ways to tighten the link between their technology development activities and the institutes mission to test and develop treatments and technological innovations for the benefit of visually impaired patients. It also appears that the team's future funding through external grants is somewhat uncertain.

Analysis of the team's trajectory

Due to the planned closure in 2025, future projects have been listed under the self-evaluation of team S18, which appear to address previous concerns regarding crosstalk with other IdV teams and relevance to the mission of the IdV to some extent. Regardless, the integration of team S11 is expected to lead to an overall improvement for team S18 as they bring valuable biological and technological expertise which team S18 would be uniquely capable of leveraging.

RECOMMENDATIONS TO THE TEAM

Team leader is an excellent researcher more interested by basic research in neurovascular imaging than by visual neuroscience. In view of his seniority, one should respect his own choices. He would make an excellent partner with the team S18. Nevertheless, the committee recommends exploring projects that more closely align with the mission of the IdV, such as neuromuscular coupling in the retina. While other groups across the world also work on this topic, it appears that team 11 would have a strong competitive advantage with their unique expertise in this field.

Team 12: PATHOPHYSIOLOGY OF THE ANTERIOR SEGMENT OF THE EYE

Name of the supervisor: ANNABELLE REAUX-LE GOAZIGO

THEMES OF THE TEAM

The team has made several excellent to outstanding contribution. It focuses on anterior segment eye diseases and peripheral and central mechanisms associated with DED and corneal pain. The team combines preclinical models and clinical studies with a strong team for innovative projects between the Institut de la Vision and Hôpital National de la Vision in Paris. Projects aim at validating new therapeutic agents for corneal pain relief; conducting translational research with the Clinical Investigation Center of the 15–20 hospital to find DED-related biomarkers. In the past term, they achieved significant scientific milestones, leveraging cutting-edge techniques (electrophysiology, fUS, omics/lipidomics) supported by academic and private grants

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

In response to the criticism regarding the quality of scientific outputs and activities, the team acknowledged a weakness in the limited presence of their numerous publications in high-impact factor generalist journals. However, they emphasised an improvement in this aspect during the 2017–2022 period, citing publications in journals such as Journal of Neuroinflammation, Communication Biology, Frontiers, Scientific Reports, Endocrine Reviews, and PloS One with high impact factors. Additionally, the team highlighted enhanced training activities, including the supervision of fourteen Master's students, ten PhD students, and two post-doctoral researchers. They also noted hosting foreign visiting PhD students and participation in a European H2020-MSCA-ITN program, where they trained two PhD students.
Concerning interactions with the non-academic world and involvement in training through research, the team identified no specific weaknesses. In unit organisation and life, a weakness was acknowledged regarding inadequate technical support given the team's size and project scope. The team addressed this by explaining their reliance on engineers hired on industrial contracts due to the competitive nature of obtaining permanent positions at institutions like Sorbonne Université, INSERM, or CNRS.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	2
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**8**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	1
Post-doctorants	0
Doctorants	6
Sous-total personnels non permanents en activité	**8**
Total personnels	**16**

EVALUATION

Overall assessment of the team

This is an excellent to outstanding team. It is the sole Institut de la Vision team dedicated to anterior eye diseases. Their interdisciplinary approach, involving clinician-researchers, scientists, and engineers, has yielded significant achievements between 2017–2022. Notably, their mouse model for dry eye disease (DED) elucidated neuroinflammatory responses, informing corneal pain mechanisms. Ultrafast functional ultrasound imaging (fUS) showcased hemodynamic changes in corneal pain, a key aspect of the ANR CONNECTPAIN project. A clinical study linked symptoms in Sjögren syndrome-related dry eye patients to gene expression. The team's expertise led to the establishment of an ocular Pain Center in 2020. Active in training, they supervised PhD students and organised a summer school. The proposed evolution under aims to deepen understanding of corneal pain pathways and neuroinflammation.

Strengths and possibilities linked to the context

Team S12 excels in setting relevant scientific objectives, focusing on translational research related to neuroimmune interactions in chronic ocular pain. Their dynamic approach, combining preclinical research in animal models and innovative methodologies, is reflected in their high-quality publications and substantial funds raised, exceeding 3.5 million euros from diverse sources. Comprised of clinician-researchers, MCU researchers, scientists, and students, Team S12 leverages complementary expertise for impactful translational work. The team's commitment to skill development and innovative themes adds depth to their resourceful composition.
Team S12's adherence to rules and directives on human resources, safety, and ethical protocols aligns with INSERM, CNRS, and Sorbonne Université standards. This ensures a robust functioning that supports their research endeavours. The team's scientific reputation is evident in invitations to conferences, organisation of scientific events, and editorial responsibilities. Presidency of the European Dry Eye Society by a team member further enhances the team's standing. In hosting policy, Team S12 actively engages with trainees, doctoral students, and post-doctoral researchers, fostering an attractive and inclusive environment. The addition of a senior EC researcher in 2022 contributes to the team's attractiveness. Success in competitive calls, including H2020-MSCA-ITN grant, ANR contracts, and collaborations with foundations, underscores the team's competitiveness. Their expertise in attracting funding positions them as an appealing choice for further support. Team S12 exhibits strength in technological skills, utilising major equipment and platforms for their projects. This technical prowess enhances their capability to achieve research objectives. With 130 original papers and 56 reviews published between 2017 and 2022, Team S12's scientific production is of high quality. The proportional distribution of scientific output among personnel, including PhD students, reflects a satisfactory balance. The team upholds principles of scientific integrity, ethics, and open science. Adherence to guidelines, authorisations, data deposition, and rigorous scientific standards ensure the reliability of their research. Team S12 excels in fostering nonacademic interactions, signing NDA/MTA agreements, and filing patents, showcasing their valuable contributions to industry and non-academic sectors. Their proactive approach to valorising research, protecting intellectual property, and engaging with the general public underscores their commitment to knowledge sharing and societal impact.

Weaknesses and risks linked to the context

Challenges lie in publication venue diversity, supervisory capacity, and technical support adequacy. While the team has made progress in publishing in generalist journals, there remains a weakness in the predominant publication in specialised journals, impacting broader visibility. The overall number of PhD students supervised by the team is considered low given its supervisory capacity, indicating a potential weakness in the capacity to accommodate more doctoral candidates. The team acknowledges a weakness in the adequacy of technical support, particularly concerning the size of the team and the projects undertaken. The reliance on engineers with industrial contracts is highlighted as a compensatory measure.

Analysis of the team's trajectory

Team S12 has positioned itself as a pioneering force in translational studies dedicated to ocular pain, distinguishing itself as the sole team in France and one of the few globally focused on this niche. The team's strength lies in its multidisciplinary approach and the use of advanced tools such as fUS imaging, electrophysiology, optogenetics/chemogenetics, and multi-omics analysis.
Two major funded projects, Project 1 and Project 2, showcase the team's commitment to addressing critical aspects of ocular pain. Project 1 focuses on dry eye disease and neuropathic corneal pain, aiming to identify a functional corneal pain network and exploring pharmacological, chemogenetic, and optogenetic approaches

for alleviating corneal pain. The team employs innovative techniques, including fUS imaging, c-Fos connectome analysis, and chemogenetic manipulations to gain insights into the complex mechanisms of corneal pain.
Project 2 extends the team's research to another type of ocular pain – photophobia. This novel initiative explores the cellular and molecular changes in the retina, trigeminal ganglion, hypothalamus, and brainstem in response to blue light exposure. Pharmacological studies involving anti-CGRP receptor and anti-opsin 4 receptor administration aim to uncover the mechanisms underlying photophobia, potentially leading to therapeutic advancements.
As of the end of 2022, Team S12 comprises a diverse and talented group, including clinicians researchers, academic researchers, PhD students, and engineers, with a notable gender balance (59% women, 41% men).
The team's translational efforts extend to clinical collaborations with the CIC and the clinical laboratory in Hôpital National de la Vision. This collaboration facilitates the study of corneal pain pathways, neuroinflammation's role in pain chronicity, and the validation of new therapeutic options for persistent dry eye disease.
Furthermore, the team's commitment to translational research on chronic corneal pain involves investigating transcriptomic and proteomic profiles of patients suffering from chronic corneal pain. The establishment of a patient cohort and fMRI studies contribute to understanding the cerebral nuclei involved in processing corneal pain.
In summary, Team S12's trajectory showcases a remarkable commitment to advancing knowledge in ocular pain, employing cutting-edge techniques, and fostering international collaborations. Their unique focus on translational studies positions them at the forefront of research in this specialised field, with potential far-reaching implications for the diagnosis and treatment of ocular pain disorders.

RECOMMENDATIONS TO THE TEAM

The team would benefit from increasing the permanent staff and technical positions to fortify its workforce. Although secured funding for the imminent term is promising, strategic endeavours to elevate the team's international profile are needed. A key objective for the upcoming term should involve coordinating multisite proposals to further heightened recognition within the scientific community at the global level.

Team 13: PHYSIOLOGY OF THE RETINAL PIGMENT EPITHELIUM AND ASSOCIATED PATHOLOGIES

Name of the supervisor: EMELINE NANDROT

THEMES OF THE TEAM

This team is investigating the cellular and molecular mechanisms that control the phagocytosis of the photoreceptor outer segment by the retinal pigment epithelium (RPE), a process highly controlled by a circadian clock and fundamental for vision maintenance. The team specifically studies the role of different receptors including the MerTK receptor in the phagocytosis by characterising their binding sites, subcellular localisation, expression level through 24 hours light/dark cycle and associated signalling pathways using in vitro and in vivo approaches. Using mutant mice models and RPE cells derived from human iPSC, the team is also examining the circadian-regulated function of the RPE and the phagocytic response in a pathological context. They developed a new project to assess the protective role of antioxidant lipids to potentially develop specific natural products relevant to humans. This research is important from a clinical point of view since phagocytosis impairment or arrhythmic phagocytosis can lead to the development of blinding diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Several weaknesses were noted in the last evaluation including the lack of innovation, the team's size in relation to the project feasibility, the research's limited dissemination and the absence of overlap between PhDs. In order to improve innovations, the team implemented new techniques and uses the IdV platforms in cell biology, biochemistry, advanced mass spectrometry and expansion microscopy necessary for the completion of their project. The team size increased up to eight members. However, the team is currently composed of only three persons: one permanent researcher (team leader), one PhD and one technical staff. One postdoc and one engineer will join the team at the end of 2023. In order to enhance the feasibility of the project, the team will collaborate with experts in cell biology, retinal inflammation and circadian biology both inside and outside the IdV. Finally, in the last five years, the team has also planned a continuum between PhDs and improved engagement with patient associations (Retina France) and lay audiences (Semaine du Cerveau with visit of the IdV) and through article and video.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	2
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	3
Post-doctorants	0
Doctorants	1
Sous-total personnels non permanents en activité	4
Total personnels	6

EVALUATION

Overall assessment of the team

The size of the team is quite small with currently three members: one permanent researcher who is the team leader of the team, one PhD and one technical staff. One postdoc and one engineer are planned to join the team at the end of 2023. During the last five years, the team has dissected part of the complex RPE phagocytic machinery. They identified the role of different scavenger receptors in various steps of phagocytosis in a precise timing. The committee considers that the team is very good and raises concerns about the weak research output that will be improved by integrating additional permanent staff. The alignment between the projects, the questions raised, technological development, and the required human skills is not explicit. The panel recommends formalising the strategy implemented to sustain the competencies inherent to the team's technological developments and determining how to enhance the attractiveness of new researchers to the team for the project's feasibility.

Strengths and possibilities linked to the context

The expertise of the team leader on RPE cell biology and phagocytosis is well recognised. The team leader was invited to national and international conferences (2 times ARVO 2018; ISER 2018, Retina France 2018, ProRetina Germany Annual Meeting 2018) and is executive editor of Exp Eye Res since 2020. The scientific production was very good with thirteen original articles as co-author in good to excellent journals (Stem Cells, IOVS, Nature Comm). The visibility of the research output is overall weak with one publication (Int J. Mol Sci 2022) and three book chapters as last author and no original publications involving the PhD (one book chapter, 2023) and are uncorrelated to the impressive capacity to raise funds over the last period for an overall amount>2.7 M€ (NIH, 2015–2020 and 2021–2026; 2 IHU ForeSight 2020 – 2023, 1 ANR 2018–2023, 1 UNADEV, 1 Retina France 2021–2023, 1 Labex) which will end for the majority in 2023. However, the involvement of the team leader is difficult to evaluate. Investment in collaborations is significant, with more than sixteen out of seventeen published papers being collaborative in the period. The team also obtained two PhD grants. The committee considers that the team is a very good one but its size is still a weakness. Since the team is composed of only one permanent staff, academic supervising activity, teaching and outreach is done only by the team leader.

Weaknesses and risks linked to the context

The committee picked up two major weaknesses. First, the low workforce of the team currently composed of only one permanent researcher that fragilizes the team productivity and the feasibility of the different projects. Second, the weak research outputs in comparison to the excellent overall funding obtained in the last period. However, two news members will join the team and the team leader has improved her collaborations inside and outside the IdV in order to overcome these difficulties.

Analysis of the team's trajectory

The future projects of the team are in direct continuity of its previous work. First, they will continue to investigate novel receptors and signalling pathways involved in the RPE phagocytic machinery and define new potential role of MerTK specifically in the resistance to light using co-cultures of RPE and different cell types expressing MerTK (retina, bone-derived macrophages). They also seek to identify the different partners of the scavenger receptors, previously shown to function at various steps of phagocytosis using cellular, biochemical and expansion microscope technique, recently implemented at the IdV. This challenging characterisation will be carried out in vitro across a 24h light/dark cycle and then in vivo in wild-type and MerTK knockout mice. This project will be completed in part through collaboration with the IdV's S5. The second project uses a mouse model of retinitis pigmentosa to characterise pathogenic mechanisms connected to RPE during ageing. Finally, the team will assess the effect of antioxidant lipids for important RPE cellular functions (phagocytosis, oxydative stress, phototoxicity…) and related to the development of dry AMD using cellular approaches in RPE cell lines and validation of the identified candidates in vivo. These last projects will be completed through strong external partnerships to the IdV. The proposed project aims to enhance our understanding of the RPE machinery which is clinically fundamental since several retinal diseases are associated with RPE malfunction or damage.

RECOMMENDATIONS TO THE TEAM

The team would benefit from an increase in permanent and non-permanent people in order to strengthen the workforce, even though they collaborate on multiple projects. The committee recommends to secure the fundings for the various projects. The diversity of the projects should be noted by the team leader as it raises questions about how effective the current team composition will allow them to be implemented.

Team 14: INFLAMMATION IN RETINAL DEGENERATION AND VASCULAR REMODELLING

Name of the supervisor: FLORIAN SENNLAUB AND MICHEL PAQUES

THEMES OF THE TEAM

The team's overarching focus is the neurobiological bases of age-related macular degeneration (AMD) and diabetic retinopathy (DR). The research team specifically addresses immunological aspects of these common blinding diseases using donor and patients' tissues (eyes/blood samples, etc.) and preclinical models. It also aims at identifying drug targets and biomarkers, and developing therapeutic strategies to inhibit the pathogenic processes.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The group faced weaknesses in Team Composition and Viability, including heavy dependence on one team leader, limited post-docs, and uncertainty regarding the funding of visiting scientists. Currently, the team boasts three INSERM researchers and two post-docs, with imminent recruitment. Despite postdoc limitations in France, the team's unique composition with three principal investigators is noteworthy.
Concerning Interactions and Translational Efforts, weaknesses included a focus on preclinical efficacy and limited engagement with Biotech/Pharma. Acknowledging the need for enhanced public outreach, especially in AMD, the group has initiated two ongoing maturation programs with Biotech/Pharma. While translationally relevant efforts persist, additional support staff may be required for increased outreach.
Regarding Involvement in Training through Research, the identified weakness was a low PhD supervisory capacity. The team is addressing this by aligning with doctoral schools' guidelines, maintaining a supervisory capacity of two PhD students per senior researcher.
Unit Organisation and Life had a gender imbalance, partly mitigated by the recruitment of Dr Cecile Delarasse as an INSERM staff researcher.
A minor concern was raised about limited collaborations with international experts in non-ocular basic immunology, with responsibility falling on the team leader. Infrastructural improvements in flow cytometry and cell sorting were deemed essential. The inclusion of a clinical colleague, while commendable, raised doubts about its adequacy for transitioning into biomarkers and clinical studies.
In response, the Institut de la Vision invested significantly in FACS and single-cell RNA seq technology, addressing infrastructure needs. Successful publications in Immunity over the last five years showcase effective communication with other immunologists, emphasising the team's commitment to enhancing international collaborations and advancing basic immunology research capabilities.
In summary, the group has made progress in addressing weaknesses, particularly in team composition, translational efforts, and PhD supervisory capacity. Ongoing initiatives demonstrate a commitment to further improvement, emphasising the need for continued support staff, enhanced public outreach, and increased interactions with Biotech/Pharma.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**8**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	3
Post-doctorants	2
Doctorants	5
Sous-total personnels non permanents en activité	**12**
Total personnels	**20**

EVALUATION

Overall assessment of the team

This is an outstanding team that demonstrates a strong focus on highly relevant scientific objectives, particularly in deciphering immunological aspects of AMD and DR Comprising three full-time INSERM researchers, five clinician researchers, two postdoctoral fellows, five research engineers, and five PhD students, the team secured €5.6M through various national and international partnerships. The team's compliance with institutional guidelines ensures ethical, safety, and environmental standards. This commitment is evident in their consistent publication record, encompassing 54 basic research articles and 50 clinical research articles during the evaluation period.

Strengths and possibilities linked to the context

The team's international recognition is underscored by invitations to conferences and participation in EU-doctoral Network EGRETAAA. The recruitment of a researcher and a postdoctoral fellow enhances the team's neuroimmunological expertise. Significant investments in technology, facilitated by the IHU Foresight, address infrastructural gaps, securing the team's long-term viability. Contribution to science is excellent to outstanding and focuses on the connection between chronic inflammation and intermediate/late AMD. The team deciphered the inflammatory mechanisms linked to key genetic risk factors for AMD, emphasising the role of inflammation in disease progression. The team's scientific production is not only prolific but also proportionately shared among team members, with PhD students contributing significantly. Moreover, the team's commitment to scientific integrity, ethics, and open science is evident in their rigorous experimental scrutiny and publication practices. The team's research integrates human data from donor eyes and experiments with AMD blood samples, emphasising translational approaches. Since 2018, they secured funds for developing clinical-grade CD47 agonists for AMD treatment and demonstrating anti-angiogenic properties of recombinant Lebecetin. Their commitment to translational efforts is underscored by a Research collaboration agreement with UPMC enterprise.

Weaknesses and risks linked to the context

Despite their scientific reputation, the team faces challenges in attracting staff due to administrative burdens, delays, and non-competitive salaries. Limited influence on institutional staff hosting policies hampers the team's attractiveness. While the team has made strides in technology and equipment, challenges in institutional support hinder their full potential. A concern arises regarding collaborations in non-ocular basic immunology, and doubts persist about the team's preparedness for a transition into biomarkers and clinical studies. The team acknowledges the need for enhanced public outreach and collaboration with Biotech/Pharma to address these weaknesses and ensure sustained progress.

Analysis of the team's trajectory

The main research areas of the team's trajectory are,

1. hiPSC-Based Model for AMD Genetic Risk**.** The team is developing a collaboration on hiPSC-based model to investigate the influence of AMD genetic risk factors on immune cells and RPE homoeostasis. The project, named AMoDel, utilises hiPSC-derived monocytes, microglial cells, and RPE in mixed cultures to study the impact of AMD genetic variants on immune cells. Longitudinal dynamic full-field optical coherence tomography, 3D live imaging, Arrayscan microscopy, and FACS analysis will be employed for comprehensive monitoring. Transcriptomics (bulk/single cell) will correlate dynamic cell phenotypes with signalling pathways and biological function, aiming to identify drug targets and potential therapeutic approaches.
2. In Vivo Model for HTRA1 Overexpression. The team is testing six transgenic mouse strains with cell-type-specific overexpression of HTRA1, a gene associated with AMD risk. Using a conditional overexpression approach, the team will evaluate the functional and morphological phenotypes of these strains under various conditions, including normal, light-challenged, and after laser-induced choroidal neovascularization. The ultimate goal is to establish an AMD mouse model based on the most critical genetic risk factor, providing insights for efficient therapies and a deeper understanding of AMD pathogenesis.
3. Investigation of Microglia and Macrophages in Retinal Pathology. The team plans to analyse different subpopulations of microglia and infiltrating MPs (CD45+CD11b+Ly6Gneg) using single-cell RNA sequencing (scRNAseq) in various retinal pathology models. This includes experimental autoimmune uveitis (EAU), choroidal neovascularization (CNV), and aged ApoE2ki mice. The project aims to identify molecular signatures of inflammatory conditions, confirm cell populations through histology and flow cytometry, and modulate signalling pathways with pharmacological agents in animal models. These research trajectories reflect the team's commitment to advancing knowledge in AMD pathogenesis, developing relevant in vitro and in vivo models, and exploring potential therapeutic avenues.

Team 15: GENE THERAPIES AND ANIMAL MODELS FOR NEURODEGENERATIVE DISEASES

Name of the supervisor: DENIZ DALKARA

THEMES OF THE TEAM

This team takes a multidisciplinary approach, harnessing the latest biotechnologies to advance gene delivery and therapeutic potential. There is an overarching translational ethos with stated goals to develop optogenetics as a therapy for inherited retinal degenerative diseases. The team also hope to advance understanding about how gene replacement can promote restoration of neural circuits in the brain and retina, an activity where the academic effort links into a spin-out company. There is also commitment to understand and ameliorate the immunogenicity and adverse effects relevant to AAV gene delivery. Together, these represent joined up, mutually reinforcing project.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The responses and actions taken by the team leader following previous recommendations are well considered and positive. For example, a flagged weakness from the previous report (Criterion 1: 'Quality of Scientific Outputs and Activities') was that the team's research effort was spread across too many collaborations and that there was insufficient focus on specific scientific questions and core (intrinsic) projects. This was reflected in the team leader leading on relatively few of her publications (6 out of 16 original publications).
In our view, the resultant actions and proactivity was convincing. Whilst continuing as a valued collaborative partner, the team leader has been the team leader and senior author on fifteen publications (11 more than the last evaluation) with evidence that PhD students and postdocs had been lead authors. The team have also produced several patents and created a spin-out company during the evaluation period. Notable is the fact that one student became a founder of this start-up. This is an exemplar of not only strong enterprise translation but also mentorship and provision of training opportunities for group members. It is an exemplar response to previously expressed criticism. Beyond the outputs produced during the reporting period, the team has also been more engaged in outreach activity which is also a positive response to a previous weakness.
Other weaknesses previously flagged to this team related to Criterion 3: 'Scientific Strategy & Projects'. This reflected concerns around numerous subprojects not building on each other, thus limiting impactful outcomes. It was felt that a more focused strategy with emphases on up to three related topics might be more efficient. Also, there were concerns expressed that the team leader, as a relatively junior partner, carries a disproportionate risk of losing independence and resources for her own independent scientific outputs. The response to this critique was also positive and thoughtful although the range of projects continues to be broad. This was questioned after the team leader's presentation. The panel took the view that there was good synergy between the projects. They were also convinced that the team leader's energy and commitment which convinced of likely delivery on all fronts. Indeed, her period of working in a spin-out seemed to have offered added perspective and added to her capability of delivering translational outcomes. There was little doubt that the team leader is a committed collaborator, and this level of collegiality and connectivity is a highly commendable facet of her research programme. The spread of collaborative efforts does need carefully handled but there can be little doubt that her input into multiple projects is critical for the overall success of the Institute.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**3**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	4
Doctorants	5
Sous-total personnels non permanents en activité	**11**
Total personnels	**14**

EVALUATION

Overall assessment of the team

This is an outstanding team. The multidisciplinary research programme led by the team leader is highly accomplished, and over the reporting period, they have delivered high-quality science in the area of gene therapy and optogenetics linked to inherited retinal degenerative diseases. It is pleasing to see the development of the team from previous evaluations. The overall translational strategy of this research team is to correct or compensate for photoreceptor loss. Under the leadership, they have delivered some successes in this arena both in terms of academic discovery research and linkage with commercial partners. This is a competitive and dynamic research arena, but it is apparent that this team are very competitive in the global landscape. The team consists of fourteen individuals, including five doctoral students and 4 post-doctoral scientists, and this reflects a strong funding base for the research. This grant income includes some impressive awards from competitive EU and International sources such as ERC. Based on this funding and with the embedded collaborative approach, the team have delivered some impressive academic outputs during the reporting period (e.g. Nature Medicine, eLife, JCI, Nature Comms, Prog Retinal & Eye Research, IOVS and PNAS) and also patents commercialisation activity. The team expertise combined with collegiality and commercialisation prowess are, in the opinion of these assessors, a critical component in the overall success of the Institute.

Strengths and possibilities linked to the context

This team has an international presence in gene therapy and optogenetics and their contribution to the cutting-edge of this field is significant. While the group are recognised for their biotechnology and discoveries, it is their joined-up approach with other colleagues in the Institute de la Vision which is particularly impressive. The collaborative approach has enabled the team leader to connect her basic science to positive patient outcomes based on gene delivery and optogenetics. In particular, the team developed the AAV2.7m8 – ChR-tdT vector that has been used for vision restoration in patients with retinitis pigmentosa. This AAV vector encoding ChrimsonR has shown some encouraging outcomes with light-activated being optogenetically transduced by retinal ganglion cells resulting and resulting in some visual restoration. This is an Institute-wide translational success story and is an exemplar for how groups can pull together to drive significant clinical impact. The optogenetic therapy, the immunogenicity of AAV vectors, and restoration of retinal and brain circuitry being pursued by the team leader is a broad portfolio, but it is supported by high grant income. Notable are several major grants such as two ERC awards (including a PI grant and the other as a partner (FET-OPEN), ANR awards and international awards from Foundation Fighting Blindness and the NIH (NEI). This is a very strong funding base and also reflects the team's competitiveness nationally and internationally. Also notable is the income stream through academic commercial partnering which also reinforces the translational relevance of the research. In terms of future endeavours, there are five exciting and ambitious projects outlined. All of them are based on the group's capability and builds on their success. The team's production is very good but is also marked by balanced recognition across the membership; with evidence of mentorship and advancement of early-career colleagues, including PhD students. There is confidence that the level of scientific training and engaged mentorship means that being in this team provides career development opportunities which adds to the strong levels of attractiveness.

Weaknesses and risks linked to the context

The strong scientific know-how of this team, coupled with their high-value income streams and publication output, has created many collaborative partnerships. Of course, team leader's willingness to collaborate with colleagues is to her credit, and this has shown value in clinical and commercial translation. Effort needs to be balanced since her expertise is clearly in high demand and it is a potential weakness that the efforts of the team could become spread too thinly. This concern is somewhat offset by the team leader's high levels of energy and productivity across numerous fronts. However, as she acknowledges in the SWOT analysis, this research sits at the cutting-edge of a highly dynamic and competitive research field, and to maintain this position, there will need to be a conscious decision to maintain focus and be highly selective on where effort is placed. As a note to the Institute's management, it is clear that Dr the team leader's expertise and input into multiple projects is critical for the overall success of the Institute. This team is delivering for the Institute and it deserves close attention and appropriate support so that this contribution is maintained and potential allowed to grow on both the academic and commercial partnering fronts.

Analysis of the team's trajectory

The research areas of the team's trajectory are aligned to retinal gene therapies for inherited retinal degenerative diseases using cutting-edge biotechnologies relating to the prevention of cell death and

restoration of function after photoreceptor loss has already occurred. The five areas of focus (Axes) are well chosen and link together. For example, the optogenetic therapy focus sits alongside their efforts to understand the immunogenicity of AAV vectors and engineer options that can evade host immune responses in the anterior and posterior segments. Likewise, the third focus on how gene therapy can restore retinal and brain circuitry synergises with the other activities across the research programme. The five axes stated by this group are:

Axe 1- Mutation-focused gene therapy relates to gene replacement strategies which seek to build on previously successful outcomes. The team have clear plans and will build on the use of animal models alongside the obvious potential of retinal organoids derived from induced pluripotent stem cells. For this, there will be continued collaboration with IdV colleagues. The team will develop innovative viral vectors that can be safely administered into the vitreous and target-specific cells. Alongside this will be further development of the gene-editing approach using CrisprCas9. While there have been successes in this approach worldwide, the stated intention to push the potential of gene editing tools alongside ongoing patient genotyping/phenotyping advances is well chosen. The panel are optimistic that this team can deliver new technological platforms allowing the implementation of these tools and provide new therapeutic options.

Axe 2-Mutation-independent gene therapies reflect the commitment to develop approaches that can be applied to broader ranges of patients with IRDs, such as where there are no known mutations or where photoreceptors have already been lost. This will play to the team's strength in optogenetics research and could also feed into the realm of photoreceptor protection. Again, this is a competitive space, including the exploration of more appropriate opsins for optokinetic strategies. Nevertheless, this team are set to make important contributions to advances in this field. Also notable in this axe is the value derived from Gamut Tx as a new spin-out company which attracted investment from Advent France Biotechnologies. Ongoing development is planned and there has been a merger with a similarly sized company called SparingVision. Technology developed by the team at the IdV has recently been transferred to SparingVision and she will continue to invest time and effort into this commercialisation action. This is worthwhile since there is potential to develop and roll out a new gene therapy in the clinic. SparingVision also provides scope for the employment of young scientists and provides a unique opportunity for members of the team.

Axe 3 AAV capsid engineering is a core activity of the team, and they will continue to seek to improve the therapeutic potential and safety of these vectors both in the retinal and also in the context of brain function. Their collaborative efforts with other idV teams will be fruitful.

Axe 4 – will continue to develop large animal models of retinal disease, especially since they carry many advantages over rodent models. This could be viewed as a unique strength of the IdV, and although it comes with obvious ethical and cost challenges, the intention to continue with macaque models displaying photoreceptor degeneration offers value for testing the efficacy of gene therapy and optogenetic therapies being developed across cognate groups.

Finally, Axe 5 seeks to more fully understand immune reactions to ocular gene therapy. This is an appropriate and well-chosen goal since the immunogenicity of vectors remains and is likely to remain a limiting factor that diminishes the potential of gene therapies. There have already been some advances looking at T-cell activation and identification of systemic antigen-specific immunosuppression (SRAII). This is referred to as a potentially useful immunomodulatory strategy to control inflammatory reactions following ocular gene therapy and seems to be a well-chosen avenue that will provide opportunities for high-quality discovery science. Moreover, advances in this area will serve to reinforce the translational potential of the parallel projects.

RECOMMENDATIONS TO THE TEAM

The team leader is highly accomplished at multidisciplinary research and her collaborative support of many projects within the Institute is commendable. That said, and as discussed following her presentation, there is a risk that her efforts are being spread too thinly by taking on too many support roles for other colleagues' research. She responded both robustly and positively to this query and the panel could appreciate the energy and capability she brings to her leadership of the group. Her collaborative ethos is to her credit but we would still advise caution and urge her to make careful choices about where to channel efforts and resources. This would serve to maximise the impact of her invested time and effort. This concern is also reflected by her input into commercialisation which is highly commended by bringing economic development and enhanced translational flow-through from her academic research. Undoubtedly, this will require further investment of effort, so we would recommend that the team leader seeks to build a team that can help to carry her ever-increasing burden of time commitment and responsibility for her academic and company work.

Team 16: AGEING IN VISION AND ACTION

Name of the supervisor: ANGELO ARLEO

THEMES OF THE TEAM

The team focuses on low-level visual perception and visuo-spatial cognition in normal and pathological ageing. Mixing psychophysical, behavioural (locomotion, eye movements) and brain imaging (fMRI, EEG) approaches it has investigated how visual sensitivity and allo/egocentric visuo-spatial cognitive systems are affected during ageing. They combine classical, highly constrained psychophysical approaches with more realistic and real-life approaches. Over the last years, the team extended its research to pathological ageing. Grounded on the SilverSight cohort running since 2015 at CNHO/CIC, the team is now refocusing on deep phenotyping and functional exploration of visual dysfunctions in pathological ageing (AMD). The team is the only one at IdV mastering human behavioural and neuroimaging approaches to investigate integrative low-to-high-level visual functions.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report made several recommendations, considering that the team was new and focusing on a new topic (normal ageing) for both its team leader and members.

A first recommendation was to improve the number and quality of research production. The team has now produced more than 40 research articles, including several in high impact journals (Nature Human Behaviour, Nature Neurosci, ELife).

The second question concerned the partnership with Essilor. The team successfully renewed the Industrial Chair with ANR/Essilor and has enlarged its industrial partnerships (SNCF) and collaborations with IdV spin-offs (GensSight, StreetLab). These new partnerships are in phase with the refocusing of the team from normal to pathological ageing, with a strong interest on AMD and clinical trials.

The last recommendation was to strengthen the team's contribution regarding undergraduate and doctoral training. The Team increased the number of PhD students with five who completed their doctoral studies and 7 ongoing over the last period. It has also boosted its contribution to undergraduate training, through hosting Master/Bachelor students and clinical assistants and coordinating BSc/MSc courses at several Universities in Paris.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**4**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	6
Post-doctorants	1
Doctorants	10
Sous-total personnels non permanents en activité	**17**
Total personnels	**21**

EVALUATION

Overall assessment of the team

Over the last years, the team has produced a series of innovative results on normal ageing vision regarding temporal noise and objects motion visual sensitivity, visuo-spatial disorders and the help of geometric cues for locomotion/navigation. In particular, the Team has shown that retinal (photoreceptor) not central neural noise is the main factor for explaining losses in temporal contrast sensitivity. The psychophysical tools designed to factor out different sources of noise have led to three patents and results have been published in very good disciplinary journals (J Vision, IOVS), Using both real-life experiment and computational modelling, the team has investigated how different visual behaviours (VOR, navigation, locomotion) are affected during normal ageing and the compensatory visual cognitive mechanisms. These studies led to several high-impact publications (Nature Human Behaviour, ELife) and complementary brain imaging (EEG, MRI) works. Finally, the team supports the SilverSight Cohort at CHNO/CIC that is an important asset for investigating early visual deficits in normal and pathological ageing. The cohort is pivotal for current and future longitudinal, deep-phenotyping studies on retinal degenerative diseases. These scientific activities are inserted within an exceptional environment for mixing human behavioural and clinical studies in vision, grounded on the Essilor Industrial chair and R&D start-up companies (mostly spin-off of the IdV). This environment allows to design and validate clinical testing and rehabilitation solution, leading to several patents and high-impact clinical studies (Nat Med). The team is now entering a new phase with the leave of its founding leader. Overall, the panel considers that this is an excellent team.

Strengths and possibilities linked to the context

The team is only one mastering human behavioural/cognitive approaches in both healthy and pathological conditions. It has built an expertise on deep phenotyping of visual function in healthy and pathological (AMD) ageing, from retinal imaging to clinical and cognitive evaluation. These activities are grounded on the SylverSight Cohort, with nearly 150 variables that are recorded in more than 300 people so far. They will complement these evaluations with brain imaging (EEG, MRI) approaches during visuo-cognitive tasks. Thus, there is a strong opportunity to investigate how early sensory loss can lead to deficits in visual cognition and autonomy across lifespan. The other strength is the transfer of knowledge from basic human neuroscience to the design of visual aids and solutions for autonomy loss. The team has already contributed to several patents and technological development. It has acquired a solid background in the use of multimodal behavioural measurements during natural tasks and natural environment. This expertise contributes to clinical trials (e.g. PIONEER clinical trial) and human factors analysis in different navigation contexts (e.g. partnership with SNCF). These expertises may be more widely used in different clinical trials operated at IdV and the CHNO/CIC.
The research activities are grounded on the strong intersectorial environment linked to the historical Essilor Industrial Chair. It has been enriched with new partnerships with large companies (e.g. SNCF) and spin-off, local R&D innovation start-up companies such a StreeLab or GeneSight. There seems to be a close scientific and technical collaboration with StreeLab to develop clinical tools for functional exploration and rehabilitation strategies that can create a vivid environment for both training and research.
Finally, the team has strong opportunities to inform the public on the societal challenges related to visual loss in ageing and retinal degenerative diseases. The team has done so through its recent scientific achievements. There is a clear opportunity to enlarge this in the interest of the whole IdV.

Weaknesses and risks linked to the context

The original research objectives targeted normal ageing, a field in which the team had no previous track record and may be unrelated to the IdV strategy regarding pathological dysfunctions. Thanks to the redirection of the projects towards retinal degenerative disease and the support of the Essilor Industrial Chair, this weakness has been largely overcome. The connections to the existing cohorts and clinical trials are also nicely developed. However, the risk is now to spread the limited, available permanent workforces across too many projects.

Analysis of the team's trajectory

The team will undergo several major changes. First, the team leader has moved to the EssilorLuxottica Company, starting a LabCom between IdV and Essilor. A new leadership shared between a young researcher and a clinician is organised, in line with the scientific objectives of the next years. The team will be also strengthen with the integration of clinicians from both Ophthalmology and Radiology. Second, the team will strengthen its interactions with clinical studies in pathological ageing (most AMD), linking deep ophthalmological phenotyping

with behavioural/perceptual studies on visuo-spatial cognition. In particular, one interesting goal is the better characterising the transition between normal and pathological age-related changes. These objectives will be articulated around the SilverSight cohort. Third, the team will build on its expertise on human behaviour in naturalistic tasks/environments to run experiments in real-word conditions, to find both behavioural (locomotion, eye/head movements) and physiological (EEG) biomarkers of autonomy loss. There will be a strong push in using machine learning and computational models to process these multimodal data in order to define better biomarkers integrating patient reported and performance-based measurements. There are also several projects related to behavioural assessment of clinical trials for retinal stimulation. The overall team's project is divided into fourteen components forming three Axis attributed to specific scientific leaders. There are two research lines, related to prefrontal cortex functions and normal ageing in rodents that are largely, if not entirely, disconnected to the team's objectives.
The trajectory is highly ambitious but also very important for the IdV, as the team gathers all the expertise on human behaviour at the Institute. It also operates the SilverSight cohort that could be of major importance, not in terms of size but being a monocentric cohort with both high quality and dimensionality. It is not entirely clear how the healthy volunteers and patients will be stratified and distributed across the different projects. The efforts around the deep phenotyping could be better linked with other teams at IdV. Moreover, there is a risk that investigating so many dimensions and relying on machine learning for extracting biomarkers lead to a descriptive, statistical approach rather than on hypothesis-driven and mechanism-testing approaches. For instance, previous work from the team had identified low- and mid-level vision deficits in normal ageing that are somehow diluted across the different research projects. In the same vein, the interesting question raised about the use of geometric cues in the lower visual field vanished behind too many behavioural indexes (posture, locomotion, gaze…) rather than trying to build a stronger theoretical framework on spatial cognition and its changes. Although the projects are interesting, one might wonder if the current workforce is sufficient to meet all these objectives. We understand that there might be external technical resources (StreetLab, LabCom with EssilorLuxica) but there is not clearly presented.

Overall the team's trajectory is clearly important for IdV and low-vision studies. The expertise and technical resources are somehow unique in France where low-vision and ageing vision research is dying out. But the team is at the crossroad: it needs to better set a scientific strategy in line with the recruitment of more clinical and scientific resources and competences.

RECOMMENDATIONS TO THE TEAM

The team should carefully consider the few key points:
1) The scientific vision and strategy of the team towards its environment (StreetLab, LabCom with EssilorLuxetica) needs to be clarified and better structured. There seems to be strong opportunities and resources available within this close environment but, with the help if the IdV Directorship, a clear strategy with priorities should be built. In the same vein, and as the team is involved in several Clinical trials, the interactions with other teams shall be improved. The team appears somehow isolated from the rest of the Institute despite the fact it good plays a key role in making IdV a true 'Vision Institute' and not just an 'Eye Institute'.
2) An effort should be made to better structure the scientific hypotheses and pathophysiological mechanisms behind all these behavioural and physiological markers. It is even more important when embarking towards brain imaging (MRI, EEG) where specific tasks and hypothesis must be made and related to current research. The team should try very hard to attract young permanent researchers investigating normal and/or pathological low-to-mid-level vision using psychophysics and/or imaging techniques. It would help to build functional models of visual perception and its loss.
3) The deep phenotyping approach is, and will produce an enormous amount of data. This is both a strong opportunity for OpenScience at IdV but also a treat as to succeed the team would need to attract Data scientists (either as engineers or researchers). Within the Sorbonne Université and CNRS/INSERM environment, there might be existing opportunities.

Team 17: COMPUTATIONAL NEUROSCIENCE OF SENSORY SYSTEMS

Name of the supervisor: ROMAIN BRETTE

THEMES OF THE TEAM

The team develops quantitative models to understand sensory systems at two different levels, (i) elucidating the neuronal mechanisms of excitability and (ii) questioning the relevance of 'neural codes' to capture the linking hypothesis between physiology and behaviour. The team has also developed several state-of-the-art tools for neural network simulations and spike sorting software. Over the last years, the team has developed a new research theme, the integrative modelling of both physiology and behaviour of the ciliate Paramecium which allows to simulate neuronal and behavioural responses to many different sensory signals. To further develop these approaches, the team has decided to quit IdV.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has not explained how it considered recommendations of the previous report.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**3**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	1
Sous-total personnels non permanents en activité	**1**
Total personnels	**4**

EVALUATION

Overall assessment of the team

The team has conducted excellent-to-outstanding research over the past years as demonstrated by a list of 30 articles, which is impressive given the small size of the team. Funding has been very good, and the team has made several major contributions, especially concerning the development of software packages for analysis of spiking activity and for simulations. The decision to move to a new lab is clearly a loss for the IdV, but it is hoped that collaborations will continue in the future.

Strengths and possibilities linked to the context

The team has produced excellent research. More specifically:
Productivity is excellent with 30 peer-reviewed research articles for three permanent researchers/engineers, including several papers in theoretical and experimental neurosciences in interdisciplinary journals (ELife, Sci Adv) and computational neurosciences journals (PLOS Comp Biol). The new research lines (postural control, Paramecilium model) have also led to several disciplinary journals (J Exp Biol, PLOS Comp Journal). The team leader has also produced several high impact review articles (BBS, Curr Opinion Neurobiol). 2) Funding; the team has been awarded with three ANR Grants, for both its legacy research (neuronal excitability) and its more high-

risk innovative research (Paramecilium model). 3) Although the research topics of the team are mostly outside the scope of the IdV, the team has developed productive interactions with at least two teams for testing the AIS positioning hypothesis and developing the Spiking Circus software, respectively. 4) Training: the team was made of three permanent researchers/engineers, with limited interactions with training courses at the local University curricula. They supervised three PhD doctoral works. 5) Impact: the development of two, widely distributed, open-source of software is a major contribution to the worldwide scientific community. They have greatly contributed to the visibility and attractiveness of both the team and the IdV.

The team It has developed the resistive coupling theory, a biophysical model of the axonal initial segment (AIS) and its contribution to action potential generation. In particular, they have shown the role of its structural plasticity, namely adjustments of AIS position, through back-current propagation. This mechanism can be essential for neuronal plasticity. This theoretical work was conducted in close collaboration with the UMR1072 (University of Marseille), leading to important publications (PNAS, ELife, Sci Adv) and funded by ANR. The team leader has also theoretically questioned the classical neural code hypothesis. This epistemological work has led to a target article in Behav Brain Sciences as well as two streams of active research: (i) a new view of postural control and (ii) the development of a new model for integrative computational modelling, the cilliate Paramecium. This last aspect has involved technological development for new experiments, in collaboration with Physicists, and has been funded by the ANR. These two lines of research being outside of the IdV objective and agenda, the team was closed as it moved to a new laboratory.

The team leader is a remarkable scientist with very diversified interests (philosophy, computational neuroscience, neuroinformatics) developing opportunistic lines of research. The panel considers that he is essentially a highly creative 'electron libre' rather than a team player. As a consequence, his departure from IdV, while a loss for the Institute, should not raise problems. All team members have been productive over the last five years, and their excellent research shall continue at the new Host laboratory.

An important contribution of the team is the development of two neuroinformatics tools which have gained very high recognition and are widely distributed. BRIAN is an open-source Neural network simulator, based on code-generation technology and is highly flexible in terms of hardware environment. The software is used for both training and research and led to several publications (ELife, Sci Rep). The second contribution is the Spiking Circus software, an open-source spike sorting tool developed in partnership with another team of the IdV. The sofware is widely distributed and led to several high-impact publications (ELife).

Weaknesses and risks linked to the context

There are no specific weaknesses to be mentioned. The reason for the team to leave IdV was the growing divergence between the team's (and team leader's) scientific agenda and the topics covered at IdV.

One risk must be mentioned and shall be carefully considered by IdV: the maintenance and continuing development of the Spiking Circus software, previously done in collaboration with Team #8 is a challenging task in a highly competitive, worldwide environment and given the lack of institutional support for such technological efforts in the French environment. It is not clear how the departure of the Team will impact this collaborative effort and whether IdV will continue to support this.

Analysis of the team's trajectory

The entire team will move to a new Host Institution to pursue his new research endeavour of building a new (unicellular) model (Paramecillium) to investigate cellular information processing and behavioural responses to different sensory information. No research plans have been provided and therefore the trajectory was not evaluated.

RECOMMENDATIONS TO THE TEAM

The departure of the team might challenge the development of the Spiking Circus software as the conceptor was a key element. The team #8 has confirmed that it will continue this effort, but a clear strategy of how this is going to be made (i.e. human resources) was not clearly proposed. This open source software is important and given the highly competitive alternatives (e.g. kilosort), both team #8 and IdV Direction shall define a well-thought strategy.

Team 18: WAVEFRONT ENGINEERING MICROSCOPY

Name of the supervisor: VALENTINA EMILIANI

THEMES OF THE TEAM

The wavefront engineering microscopy group is an interdisciplinary team composed of optical physicists, engineers, computational neuroscientists, biophysicists, and neurobiologists. The group has pioneered the use of wave-front engineering for neuroscience, including approaches such as computer-generated holography, generalised phase contrast and temporal focusing. While the bulk of the work is focused on methods development, the group also combines these approaches with optogenetics and functional imaging to investigate neuronal visual circuits with unprecedented spatial and temporal precision. The research focus of the group is twofold, with both a technological and neuroscientific goal: (1) continue to innovate abovementioned all-optical approaches, and (2) use this for the investigation of visual circuits.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The following weaknesses were identified during the previous evaluation: (1) The biological problems could have been more clearly elucidated and described to emphasise the novelty and their context with regard to previous published work in the field; (2) there is probably greater capacity for PhD students training and little information is provided on the PhD mentoring; (3) Small core staff and relying on a single software maintenance person who has been around for a decade; (4) The time taken to reap the benefits of the new collaborations within the IdV is likely to be long and may therefore impact on the publication rate. These weaknesses have been largely addressed. The team further anticipates that the inclusion of the team S11 will strengthen even further the possibility to focus on clearly identified biological questions. However, while this is certainly possible, the alignment of S11's research agenda with the mission the IdV is not as strong as it could be and therefore may not be as straightforward as suggested.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**7**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	4
Post-doctorants	3
Doctorants	5
Sous-total personnels non permanents en activité	**12**
Total personnels	**19**

EVALUATION

Overall assessment of the team

This is an outstanding team on all fronts including scientific production, outreach and relevance to the field and the mission of the IdV. Despite moving to the IdV relatively recently (March 2018), the team produced sixteen research articles, seven review articles and four book chapters during the evaluation period. The team's two-folded approach can be viewed as an excellent template for other teams in the unit. It is unfortunate therefore that the team appears to experience substantial hindrance by systemic issues at the institutional level.

Strengths and possibilities linked to the context

The team has delivered scientific outputs in multiple domains that are all highly relevant for neuroscience in general as well as the mission of the IdV. Focusing on methods development, they have delivered substantial advances in volumetric photostimulation, holographic endoscopy and 1 P-2P Scanless voltage imaging, optogenetic actuators and high-throughput connectivity mapping. These developments are considered relevant because they enable e.g. investigations into deep brain regions processing visual information, as well as studying the neural circuits supporting vision in freely moving rodents. The relevance of these methods to the mission of the IdV is further demonstrated based on basic science studies that use the new technologies: though not the primary focus of the group, they have also successfully collaborated to apply these developments to answer biological questions, including e.g. functional connectivity in the mouse retina, and the emergence of hub cells in the developing cortex, which play an important role in the processing of sensory input from other brain areas.

The team leader can be considered a world-leading expert in the field and has an outstanding record both in terms of scientific contributions and obtaining prestigious national and international grants and awards (e.g. ERC Advanced Grant in 2020; 3 NIH-Brain initiative grants, 2 HFSP grants, etc. 1MTEC). The team is also exceptionally well equipped with eight optical microscopes for all-optical circuits manipulation, some of these systems (3P holographic patterned microscopes, holographic micro-endoscope, 2P scanless microscope for voltage imaging) are unique worldwide and has excellent positioning in national and international research networks and several high-level scientific and industrial (3i, Amplitude Systems, NKT Photonics) collaborations. The team's strong implication in the promotion of science (participation in several high-level training schools specialised seminars and teaching) is also commendable.

Weaknesses and risks linked to the context

Team S18 has few inherent weaknesses. Some minor concerns are: (1) While the team delivered several outstanding scientific contributions and is certainly prolific in terms of conference communications, the number of research outputs (16 original research articles) in relation to team size over a period of five years seems more modest. (2) While the high visibility and international reputation of the team leader certainly contribute significantly to the attractiveness of the team, it could overshadow the visibility of team members working their way up to independence.

Besides these, it is important to acknowledge the possible inheritance of weaknesses of Team S11, which will close in 2025 and is planned to integrate into S18.

There are also some weaknesses related to the team's enabling environment and the embedding of the IdV. While the team already has multiple collaborators, it would benefit from closer collaboration with the university physics department. The attractiveness of the team for recruitment of young students or postdocs is lessened because the salaries are not competitive with what can be offered by other European countries or even other local institutes. Further, as noted in both the group's self-evaluation and SAB report, urgent attention is required to address infrastructure issues such as temperature control, electrical stability, and internet connectivity. These challenges are adversely affecting productivity and endangering crucial equipment essential for the group's work. Finally, the reduced available space and high rental costs for offices and research laboratories is a general weakness of the IdV that also seems to affect this team.

Analysis of the team's trajectory

The team has a clear roadmap for the near and mid-term future. The plans include a multitude of research directions that all follow logically from past work and remain relevant to the field and the mission of the IdV and have already established funding support. Specifically, the plan to develop new volumetric photostimulation approaches for bidirectional neuronal control on large volumes, links tightly to past work and promises to deliver novel in vivo investigations into visual cortex that rely on perturbing neuronal activity across multiple connected brain regions. The aim to optimise photostimulation depth using three-photon and holographic microscopy is relevant in the context of imaging deep brain regions that contribute to visual processing and likely play a large role in neural adaptations to eye disease. The projects on 2P scanless voltage imaging are similarly expected to advance investigations into the functional organisation and dynamics of cell-type-specific excitatory and inhibitory cortical circuits, and the same is true of the aim to deliver high-throughput connectivity mapping. There are also plans to combine the previously mentioned developments to enable restoration of vision, control of excitatory circuits in visual cortex, the control of neuronal circuits in freely moving mice, and mapping connectomic, synaptic and functional connectivity of commissural neurons in the zebrafish visual system. These application projects not only clearly contribute to the mission of IdV but also push the frontiers of the field.

Further, it is reassuring to see concrete plans for the continuation of team S11's work into neurovascular coupling and brain oxygenation using in vivo 2 P-3P and fUS imaging of blood flow regulation. However, it is not directly

clear to what extent some of the planned projects will be specifically focused on the visual system (this might be expected based on the overall strategy of S18 and address concerns regarding alignment of S11 and the mission of the IdV).

RECOMMENDATIONS TO THE TEAM

The team will presumably grow significantly after 2025 with the incorporation of S11. This, and the fact that the team already includes 'subunits' lead by mid-level staff looking to increase their independence, raises concerns about the team becoming too fragmented and/or too big to manage properly. Plans need to be developed to mitigate this risk. The team could also increase their efforts to create space for team members to increase their visibility in the community. The team's concerns regarding the lack of a formal collaboration with the physics department does not seem too difficult to overcome, although it is not entirely clear to this committee what factors currently prevent this to being pursued.

Scientifically, the plans to hire are research biologist is applauded, and with them it could be worth engaging in more clinically oriented application studies to strengthen the alignment with the mission of the IdV even further.

Team 19: 3D MICROSCOPIES

Name of the supervisor: GILLES TESSIER

THEMES OF THE TEAM

The S19 3D Microscopy group started in 2019 is a relatively new group (although already evaluated in the previous evaluation after being at IdV for several months) that has experience in experimental physical optics in the imaging area with additional expertise in the use of new materials and applications in biological imaging. This is a unique interdisciplinary combination that guarantees a major impact on the field if the high level of research conducted is maintained. In particular, the group is working on holographic methods in imaging, in which the use of the phase and amplitude of the measured light returning from a sample, together with appropriate methods for controlling the phase and amplitude of the light incident on the sample, and digital acquisition with the ability to perform advanced calculations, makes it possible to circumvent fundamental limitations in imaging.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Most of the objections from the previous evaluation were related to the early stage of the group, which was just forming, and the answers to the objections have been aptly addressed and most of them are no longer debatable. Thus, several objections to the group's insufficient size and critical mass in terms of organisational sustainability, ability to promote or build long-term stable expertise have been resolved. Another objection was limited participation in overseas conferences. The current list of fifteen invited papers and more than 35 conference contributions is extensive. A final objection in the previous assessment was the apparent lack of connection of the team's activities to the research topics at IdV and potential links to the activities of other groups. However, in the context of the group's current state of activity, I see no danger of thematic inconsistency here. The optical methods being developed by S19 are in the forefront of imaging methods and, if developed to an appropriate level, could be translated into imaging studies of the eye. In particular, solutions concerning auto referencing in the quantitative phase imaging or the use of new wavefront modulators could find application in fluorescence imaging methods for the eye and in interferometric techniques (being developed in Team 20) both in the context of scientific research (e.g. optogenetics) and diagnostic imaging (e.g. dynamic Full Field OCT).

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**3**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	1
Doctorants	4
Sous-total personnels non permanents en activité	**7**
Total personnels	**10**

EVALUATION

Overall assessment of the team

Globally, this is an excellent to outstanding team. It is active in publishing across the spectrum of possibilities: 28 high-quality scientific articles of high novelty and relevance to the field, published in outstanding journals (quality and availability in open science), two chapters in books, six patent applications. With the current staff resources, it is an excellent result. In addition, the teaching, conference and popularisation activities carried out by the leaders and members of the team are impressive. The group also patents and licenses its solutions increasing the utility value of the entire IdV activity.

Strengths and possibilities linked to the context

The new methods introduced by S19 are innovative and have great application potential. The topics of the activities carried out are well thought out by the leader and well integrated with the activities of the community in this area, providing opportunities for team members to develop in a wide spectrum from basic research in physical optics and material sciences (development of holographic methods and phase and interference microscopy methods) with application work towards structural (wavefront control) and functional (active observation of nanoparticle interactions) biomedical imaging. All in all, the group is operating at the world's highest level, developing into a very strong, well-managed team, operating in a vertical integration scheme. A major strength of the team is a new aspect of research in the IdV-wide portfolio, which can greatly enhance scientific work on vision through the introduction of new unconventional techniques, especially positively influencing other groups contributing to the photonics facility. For example, methods for phase registration of incoherent light, such as fluorescent light, or a technique for locating and tracking nano-objects can be used in research into new therapeutic techniques or studies of the biology of the vision process, and with further development can be used as diagnostic tools. These techniques guarantee the introduction of new, out-of-the-box solutions. The very presence of the S19 group with its profile of activities benefits the functioning of other teams with similar themes (S20, S21) by aggregating knowledge from related but not overlapping fields.

Weaknesses and risks linked to the context

The current results obtained by the group are very convincing, but they are still quite preliminary and require much additional work before they are translated to eye imaging. For example, in the case of the wavefront modulation method using the thermo-optical refractive index effect, the limitation is the time of wavefront changes and crosstalk effects which will significantly limit the applicability of this technique for in vivo applications. One direction that could make things more interesting is to expand close collaboration to adapt methods to vision science. It has been shown that steps have already been made in this direction through zebrafish imaging, but it seems to me that the spectrum of potential applications could be increased. The group's existing portfolio is somewhat lacking in such vision collaborations. In addition, the teaching load on the leader (~200 h/year) and team members is very high.

Analysis of the team's trajectory

The projects carried out by the S19 team and described in the portfolio show the great potential of the topics pursued although they are loosely related to the study of the eye itself. However, I consider this more of an advantage than a disadvantage. An example of this is a new method for adaptive tracking of nanoparticles with localisation using a holographic system and spectroscopic observation of the nanoparticle's interaction with the environment. Another example presented in the portfolio is a new alternative approach to wavefront modulation using the thermo-optical refractive index effect – a concept that is quite simple, but very difficult to implement in practice (which S19 researchers have successfully achieved). Another example is the use of phase-sensitive methods for recording incoherent light, such as fluorescence or autofluorescence light, using self-referencing on appropriately designed phase masks and reading from an appropriately processed specular pattern. The planned research work adequately corresponds to the possibility of applying previously developed knowledge in eye research. Nanoparticle localisation or label-free imaging applied to flow cytometry or tissue imaging is a direction that is in line with expectations and natural in adapting the obtained solutions to the needs of IdV. It is also in line with the group's basic knowledge. Just one minor comment that, for example, the attempt to develop a deformable lens – so relevant to the work of Team 20, in my personal opinion would be a more interesting direction than the proposal to develop a microendoscope head using smart lenses.

RECOMMENDATIONS TO THE TEAM

IdV may consider creating an interface between the activities of group 19 and other groups. One suggested possibility is to introduce a core engineering facility to support the activities of other groups, where group 19 and 20 could share their results and suggest how to implement these findings in other collaborating teams. It would also be a good way for the research trajectory to approach and effectively influence eye research.

Team 20: LIVE IMAGING: PATIENTS AND CELLS

Name of the supervisor: KATE GRIEVE

THEMES OF THE TEAM

The S20 Live Imaging Group, which began operations in 2021, is a new interdisciplinary team with core expertise in optical engineering, concentrating mainly on *in vivo* biomedical optical imaging. The main research focus of S20 is the development of new imaging techniques and their immediate translation to the clinic or research laboratories. The main research efforts are related to the development of methods related to ophthalmoscopy and *in vivo* microscopic techniques, such as Scanning Laser Ophthalmoscopes using Adaptive Optics (AO-SLO), full-field interferometric imaging, Optical Coherence Tomography (OCT), and Laser Doppler Holography (LDH). The activity of the S20 group is a technical support for translational work related to ophthalmology matching well with the overall IdV operation.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The group activity was not assessed in the previous evaluation.

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**3**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	4
Sous-total personnels non permanents en activité	**5**
Total personnels	**8**

EVALUATION

Overall assessment of the team

This is an outstanding team. The group is engineering-oriented and is engaged in highly charged development work to advance and then introduce new instrumentation into clinical settings. With this scope of work, S 20 has an excellent publication record with 34 original publications well recognised in the optical engineering, OCT and ocular imaging community. This output is complemented by three review publications, three patent applications and two chapters in books. Particularly noteworthy is the extraordinary effort to disseminate research results in 103 conference reports, many of which are invited papers.

Strengths and possibilities linked to the context

The group has very good national and international visibility, as evidenced by staff awards, participation of the manager and team members in organising committees of international conferences and editorials of leading professional journals in their field. Pioneering work using dynamic contrast FF-OCT in organoids has inspired the activities of many research groups. It is currently one of the hot topics in the field of in vivo optical imaging. The group has achieved great success in translating FF-OCT technology into clinical applications in ophthalmology, overcoming all the fundamental and technical limitations of the technology and making a paradigm shift in

OCT imaging of the eye. In addition, these activities resulted in the founding of a start-up. Noteworthy is the custom operability of the group having a clinic facility and direct access to the best experts in clinical ophthalmology, as well as patients with eye diseases. This creates an interface that allows for immediate socio-economic impact, which is extremely important in the high-profile activities of scientific institutions. At the same time, the group is anchored at the Institute de la Vision itself, having close contact with biologists and having animal models or organoids at its disposal. Moreover, the scientific environment at the IdV enables the identification of new and attractive therapeutic directions in ophthalmology, providing inspiration for further efforts to develop optical technologies. Apart from anything else, the experience of constructing devices from scratch and then developing the technology and translating it into clinical settings is an extremely demanding challenge that few research centres in the world are able to meet. This is a time-consuming activity due to the process of ergonomizing measurement devices and performing many tests before reaching a satisfactory level in the development of potential biomarkers. This makes the S20 group a very attractive partner for other research teams at IdV. Another strength of the S20 group is its leader, who in addition to great competence and creativity has extensive international experience, understands cultural nuances and is able to lead international cooperation and attracting international funding – giving more opportunities for her co-workers to grow.

Weaknesses and risks linked to the context

Developing technology and satisfying scientific ambitions in engineering fields are difficult to reconcile with personnel deficits. Unfortunately, sustaining a high level of competitiveness with other groups or companies producing instruments with similar technologies requires maintaining technical expertise at a constant level – and this, in turn, requires maintaining a core engineering staff of at least one senior engineer (either in optical engineering or software engineering) to pass on core technical competence to the next generation of PhD students and postdocs. Another minor deficit is the dispersion of group members between IdV and the ophthalmic hospital. The self-assessment does not describe a plan for managing such a group in terms of maintaining integrity – it would be important to have procedures in place to allow all team members to meet frequently.

Analysis of the team's trajectory

The planned development direction and research project focusing on the introduction of a functional FF-OCT technique is fully justified. Given the experience and past achievements of the S20 team in the development of FF-OCT and dynamic contrast in cellular imaging, the planned further development of these techniques in the context of monitoring experimental therapies for retinal degenerative diseases is most advisable. In particular, optogenetic or cell-based therapies require the introduction of new instrumentation to monitor photoreceptor function at the cellular level in an objective and measurable manner. Light-induced retinal responses can be monitored using the dynamic contrast (D-FFOCT) method introduced by the team leader and co-workers. Admittedly, this requires speeding up the imaging system and stabilising patient movements by actively tracking the eye position. Although ambitious, such improvements are possible with the expertise of the S20 staff. The development of such a method will have a huge impact on introduced therapies by speeding up the validation process and increasing efficacy which will consequently lower their final cost.

RECOMMENDATIONS TO THE TEAM

The team is impressive and remarkably tonic. It should be given enough space to conduct their excellent research work. Kate Grieve needs help (SAT assistance) to be discharged from the extra workload associated with translational issues. Again, a core engineering facility would be helpful for faster translation and better communication between groups.

Team 21: QUANTITATIVE IN VIVO CORNEAL AND OCULAR MICROSCOPY

Name of the supervisor: KRISTINA IRSCH

THEMES OF THE TEAM

The SE/21 team of Quantitative in vivo corneal and ocular microscopy focuses on the development of new technologies for improved ophthalmic diagnosis during actual pathologies. Addressing issues with imperfect transparency (scattering) has been an important topic for the PI since her arrival to IdV and persist to remain one of the most important objectives. The activities focus uniquely on precise quantification of the problem as well as finding routes towards its mitigation. Further, scattering is planned to be exploited for improvements in imaging capacity (better resolution due to the access to higher spatial frequencies found in diffuse light (speckle). Finally, exploiting the involuntary motion of the eye is planned to be exploited as a novel scanning mechanism, where the PI's expertise in eye- and head-motion tracking can efficiently be utilised.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

N/A, this is a new team started in 2022

WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**1**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	0
Sous-total personnels non permanents en activité	**0**
Total personnels	**1**

EVALUATION

Overall assessment of the team

The group was established in 2022, although the PI's history at IdV dates back to 2014. The team has only just started, and it is yet to be assembled and populated. Still, the trajectory and the aspirations are undeniable. The PI is very well engaged with the relevant community and is involved in numerous collaborative activities. Twelve publications in peer-reviewed journals (including these in prestigious journals), 24 in conference proceedings, one editorial, two books, and five book chapters is a very decent sign of productivity. Further four patents issued and two applications filed signifies a strong engagement with transfer. While some aspects of the team's activity were considered to be excellent, the panel identified a certain number of weaknesses that mean that it may be premature to establish the team as an independent entity.

Strengths and possibilities linked to the context

The PI is very well connected to the international scientific community, having well-established links with the University of Colorado-Boulder, Hôpital National de la Vision, Rothschild Foundation, Langevin Institute, Johns Hopkins University, École Polytechnique, French Eye Bank, Kastler – Brossel Laboratory. The PI is a frequent invited

speaker at important meetings including SPIE Photonics West, Frontiers in Optics, and a Gordon Research Conference. With respect to the funding situation, the self-report indicates a number of important grants from various sources (NIH R21 funding, Horizon 2020 Marie Curie Reintegration funding, IHU FOReSIGHT, ANR). Further, she is no stranger to public media. The team combines efficiently the fundamental considerations of light propagation in complex environments with the relevant technologies of adaptive optics, OCT and others and identifies their optimal use for advancements in ophthalmic diagnostics. The team focuses on very important limitations which have not sufficiently been addressed in the past, mainly because their overcoming or mitigation has been considered ranging between extremely difficult and impossible. On the scale of risk/gain, the portfolio of research directions is very diverse. While some activities seem near completions (e.g. characterisation of corneal transparency), it may be a long journey to see other ideals turned into practical instruments (super-resolution image reconstruction using speckle). It is the very presence of the ambitious goals which gives hope for successful pursuit of the team and the acquisition of sustainable funding.

Weaknesses and risks linked to the context

All planned activities are essentially collaborative with the involvement of external partners, which include some very influential names such as Piestun, Gigan, Fink, etc. as well as some strong rising stars. While it is a great reassurance that the team's research is being taken very seriously, it is hard to recognise whether it will be the PI or some of the partners steering the research. The team is just starting and it operates under personnel deficit. Building the expertise of future team members from scratch will require a large time involvement. Especially in turning the ideas to instruments, the absence of skilled engineers/technician with deeper insight into photonics can be particularly problematic. If funding becomes successful, the fast growth can be difficult to accommodate as the institute seems to face difficulties with laboratory and office space globally.

Analysis of the team's trajectory

The team's trajectory is yet to be built. All research ambitions stand on solid grounds with strong PI's expertise in all aspects. There are no obvious factors which would prevent the PI in continuing along the already successful path, building a steep publication track record, applying for and receiving further funding and be even more recognised by the scientific community. I am particularly excited to see the complex media photonics finding its way to such an important field of application and I would very much wish to see the new team becoming the world-leading driver of this domain. Beyond the PI, the team needs to build itself and diversify its expertise very soon. While looking into new concepts and performing proof of concept experiments can be successful and productive in a very small team, translational activities will require many synchronised minds and hands. Given that this is a very competitive domain it would be a shame to give up on exploiting the full application potential due to personnel deficits.

RECOMMENDATIONS TO THE TEAM

It is not yet clear whether the team is sufficiently solid to be established as an independent entity. A solution to consolidate the teams maybe to attach to the team #19. This merging would have the advantage of establishing a natural link between fundamental and applied research.

CONDUCT OF THE INTERVIEWS

Dates

Start: 30 November 2023 at 9:00

End: 01 December 2023 at 17:00

Interview conducted: on-site

INTERVIEW SCHEDULE

November 30th

9:00-9:30 Welcome coffee (closed-door): Visiting committee with the Hcéres advisor (Conference Room IdV)

9:30-9:45 Presentation of the evaluation process to the unit by the Hcéres advisor

9:45-10:45 Presentation of the unit scientific outputs and strategy by the lab director Serge PICAUD (30′ presentation + 25'discussion) – Conference Room IdV

10:45-11:15 Coffee break (conference room IdV)

11:15-12:15 Visit of the facilities (Photonics, Imaging and streetlab, in two groups).
- Group 'Imaging' (IdV + Hospital)
- Group 'other facilities': Streetlab (20′)/Photonics (20′)/Imaging (20′)

12:15-1:30 p.m. Lunch (closed-door with the committee and Hcéres advisor) – Cafeteria

1:30 p.m.-3:30 p.m. Presentation of the scientific programs and research results by group leaders

PANEL A
Therapeutics

1 h 30 – 2 p.m. - S12 ANNABELLE REAUX-LE GOAZIGO: PATHOPHYSIOLOGY OF THE ANTERIOR SEGMENT OF THE EYE
2 p.m.-2:30 p.m. - S13 EMELINE NANDROT: PHYSIOLOGY OF THE RETINAL PIGMENT EPITHELIUM AND ASSOCIATED PATHOLOGIES
2:30 p.m.–3 p.m. - S14 FLORIAN SENNLAUB AND MICHEL PAQUES: INFLAMMATION IN RETINAL DEGENERATION AND VASCULAR REMODELLING
3 p.m.–3:30 p.m. - S15 DENIZ DALKARA: GENE THERAPIES AND ANIMAL MODELS FOR NEURODEGENERATIVE DISEASES

PANEL B
Photonics

13:30-14: 00 - S19 GILLES TESSIER: 3D MICROSCOPIES
14:00-14:30 - S18 VALENTINA EMILIANI: WAVEFRONT ENGINEERING MICROSCOPY
2:30 p.m.–3 p.m. - S20 KATE GRIEVE: LIVE IMAGING: PATIENTS AND CELLS
3 p.m.–3:30 p.m. - Emerging team KRISTINA IRSCH: QUANTITATIVE IN VIVO CORNEAL AND OCULAR MICROSCOPY

3:30 p.m.-4 p.m. Coffee break (conference room IdV)

4 p.m.-5:30 p.m. Debriefing (only committee members and Hcéres Scientific advisor) Amphitheatre Hospital 15–20 for 'Panel A'/Conference Room IdV for 'Panel B'

December 1st

9:00-9:30 Welcome coffee (closed-door): Visiting committee with the Hcéres advisor

9:30-12:30 Presentation of the scientific programs and research results by group leaders Amphitheatre Hospital 15–20 for 'Panel A'/Conference Room IdV for 'Panel B'

PANEL A
Development

9:30-10: 00 - S1 ALAIN CHEDOTAL: DEVELOPMENT, EVOLUTION AND FUNCTION OF COMMISSURAL SYSTEMS
10:00-10:30 - S2 OLIVIER GOUREAU: RETINAL DEVELOPMENT AND REPAIR: USE OF PLURIPOTENT STEM CELLS
10:30–11:00 - S3 FILIPPO DEL BENE: DEVELOPMENT AND FUNCTION OF THE VERTEBRATE VISUAL SYSTEM

PANEL B
Visual information

9:30–10:00 - S8 OLIVIER MARRE: VISUAL INFORMATION PROCESSING: NEURAL CODING AND VISION RESTORATION

10:00-10:30 - S16 ANGELO ARLEO (DENIS SHEYNIKHOVICH & MICHEL PAQUES): AGEING IN VISION AND ACTION

10:30–11:00 - S11 SERGE CHARPAK: IMAGING OF SENSORY PROCESSING AND NEUROVASCULAR COUPLING

11:00-11:30 Coffee break (Amphitheatre for Panel A and conference room IdV for Panel B)

PANEL A
Development

11:30-12:00 - S4 JEAN LIVET: NEUROGENESIS AND CIRCUIT DEVELOPMENT

12:00 – 12:30 - S5 XAVIER NICOL: MECHANISMS OF SENSORY MAP DEVELOPMENT

PANEL B
Genetics

11:30–12:00 - S6 ISABELLE AUDO AND CHRISTINA ZEITZ: IDENTIFICATION OF GENE DEFECTS LEADING TO NON-PROGRESSIVE AND PROGRESSIVE OCULAR DISEASES

12:30-1:30 p.m. Lunch (closed-door with the committee and HCÉRES advisor)

From 1:30 p.m. Meetings with the various categories of personal with both panels

1:30 p.m.-2 p.m. Discussion with scientists (without team leaders)
2 p.m.-2:30 p.m. Discussion with PhD students and post-docs
2:30 p.m.-3 p.m. Discussion with engineers, technicians and administrative personnel (in French)
3 p.m.-3:30 p.m. Discussion with the team leaders (closed-door)

3:30 p.m.-4 p.m. Private meeting of the visiting committee (closed-door) (Conference Room IdV)

4 p.m.-4:30 p.m. Discussion with the director (Serge PICAUD) and assistant director (Isabelle AUDO) (closed-door)
4:30 p.m.-5 p.m. Discussion with the representative of the managing bodies (closed-door)& local representatives

5 p.m.-6 p.m. Private meeting of the visiting committee (closed-door) (Conference Room IdV)
6 p.m. End of the visit and Departure from Paris

GENERAL OBSERVATIONS OF THE SUPERVISORS

Marie-Aude Vitrani
Vice-Présidente Vie institutionnelle et démarche participative
Sorbonne Université

à

Monsieur Eric Saint-Aman
Directeur du Département d'évaluation de la recherche
HCERES – Haut conseil de l'évaluation de la recherche et de l'enseignement supérieur
2 rue Albert Einstein
75013 Paris

Paris, le 10 mai 2024

Objet : Rapport d'évaluation DER-PUR250024399 - IdV - Institut de la vision

Cher Collègue,

Sorbonne Université vous remercie ainsi que tous les membres du comité HCERES pour le travail d'expertise réalisé sur l'unité de recherche « IdV ».

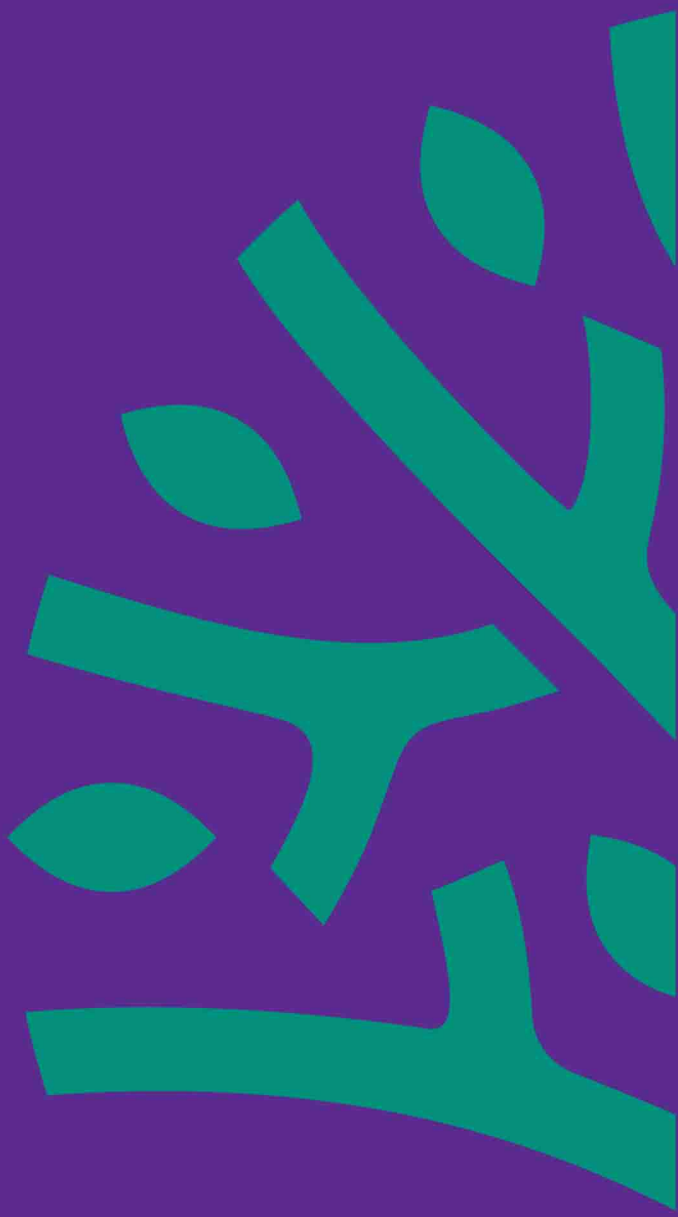
Sorbonne Université n'a aucune observation de portée générale à formuler sur le rapport d'évaluation transmis.

Je vous prie d'agréer, Cher Collègue, l'expression de mes cordiales salutations.

Marie-Aude Vitrani
Vice-Présidente Vie institutionnelle
et démarche participative

The Hcéres' evaluation reports are available online:
www.hceres.fr

Evaluation of Universities and Schools
Evaluation of research units
Evaluation of the academic formations
Evaluation of the national research organisms
Evaluation and International accreditation



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