Research evaluation

EVALUATION REPORT OF THE UNIT

BIGR – Biologie intégrée du globule rouge

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Paris Cité,
Institut national de la santé et de la recherche médicale – Inserm,
Université de La Réunion,
Université des Antilles

EVALUATION CAMPAIGN 2023-2024
GROUP D

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High Council for evaluation of research and hignter education

In the name of the expert committee[1] :

Eric Soler, Chairman of the committee

For the Hcéres[2] :

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.

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Mme Hélène Rouard Directrice scientifique EFS Ile-de-France

CHARACTERISATION OF THE UNIT

- Name: Integrated Biology of the Red Cell
- Acronym: BIGR
- Label and number: UMR-S1134
- Composition of the executive team: Yves Colin & Caroline Le Van Kim

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE6 Physiologie et physiopathologie humaine, vieillissement

THEMES OF THE UNIT

The unit UMR_S1134 'Integrated Biology of the Red Blood Cells (RBC)' is dedicated to the comprehensive multiparametric analysis of human erythroid cells and associated disorders, which represent worldwide health concerns. The unit is composed of four teams working on:

(i) the physiopathology of sickle cell disease (SCD) and other major erythroid disorders (polycythemia vera, Gaucher disease, central retinal vein occlusion), red blood cell transporters and rare (novel) human blood groups (TEAM 1);
(ii) Bioinformatic modelling and molecular dynamics of macromolecular protein complexes involved in red blood cells and platelet functions (TEAM2);
(iii) host-parasite interactions and molecular mechanisms of plasmodium falciparum infection, parasite homing and persistence in humans (TEAM 3);
(iv) and the interactions existing between red blood cells and the spleen with the aim to understand the mechanisms of red blood cell clearance and malaria (TEAM 4).

All teams share a common objective of proposing innovative therapeutic strategies and optimising existing medical interventions.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The unit has been historically located at the 'Cabanel Premise' Paris 15e within the National Institute of Blood Transfusion (INTS). However, due to significant policy changes implemented by the government, the INTS was dismantled in 2021. As a result, the unit has temporarily relocated to a remote site at Broussais Paris 14e (AP-HP premises). The unit is scheduled to move to its final location at the Necker hospital campus site by early 2024. In addition to these important changes, the unit has historically maintained two remote locations: a Caribbean site at Pointe-à-Pitre University (Guadeloupe), and one at Saint-Denis de la Réunion, Université de la Réunion (Réunion). This is a peculiar and quite unique situation, allowing the unit to get access to territories directly impacted by the major erythroid disorders that are under study (e.g. SCD).

RESEARCH ENVIRONMENT OF THE UNIT

In the previous mandate, the Unit has been operated in an optimal environment at the INTS location (Cabanel premise). This location provided a central position for red blood cell research, with close proximity to the Necker Hospital and Imagine Institute. However, following the dismantling of the INTS, the Unit underwent a significant reorganisation and temporary re-localisation to a remote site at Broussais, AP-HP. By the end of 2023 or early 2024, the Unit will reach its final location at the Necker Hospital campus. This move will provide an optimal environment for the Unit, as the campus is known for its strong focus on erythroid cell biology and hematology. Additionally, the Unit will benefit from its immediate proximity to the IMAGINE institute. Being embedded within the Necker ecosystem, the Unit will have privileged access to the SFR ('Structure Fédérative de Recherche') Necker (with state-of-the-art support and technology platforms). Furthermore, the Unit plays a significant role in the PIA Labex GR-Ex, which is co-headed by the Unit Director and has its central management located on-site at IMAGINE Institute.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	7
Maîtres de conférences et assimilés	11
Directeurs de recherche et assimilés	4
Chargés de recherche et assimilés	7
Personnels d'appui à la recherche	19
Sous-total personnels permanents en activité	**48**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	8
Post-doctorants	3
Doctorants	21
Sous-total personnels non permanents en activité	**34**
Total personnels	**82**

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

Nom de l'employeur	EC	C	PAR
INSERM	0	7	11
UNIVERSITÉ PARIS-CITÉ	12	0	3
AUTRES	0	4	4
UNIVERSITÉ DE LA RÉUNION	3	0	1
UNIVERSITÉ DES ANTILLES	3	1	0
Total personnels	**18**	**12**	**19**

GLOBAL ASSESSMENT

The UMR_S1134 'Biologie Intégrée du Globule Rouge' (BIGR) is a biomedical unit created in 2014 at the 'Institut National de la Transfusion Sanguine' (INTS), Paris. It is endorsed by INSERM, Université Paris Cité, as well as Universities of Antilles and Reunion. The unit is composed of four teams. The primary focus of the unit is on RBC biology and associated disorders, encompassing research ranging from basic to translational studies on erythroid cells. By combining fundamental and applied research to produce models for therapy development in major global diseases, the unit holds a prominent position in the field of clinical innovations.

The overall scientific output of the unit is excellent to outstanding with numerous publications in the top speciality journals (Blood, Haematologica, NAR) and outstanding contributions to highly ranked generalist journals (2xNEJM, Nat Commun 2023, Cell Host Microb 2023, Sci Transl Med, PLoS Biol) as lead authors. The scientific production of the unit is remarkable given the unexpected challenges faced by the unit following the closure of INTS by the government.

The attractiveness and visibility of the unit are both excellent to outstanding. The unit has created several international networks and collaborations with South American (Argentina, Uruguay, Brazil), Caribbean (CAREST network with 11 Caribbean sites), African (Mali, Senegal) countries, and with India, establishing connections with areas where people suffer most from the RDB disorders under study. The unit has organized>10 national, and>20 international meetings. At the national level, the unit has made a significant impact on the erythroid research field through shared governance of the PIA network of excellence Labex GR-Ex focused on RBCs. This Labex has played a critical role in promoting erythroid research at both the basic and the clinical level in France. All 4 teams within the unit are deeply involved in the Labex, with Team 1 sharing leadership responsibilities and Team 4 playing a strategic role in establishing a dedicated clinical protocol enhancing clinical valorization. This outstanding collaboration and structuring of the research community, extending beyond the unit's perimeter, exemplify the collaborative spirit of the unit and all its teams.

The unit's total budget is in the range of ~2–3 M€ per year, 90% of which is from external sources including, since 2017:9 European contracts (including 8 as PI for a total amount of ~3M€), five international non-European contracts (including 4 as PI, total amount ~1M€), public agencies (6/14 ANR contracts as PI, total amount ~2M€), associations (33 contracts as PI, e.g. Gates foundation, FRM team label, SFH, CGRF, total amount ~1.3M€), PIA/IDEX/LABEX (>30 contracts, total amount ~800k€), and fifteen industrial contracts with eleven different pharmaceutical/biotech companies, including two CIFRE contracts (total amount ~1.6M€). The overall budget of the unit has been continuously increasing since 2018, reaching its maximum (~3M€) in 2022.

The unit involvement in clinical valorization is excellent to outstanding as a result of their combined efforts in basic and clinical research and their pursuit of innovative disease management strategies. The unit has achieved remarkable outputs in terms of patents (13 patents produced) and clinical discoveries (1 phase II clinical trial led by the unit, two phase II clinical trials deriving from the unit's discoveries), providing valuable leads for more efficient disease management in conditions such as SCD, malaria, Gaucher disease, central retinal vein occlusion, or Polycythemia vera. The involvement of two teams in clinical trials to suppress malaria progression through vaccination (PRIMAVAC) and in discovery of compounds to manage the disease progression is an outstanding feature strengthening the international visibility of the unit. The involvement of one team in the systematic discovery of novel blood group antigens is also an outstanding aspect of the research performed in the unit (4 new blood groups discovered) and strongly contributes to its international visibility and leadership in this field. The interactions with the non-academic sector are also excellent to outstanding. A notable aspect of the unit is its exceptional involvement in specialized scientific education. The unit director and future director hold positions in the doctoral school at Paris Cité University. They have established a dedicated Master's program focused on RBCs, which has been successfully running for the past two years. Teams 1, 2 and 4 actively contributed to this Master's degree by organizing 3 specific courses. One significant strength of the unit is its strategic positioning at remote sites such as the Caribbean or Reunion Island, as well as its connections with various continents, including South America, India and Africa. This unique positioning of all 4 teams within the unit allows for increased patient outreach, and provision of education and health where it is the most needed (e.g. the CAREST network gathering multiple sites/countries in the Caribbean). Therefore, the unit's commitment to education extends globally, including outreach efforts in area where people are most affected by major global erythroid diseases. The unit's outreach activities are therefore excellent to outstanding and they strive to share their knowledge within the community, including bioinformatic resources and education (EUR Graduate School in Bioinformatics and Genomic Medicine at Paris Cité University). Therefore, all four teams strongly contribute to the knowledge dissemination and two teams are particularly involved in structuring scientific education programs within the Paris Cité University.

The unit's arrival at its final location on the Necker Hospital campus presents a great opportunity to strengthen connections with leading teams in the fields of erythropoiesis and clinical management of red blood cells disorders. However, it also represents a new challenge, as successful integration will depend on the ability of all teams within the unit to maintain their leading positions in their respective fields and expand their leadership to achieve full international recognition. Seeking integration to European programs and networks will be crucial in strengthening the Unit's leadership and increasing its attractiveness within the complex, stimulating and competitive research environment at the Necker campus.

In conclusion, BIGR is an excellent biomedical research unit, well positioned both at the national and international levels, with a clear potential to expand further its current achievements at the EU level.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The BIGR unit has actively taken into account the recommendations provided by the previous HCERES committee and incorporated them into their overall strategy. Here are some examples of how the unit has addressed these recommendations:

1. Increasing visibility through publications in top journals: The unit has made significant progress in this area by publishing their research in highly ranked and visible journals. Notable publications include articles in prestigious journals such as the New England Journal of Medicine, PLoS Medicine, Nature Protocols, Science Translational Medicine, Science Advances, Blood, Nature Communications 2023, Lancet Infectious Disease, PLoS Biology, Nucleic Acids Research, and EBioMedicine. These publications have helped to enhance the unit's visibility and impact within the scientific community.

2. Integration of animal models: Although the unit did not have an on-site animal facility at INTS or Broussais premises, they have established strong collaborations with national and international teams to conduct in-vivo assays, primarily using mouse models. These collaborations have allowed the unit to test the physiological relevance of their findings and therapeutic strategies. The upcoming relocation of the unit to the Necker campus will provide direct access to an animal facility through the SFR Necker, resolving the previous lack of on-site access to animal models.

3. Addressing the underrepresentation of molecular biology and genetics: The unit has taken steps to address this issue by implementing CRISPR technology through the recruitment of dedicated staff. They have also incorporated genome editing in primary human cells and conducted high-throughput human genetic analyses, such as Exome-Seq. These advancements have strengthened the unit's capabilities in molecular biology and genetics research.

4. Enhancing internal exchanges between teams: The unit has fostered increased collaboration and communication among the four teams through the creation of a scientific organizing committee (COSU). This committee facilitates regular presentations of projects by researchers and young scientists from all teams, allowing for critical thinking and constructive criticism. These meetings also include remote staff through video conferences. Additionally, the unit has re-evaluated and adjusted the composition of the teams to reinforce Team 4 through the mobility of one researcher and two engineers, as well as Team 3 with the addition of two engineers.

By implementing these measures, the unit has demonstrated its commitment to address the recommendations provided by the previous HCERES committee and continuously improving its research capabilities and collaborative efforts.

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 scientific objectives of the unit have expanded over the past contract to cover novel aspects of erythropoiesis including for instance the interactions and crosstalk between RBCs and their tissular environment. While expanding the focus, the unit teams manage to maintain their potential to reach clinical valorisation and innovation. New teams will emerge or join the unit for the next contract and will bring in their specific complementary expertise. Another notable aspect of the unit is the historical and continuous integration of a protein modelling bioinformatics team, providing an interdisciplinary environment, creating unique opportunities for the combination of clinical findings with bioinformatics and mathematical modelling, and fostering a win-win situation. This is overall excellent.

Assessment on the unit's resources

The unit potential to attract extramural funding from varied sources (academic, private, international) is excellent. This applies to all teams. In addition, the unit assembled a unique collection of (biophysical) expertise and technologies into an integrated 'red cell clinic' dedicated to the multi-parametric analysis of RBCs. This multidisciplinary platform is unique in Europe and contributes to the unit's visibility. The inclusion of dedicated bioinformatic expertise in modelization of macromolecular assemblies also strongly contributes to the unit's complementary environment and resources.

Assessment on the functioning of the unit

The functioning of the unit is excellent and satisfactorily covers human resource management, safety, environment, ethical protocols and protection of data and scientific heritage.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The unit has established a strong international visibility in the field of RBC biology, particularly in the discovery of rare and novel blood groups, as well as expertise in transfusion research, and RBC disorders such as SCD, rare anemias, etc. The unit has also gained recognition for its contribution to malaria research and has conducted clinical trials in this area. In addition to focusing on RBCs themselves, the unit has expanded its research to include the interactions between RBCs and surrounding organs and tissues such as adhesion with the endothelium and the complex interactions with the spleen. These areas of study have direct implications in the fields of parasitology (i.e. malaria) and (rare) anemias. One interesting aspect of the unit's strategy is its incorporation of bioinformatics modelling in the study of RBC biology. This approach is considered innovative and up-to-date, especially given the increasing use of deep modelling strategies in biological applications on an international scale. Another outstanding feature of the unit's working environment and strategy is its close proximity and strong connection with the clinical world (6 hospitals, EFS, IMAGINE). The short-term (early 2024) planned move to a top-level clinical campus (Necker) will further strengthen these existing relationships and enhance the unit's ability to collaborate with clinical institutions, including the IMAGINE institute.

Weaknesses and risks linked to the context

The process of settling down in their final location on the Necker Campus is expected to be time-consuming for the BIGR unit. While the unit has demonstrated exceptional adaptability during their previous move from INTS to the Broussais location, it is important to acknowledge that another relocation may temporarily impact their activities. Evaluation panels and supervising bodies should consider this aspect when assessing the unit's progress. However, it is worth noting that the Necker campus environment presents a significant opportunity for the unit to realise their ambitious project to enhance their international visibility within a multidisciplinary setting that encourages clinical interactions.

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

Strengths and possibilities linked to the context

The unit teams have demonstrated their capability to secure funding at the national and European levels, enabling them to pursue their ambitious research goals. It is noteworthy to highlight the development of the 'Red cell platform', a remarkable collection of technologies dedicated to the study of red blood cells. This platform, which is unique in Europe, and absent in many other countries, has been established through the collaborative expertise in erythrocyte physiology and physiopathology from the 4 teams within the unit. The presence of such a structure serves as a valuable asset, enhancing the attractiveness of the teams/unit in the field, while also increasing their national and international visibility.

Weaknesses and risks linked to the context

As previously noted in the previous evaluation report, the absence of animal facilities was identified as a limitation that hindered the investigation of molecular and pathophysiological mechanisms at the organismal level (e.g. mouse, zebrafish). However, this limitation will no longer be applicable as the unit will join the Necker campus, where they will get access to state-of-the-art animal facilities. This move will provide the unit with an opportunity to be immersed in a stimulating environment that offers strong expertise in (onco-) hematology and in in *vivo* studies. However, a major fragility remains concerning the administrative support staff: the whole unit is currently managed by a single person who is on a fixed-term contract i.e. non-permanent position. This situation places the unit at risk and it should be fixed by either getting a permanent position for the person in place or getting permanent support staff via internal mobility campaigns (INSERM or University) to maintain the necessary administrative support of the unit.

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

The BIGR unit has appointed a dedicated quality manager who is responsible for promoting and monitoring quality procedures related to laboratory notebooks and traceability. This is particularly important due to the close collaborations between the unit teams and private companies through ongoing collaborative contracts. The unit recognises the significance of maintaining high standards in these areas. The prevention of psychosocial risks, non-discrimination politics, and gender parity are all actively managed by the unit directorship and a dedicated staff. The current unit director holds a prominent role at Paris University and possesses extensive experience in addressing these aspects of scientific life at all levels (students, permanent/non-permanent staff, support staff). This expertise serves as an asset in effectively managing human resources and addressing any potential issues that may arise.
The protection of intellectual property and digital resources falls under the responsibility of the INSERM IT department, which is well versed in safeguarding research datasets at the national level. This ensures that the unit's intellectual property and digital assets are adequately protected.

Weaknesses and risks linked to the context

There are no weaknesses according to this criterion for this Unit.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The unit benefits from an excellent to outstanding visibility, particularly at an international scale. It has set up several networks: International Research Network in Hematology with Brazil, Caribbean Network of Researchers on sickle cell disease and thalassemia (CAREST) with eleven Caribbean countries, and has set up dedicated partnerships with Argentina, Uruguay, Africa for sickle cell disease and India for BioInformatics. The unit has participated in the organization of numerous international meetings (Global Congress on Sickle Cell Disease, Gordon Red Cell Conference, Int Conf on BioInformatics and Biomedicine, etc.). In addition, the unit is a reference center for sickle cell disease and rare blood groups. At the national scale, the strong involvement of the unit in the PIA Labex GR-Ex-governance has been instrumental to structure the entire research field at the national level, with a significant impact at the basic, clinical and educational levels. Average annual funding has been 2100 k€, with international (ANR with Brazil, 2 NIH for a total amount 667 k€, Japanese GHIT Fund), European (3 FEDER, 2 H2020, 2 Marie Curie) and national (13 ANR; 6 as PI, 1 'labellisation équipe FRM») funding. The unit has supervised 49 PhD theses (27 defended) for 23 HDRs. All teams contribute to the excellent visibility and attractiveness 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

The unit possesses an excellent to outstanding visibility in the fields of basic RBC structure and physiology (RBC surface proteome, complex protein dynamics, tissular interactions and clearance), major disorders involving RBCs (such as SCD, or CRVO), transfusion medicine and blood group antigens, and in the fields of malaria research and malaria vaccine development. The unit is also heading the National reference center for blood group antigens (CNRGS), and is at the forefront of novel blood group antigens discovery, with the identification of 4 new blood groups in the past 4 years. As a result, the unit holds a prominent position in transfusion medicine and contributes significantly to the visibility of French research in this area. The positioning of the unit at the forefront of clinical innovation in the fields of SCD, CRVO, malaria vaccine, and anti-malaria drug development puts the unit in a prime position in the European landscape of clinical research in the field of erythroid (-related) disorders. Besides these key achievements, the unit has set up important online bioinformatics resources dedicated to RBC structural proteins, and their dynamic folding which are widely open to the research community, thereby boosting their visibility in the field. Additionally, the unit contributes to European research through a Marie Curie Innovative Training Network (ITN) coordinated by a former member of Team 1.
The unit has organized more than twenty international meetings covering the full range of their scientific topics, including the prestigious GRS Gordon Conference on Red Cells (USA, 2017), the 4th Global Congress on Sickle Cell Disease (Paris 2022), the 7th International conference on Plasmodium vivax research (Paris, 2019), and more than ten international conferences on biomedical engineering and bioinformatics (between 2015–2021).
Unit members are also involved in scientific publishing and evaluation, and act as Associate Editors in eight different specialty journals (including Frontiers journals, IJMS, Transfusion, BioMed Informatics, Amino Acids), Editorial board members in fourteen specialty journals (including Blood, Open Life Science, Scientific Rep, and Frontiers journals).

The BIGR unit has a unique geographical organization, with remote sites at the Caribbean (Guadeloupe) and Reunion Island. This strategic deployment allows the unit to benefit from a central national location in Paris, while being in close proximity to patients and individuals most affected by widespread RBC pathologies (e.g. SCD). This distinctive setup has proven to be a significant advantage in developing local monitoring networks that are clinically relevant and improving patient care (e.g. CAREST). The unit's ability to host staff from remote locations and establish collaborations with universities in these areas has been instrumental in fostering fruitful partnerships and generating productive scientific output. The unit has made important contributions to collaborations with the South American continent (Team 1), India and Lebanon (Team 2), through international invitation programs (Argentina, Uruguay, India). Additionally, initiatives like the ECOS Sud program and PHC CEDRE (Lebanon) have facilitated the training of several students, professor invitations and knowledge exchange. Training of students from UK has also taken place (Team 3), underscoring the attractiveness of the Unit as a whole. The unit has supervised 49 PhD theses (27 defended) for 23 HDRs.

The unit and its team leaders have demonstrated a high level of attractiveness and recognition at the national level. The unit played a pivotal role in founding the Labex GR-Ex, a network of excellence that has significantly advanced the field of RBC/erythropoiesis research in France. This prominent position has also facilitated international collaborations (e.g. with the New York Blood Center). Researchers from three out of the 4 teams within the unit actively participate in the management of the Gr-Ex Labex, with Team 1 leader acting as deputy director of the network, Team 4 leader being in charge of the Clinical committee, and Team 1, 2 and 4 current/former members being in charge of the Education committee (Team 1), Bioinformatic committee (Team 2), Translational Biology committee, Red Cells committee and Blood Transfusion committee (Team 1). Additionally, Team 4 leader has been appointed as the Head of Medical Direction at the Pasteur Institute in Paris, further highlighting the attractiveness and expertise of the unit's members in the biomedical field. The unit's success in securing funding from highly competitive research programs, such as international (non-EU) contracts (5 in total, including 4 as PI: 2x NIH grants, GHIT FUND, etc.), European contracts (9 in total, including 8 as PI: PRIMAVAC, FEDER, INSPIRE, etc.), the ANR (14 in total, including one with Brazil, 6 as PI), and FRM (1 team FRM label), serves as a strong indicator of its attractiveness and achievements in national and international research calls.

The BIGR unit has successfully brought together multidisciplinary expertise focused on a singular biological entity: the RBC. A significant achievement of the unit is the establishment of the 'Red Cell Clinic', a cutting-edge technological platform that combines biophysical, cell biology, microscopy, bioinformatics assays and tools specifically designed for the study of primary RBCs. This unique facility enables researchers to investigate various aspects of RBC biology and function. Furthermore, the unit has leveraged innovative technologies to replicate interactions between whole organs and RBCs, such as microsphiltration, which allows for the monitoring and modelling of RBC clearance within the microcirculation of the spleen. These technological advancements provide exceptional opportunities to study important pathophysiological conditions related to RBCs. The presence of such state-of-the-art technologies and facilities within the unit creates a distinctive research environment in France, enhancing its international visibility and recognition as a leading institution for RBC research.

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

While it is true that the BIGR unit has experienced the departure of some productive researchers and work group leaders, and Team 3 will separate from the unit due to site-specific scientific policies at the Necker campus (not hosting parasitology-oriented working groups), the relocation of the unit to the Necker/Imagine campus presents a significant opportunity to enhance visibility and attractiveness. The unit can benefit from the strong and stimulating environment provided by the new campus, which will support the development of its strengths in RBC research and medical innovations. The move to the Necker/Imagine campus offers the unit access to a vibrant scientific community and state-of-the-art facilities, fostering collaboration and interdisciplinary interactions. This favorable environment can contribute to the unit's growth and enable it to further advance its research in the field of RBCs. While changes in team composition and location can present challenges, the unit has the potential to leverage the opportunities provided by the new campus to strengthen its position and continue making valuable contributions to RBC research and medical advancements.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The unit's scientific output is excellent to outstanding (390 original publications, 168 of which have a leading position), with publications signed as lead authors in highly ranked generalist journals (NEJM, Sci Adv, PLoS Biol, Nat Commun 2023, Nat Protoc), and in the best specialist journals (Blood, Blood Adv, Haematologica, NAR, Cell Host Microbe2023, Lancet Inf Dis, EBio Med, ,.)., thereby producing impactful research. All teams within the unit have contributed to this output, with a balanced contribution relative to team size. It is worth noting that the unit has achieved this remarkable scientific output despite facing the organizational challenges caused by the closure of INTS.

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 BIGR unit has increased its publication rate in top-level journals where they are lead authors, since the past contract. The unit produced a total of 390 scientific articles (168 of which were signed as lead authors) and 68 review articles, with a well-balanced contribution of the 4 Teams respective to their size and staff composition. Each team contributed to articles published in the best journals in their disciplines (specialty journals) such as Blood, Blood Adv, or Haematologica (Teams 1 & 4), Transfusion or Nucleic Acids Res (Team 2), EBio Med (Teams 3&4), and outstanding contributions to highly ranked generalist journals such as New England J Med, Nat Commun, Nat Protoc, PloS Med (Team 4); Sci Adv, Lancet Inf Dis, PloS Biol, Cell Host Microbe2023 (Team 3).
The unit's work has resulted in an excellent to outstanding level of clinical discoveries and valorization (clinical trials such as placental malaria vaccine PRIMVAC, clinical investigations in the field of doping in sport,

production of thirteen patents, identification of drugs involved in plasmodium clearance by the spleen, optimisation of blood storage, discovery of new blood group antigens, etc.).

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

There are no weaknesses according to this criterion for this Unit.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The unit's valorization activities are excellent to outstanding. The unit has filed thirteen patents and is involved, as principal investigator, in clinical studies and clinical trials (including one phase II trial) which have produced promising results for the P. falciparum vaccine and the treatment of central retinal vein occlusion. This output showcases the unit's commitment to innovation. Numerous industrial collaborations (Imara, Genzyme, Shire, Addmedica, BioRad, etc.) have brought in over 1000 k€. Two CIFRE grants have been obtained. The unit has set up several databases for hematologists (RESPIRE, CALR-ETdb, RHeference, etc.) and made available to the community various web servers and tools for protein structure analysis (SWORD2, MEDUSA, PYTHIA). It is also involved in informing the general public on a regular basis through various communication media with more than 50 radio or television interviews and written press communications.

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

The BIGR unit has demonstrated an excellent to outstanding level of product development, particularly in the medical field. They have established numerous industrial partnerships, including twelve R&D contracts with ten different biotech companies (including Biorad antigenes, Addmedica, Imara, Cerus, Giullin Pharma, Annexin Pharma, etc.), and two industrial contracts for PhD students (CIFRE). These collaborations encompass a wide range of projects, including the development of drugs to treat plasmodium, novel techniques for detecting and treating red blood cell disorders, as well as research on malaria in Africa in infected regions to their benefits. Additionally, the unit has filed thirteen patents, showcasing their commitment to innovation. As principal investigators, the unit has participated in several clinical studies and in clinical trials (PRIMVAC Phase II being led by the unit, and two Phase II clinical trial on central retinal vein occlusion deriving from an original patent from the unit, and led by the CHRO hospital, or the Biotech Annexin Pharmaceuticals). They have also been involved in one PHRC (Programme Hospitalier de Recherche Clinique) project. This extensive involvement in clinical research highlights the unit's dedication to translating their scientific findings into practical applications.
In addition, the unit's unique expertise in bioinformatics analysis of complex protein folding dynamics and collection of technologies focused on RBC biology (the Red Cell Clinic) has led to the dissemination of several online tools and databases (RESPIRE, CALR-ETdb, RHeference, SWORD2, etc.) for the research community, and has attracted industrial partnerships for drug testing and evaluation (as in the case of anti-PD9 testing in SCD with Cydan/Imara; Annexin testing in CRVO with the Annexin Pharmaceuticals company; or phenotyping of stored RBCs with Zimmer Biomet, New Health Science, Cerus, or GSK OpenLab Foundation).
The unit has also been actively engaged with civil society on a regular basis. This includes participating in scientific presentations aimed at the general public, engaging in meetings with various patient associations and participation to more than 50 TV and radio shows, including national prestigious media such as 'France Info' and 'Le Monde'. To reach a wider audience, the unit utilises various media platforms, including television and radio programs, as well as scientific tools available on the web. These channels allow them to disseminate their research findings and contribute to public understanding and awareness of their work.

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

The unit has difficulties in maintaining a sufficient and stable administrative staff that could be devoted to the partnerships to be developed with industrial and associative actors.

ANALYSIS OF THE UNIT'S TRAJECTORY

The scientific trajectory of the BIGR unit has undergone significant evolution since its initial focus on red blood cell membrane proteins associated with blood antigens and carriers of blood groups. Over time, the unit has become a global reference in the identification and characterization of new blood groups, as well as their clinical significance. This expertise has contributed to the unit's strong visibility and recognition in the field. Furthermore, the unit has expanded its research scope to include major red blood cell pathologies such as sickle cell disease (SCD) and Diamond-Blackfan anemia (DBA). The unit has also delved into areas such as immunohematology, transfusion medicine, malaria, RBC-spleen interactions, malaria vaccination, and the study of RBC structural proteins and their modelling. This diversification has allowed the unit to gain prominence and establish itself as a leading entity in these research domains. In addition to its research endeavors, the unit has developed a unique multimodal technical platform known as the red blood cell clinic. This dedicated facility is solely focused on the study of primary red blood cells, providing the unit with a distinct advantage within the European research ecosystem. Over the past fifteen years, the unit has also made significant investments in cutting-edge bioinformatics. A dedicated team within the unit focuses on protein dynamics and modelling, seamlessly integrating with the wet lab activities. This integration allows for fruitful cross-fertilisation between wet and dry science activities, enabling the unit to leverage patient genetic data and assess the dynamic architectural complexes of red blood cells.
Overall, the BIGR unit's scientific trajectory has expanded and diversified, encompassing a wide range of research areas related to red blood cells. The unit's expertise, unique facilities, and interdisciplinary approach have contributed to its strong visibility and impact in the scientific community.

The BIGR unit has faced a unique trajectory as a result of the major restructuring of the French blood centers, particularly the dismantling of the INTS and the transfer of most activities to EFS. This restructuring necessitated the unit's relocation from the Cabanel premise and the challenges of maintaining staff positions. The unit had to adapt to a temporary research site at the Broussais premise before eventually reaching its final location at the Necker campus, which is planned for the end of 2023 or the beginning of 2024. Despite the uncomfortable and hazardous situation, the unit successfully navigated through these challenges. The unit's governance demonstrated exceptional capacity in dealing with multiple supervising bodies and institutions such as INSERM, EFS, the university, and AP-HP hospital. They effectively managed the complex task of restructuring, maintaining staff positions, coordinating with multiple partners, and working on new building plans. Throughout this process, the unit maintained its ongoing research lines and continued to produce high-level scientific output.
The unit's staff also played a crucial role in keeping the research going and publishing in highly ranked journals despite the numerous issues associated with large-scale lab restructuring. They managed experiments, logistics, and working habits while dealing with personal challenges such as commuting and stress. The unit demonstrated exemplary strength and dedication to scientific research and education.

The implementation of the unit in the Necker research campus will bring new opportunities and address historical issues, such as the lack of direct access to animal facilities. The unit will have access to cutting-edge core facilities and an animal experimentation facility. Being embedded within the Necker hospital, the INEM, and the IMAGINE institutes will provide a rich scientific and clinical environment, fostering collaborations with internationally recognized laboratories. The unit will also participate in the scientific life of the IMAGINE institute by joining as an Associate Laboratory. Furthermore, the restructuring within the unit will better balance different research lines and promote young leaders who will co-head independent teams in the next mandate. The unit aims to promote the emergence of young researchers and clinicians, who will co-lead a team on blood antigens and sickle cell disease. The unit's recognition in the field has also attracted a new team focused on anemia and overload diseases, that will be co-led by a young University assistant professor and a PU-PH. This restructuring brings in new talent and demonstrates the dynamic environment of the unit and the long-term vision of the past and future governance for the next contract.

RECOMMENDATIONS TO THE UNIT

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

The BIGR unit is recognized as a fully functional and well-organized structure with complementary research themes and adequate resources. In addition to its scientific activities, the unit also prioritizes non-scientific aspects such as the prevention of psychosocial risks, the establishment of non-discrimination policies, and monitoring gender parity. These efforts demonstrate the unit's commitment to creating a supportive and inclusive work environment. Given the unique and challenging context that the unit is faced with the closure of INTS and multiple moves to remote locations, the panel recommends paying particular attention to signs of acute stress or psychosocial issues within the staff. It is crucial to acknowledge the difficulties that the entire staff has encountered, independent of their own will. Moving forward, it will be essential to reassure and support the personnel, ensuring that everyone can settle in the best conditions possible. This will contribute to maintaining a positive and efficient working environment as the unit transitions to its final implementation site at the Necker campus. By addressing these concerns and providing the necessary support, the unit can foster a sense of stability and well-being among its staff. This, in turn, will contribute to the unit's continued success and productivity as it embarks on the next contract in the new and stimulating environment of the Necker campus.

Concerning the students and postdocs, identifying one or several trusted persons to whom the students may turn to in case of professional issues or need for independent advice would be a great addition to the current organization. Furthermore, Implementation of yearly evaluation/follow-up of PhD students (in the form of CSI 'Comité de Suivi Individuel') is currently needed.
Another interesting point would be to create an internal young scientist organization for PhDs and postdocs to stimulate scientific exchange and manage social events to maintain and/or create a warm and supportive internal atmosphere. Technical staff should also create a similar association and benefit from the same type of organization for exchange.
While the panel acknowledges the difficulty to deal with such an issue in the French system, and as mentioned previously, additional administrative staff are currently critically needed. Only one dedicated staff on short-term contract is in charge of the management and administration of the whole unit. This undersized manpower jeopardizes the future and puts the unit as risk. Strengthening the administrative support staff is therefore absolutely essential for the unit to prevent slowing down their activities and overloading the unit direction, scientists and PIs with unnecessary administrative burden.

Recommendations regarding the Evaluation Area 2: Attractiveness

The BIGR unit has made significant strides in increasing its international visibility and recognition. The unit's efforts in promoting the independence of young group leaders have been fruitful. Additionally, the unit has successfully attracted a new group, which brings recognized expertise in the field of anemias and porphyria. This influx of talent compensates for the departure of some researchers and staff retirements during the past and future contracts. The attractiveness for foreign students/postdocs could, however, be strengthened (e.g. there are currently no Marie-Curie or EMBO fellowships).
To maintain and strengthen the workforce, it is crucial to organize two types of calls. 1/ an internal mobility call should be implemented to encourage staff to relocate or work remotely at the Guadeloupe and Réunion sites. This will help maintain and reinforce the workforce at these remote locations. 2/ a call for new PIs and group leaders should be initiated to sustain the unit's attractiveness and preserve its current scientific dynamism for the next contract. Furthermore, the unit should strive to renew their Labex GR-EX to ensure the continuity of their network of excellence. This renewal can be pursued in its current form or adapted to a new format in alignment with the supervising bodies and the university. Maintaining such a structure will undoubtedly provide invaluable support to scientific activities, as well as contribute to clinical and societal valorization.

Recommendations regarding Evaluation Area 3: Scientific Production

The BIGR unit has achieved a remarkable increase in the quality of its scientific production while maintaining a high publication rate. The unit has excelled in publishing in top specialty journals, such as Blood, with an impressive number of articles published between 2019 and 2021. Additionally, the unit has made significant contributions to highly ranked broad audience journals, including the New England Journal of Medicine, Science Translational Medicine, Nature Communications, and PLoS Biology. Furthermore, the unit has demonstrated its innovative capabilities by generating thirteen patents during the past contract period. To sustain this high level of scientific output, we recommend that the unit continues to leverage the opportunities provided by its new environment, particularly the reference clinical centers at Necker Hospital and the fruitful collaborations with the IMAGINE Institute. These collaborations and synergies will contribute to maintaining the

current production rate and enhancing the unit's research activities. It is also important to recognize and capitalize on the strong potential of the activities carried out at the remote sites in Guadeloupe and Réunion, ensuring that they continue to contribute to the overall scientific excellence of the unit. By exploiting the full range of possibilities offered by the new environment and fostering collaborations, the unit can sustain its high-quality scientific production and further advance its research endeavors.

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

The BIGR unit has several opportunities to maintain or strengthen this Area 4, including the development of expert patient cohorts for participating science, a strong partnership with industries, and the participation of members to TV and radio shows.

TEAM-BY-TEAM OR THEME ASSESSMENT

Team 1: Normal and pathological red cell physiology

Name of the supervisor: Caroline Le Van Kim

THEMES OF THE TEAM

The team focuses on red blood cell physiology in several pathologies in which red cell function is impaired, most prominently on Sickle Cell Disease (SCD), but also on other pathologies with red blood cell involvement. Specifically, they analyse the role of red blood cell transporters and channels in normal and disease states, membrane structural components that function as blood group antigens, and transfusion biology.

These topics are studied in four scientific working groups (SWG): SWG1 studies the physiopathology of SCD, exploring disease variability (aim 1), ineffective erythropoiesis (aim 2), neutrophils dysfunctions and IFN-1 pathway activation in SCD (aim 3), chronic inflammation in SCD patients receiving chronic transfusions (aim 4), and the role of circulating microparticles (MPs) (aim 5). SWG2 studies the role of red blood cells and erythroid progenitors in other human pathologies, specifically in Polycythemia Vera (PV, focus on treatment), Central retinal vein occlusion (CRVO, focus on candidate genes), and Gaucher disease (GD). SWG3 studies the function and structure of red blood cell transporters and channels with a focus on the function of red blood cell transporters in normal homeostasis in membrane pathologies and in erythropoiesis. SWG4 studies the immunohematology and Biology of Human Blood Groups and specifically the role of nucleotide metabolite transporters in erythropoiesis and RBC function (aim 1), the role of ENT1-mediated adenosine transport in the physiopathology of SCD, and the molecular basis of new blood group systems (aim 3).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

There were no urgent recommendations in the previous report.

The only recommendation was to reduce the number of research lines and focus on fewer topics to excel in these topics. This was not executed in the past evaluation period, which is understandable given the fact that the INTS was dismantled and the unit had to move twice.
For the coming period, there is a clear plan to split the team in two more focused teams (for the next contract) that have the potential to be leaders in the field.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maîtres de conférences et assimilés	5
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	5
Personnels d'appui à la recherche	9
Sous-total personnels permanents en activité	**25**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	3
Post-doctorants	1
Doctorants	9
Sous-total personnels non permanents en activité	**13**
Total personnels	**38**

EVALUATION

Overall assessment of the team

This is an excellent team, outstanding in part of its performance. The production of the team is excellent with several publications in highly esteemed journals such as Blood. The attractiveness of the team is excellent to outstanding as indicated by the grants obtained (including ANR, EU Horizon program), their leading role in large consortia including GR-Ex and Carest, and the recruitment of a young group leader and several postdocs. The involvement in education (management of a doctoral school, creation of an entirely new Master program, teaching) is outstanding. The valorisation is outstanding with multiple patents and research contracts with several (industrial) partners.

Strengths and possibilities linked to the context

The team's research is divided in four scientific working groups (SWGs). Each SWGs is led by a group leader and a senior scientist as deputy. Thus, the team allows young group leaders to gain managerial skills. The management of the team is divers. The team has a unique platform to study all aspects of red blood cell (RBC) integrity and function.

The production of the team is very high with 174 publication (46% first, last or corresponding author), some high-end specific journals such as Blood, Am J Hematol, Haematologica, Br J Haematol, 35 posters presented at scientific meetings, 93 invited seminars at (inter)national meetings. The team's output included twelve thesis and four HDR. The team uncovered the role of novel red blood cell antigens, which is an important contribution to transfusion research.
The output of the different SWG in team 1 shows how their collaboration leads to synergy. Weekly team meeting facilitates productive collaboration between the SWG of team 1, but also between the teams of the unit.

The team is an important member of the prestigious Labex GR-Ex consortium on red blood cell research with the team leader being deputy director of GR-Ex. The role of the team in GR-Ex is crucial and results in high visibility both national and international. The team recruited a young, successful scientist as leader of SWG1. Over the evaluation period, they employed fourteen PhD students and five postdocs. The team obtained many grants (worth 4,066 k€) among which grants from the ANR (2 contracts as partners) and the EU Horizon program (MSC-ITN and European Innovation Council).
The Carest network established by team members is a powerful network to support both patients and patient-related research on SCD.
The team secured five patents over the evaluation period as well as contract research with several partners (Imare, Genzyme, Shire, Addmedica, BioRad). The team contributes significantly to the treatment of sickle-cell disease.

The team is very active in knowledge dissemination to the general public and to provide information for sickle cell patients both in Paris and in the overseas regions.

Weaknesses and risks linked to the context

This team is very large. The collaboration between the four SWG was initially not clear from the report but was clearly presented at the visit of the committee. From the report the team appeared too large and slightly fragmented, but the presentations showed how each SWG profited from the collective expertise in the team. In the final output, it becomes clear that the large team is an asset resulting in synergy.

Part of the team is located in Guadeloupe, which creates more opportunities in the research on SCD. However, the researchers indicate themselves that the collaboration between the team members in Guadeloupe and those in Paris is hampered by high travel costs that are not compensated for in the team's budget.

Whereas the team is very active in public outreach, this is mainly 'sending information'. The new challenge will be to actively involve patients (patient organisations) upfront in the process, for instance by asking them what their main concerns are and how research can work on solutions.

Analysis of the team's trajectory

The team will split and will start as two teams in the new Necker location. The two future teams will each be led by two team leaders that represent the fundamental science and clinical experience.

The combination of SWG1 and 4 will form the new team 1, 'Blood Group Antigens and Hematopoiesis in Health and Sickle Cell Disease', focusing on immunohematology, transfusion and SCD. This is a very logic combination because antibodies against RBC antigens constitute a particularly serious problem in SCD.

Parts of SWG2 and 3 will be incorporated in a new team named PAM, 'Physiopathology of anemias and metabolites-overload diseases'. From the pathologies studied in SWG 2 only the red cell physiology in Gaucher disease will be continued within this new team, in combination of overload metabolism (e.g. iron). This team will also incorporate the research on transporters in the RBC membrane (currently SWG3).

The reorganisation of the research in two new teams is a logic step. The goal of each of the new teams will be much more focused, which will further increase the attractiveness of the teams. The collaboration with stakeholders such as the EFS will remain strong.

RECOMMENDATIONS TO THE TEAM

We trust that the new teams will be able to present with a strong, focused research line.
The new teams presented several themes within the new teams. Given the track record, we are confident that the new teams will be productive. The only recommendation would be to formulate a strong central aim and to make a strong narrative on how the different themes of the team synergise to reach the aim.

Team 2: Name of the team

Name of the supervisor: Alexandre de Brevern

THEMES OF THE TEAM

Team 2 develops means for combining method development and translational research on RBCs and platelets proteins. It focuses on analysing large transmembrane proteins from RBCs and platelets using molecular dynamics and bioinformatics as well as it develops new methods for analysing the impact of protein modifications and dynamics. Team 2 provides the scientific community with online databases for proteins from RBCs and platelets, and with tools for analysing and predicting characteristics of protein structures.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Of the five major recommendations in the previous report, the first one stated that the low success rate at ANR applications should be improved and that an effort should be made to increase the team visibility in international meetings. This point was adequately addressed as the total amount of grants has substantially increased including international grants and funding from several grant-awarding bodies (European FEDER projects, ANRs, INCA, Labex and IdEx). Team 2 has also increased its attendance at international meetings (5 talks and 4 invited seminars abroad). The second issue regarding the low number of postdocs was also addressed since thirteen new postdocs were recruited. The third point related to lack of computer time has not become a problem due to adequate computational resources supported by GENCI/CINES. The fourth recommendation related to the balance between the methodological developments and the applications to the GR proteins is well addressed as the scientific production of team 2 reflects a good balance between methodological and applied research. The fifth recommendation related to strengthening the relation with team 3&4 and improving the ratio women/men. Team 2 has an ongoing ANR project with team 3 and the gender ration has improved. In addition, it was suggested that the ties between team members working in different sites should be reinforced and even this weakness has been addressed well as there are several ongoing FEDER projects and many joined postdocs.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	5
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	**11**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	9
Sous-total personnels non permanents en activité	**11**
Total personnels	**22**

EVALUATION

Overall assessment of the team

The structural bioinformatics team is an excellent team with an excellent scientific production (>90 publications, 43 corresponding authorship, e.g. in 2xNucleic Acid Research, Sci Adv, Int J Mol Sci, J Mol Biol, Biomolecules. The attractiveness is outstanding with 2.5 M€ funding incl. 4 ANR (2 as coordinator), one INCa and three FEDERs, organisation of eighteen international and eight national symposiums and successful future career paths for recruited PhDs (15, postdocs/companies) and postdocs (13, assistant professors/IR CNRS/companies). The valorisation is excellent including two patents, industrial collaboration, graduate school and up-to-date databases and tools.

Strengths and possibilities linked to the context

Over the years, team 2 has developed a widely recognised expertise in molecular dynamics and bioinformatics concentrated on RBCs and platelets proteins. Team 2 publication record for the reviewed period includes 90 articles in peer-reviewed journals. Team 2 had two patents, has created over thirteen databases that lead to many web servers and tools. Team members were invited speakers to several national and international meetings and fifteen Ph. D thesis were completed over the reviewed period. All of these ascertain of the recognition of team 2 by the scientific community. They are many interactions between team 2 and the other teams within the unit as illustrated by several joint publications. The presence of Team 2 within the unit is mutually beneficial as team 2 provides the unit with molecular dynamics and bioinformatics tools and the unit provide a framework for their topic. Team 2 has specialised in developing tools and databases, which are attractive and useful for researchers in the field, which increases the scientific impart of their research. The number of permanently employed personnel has increased from 40% to 50%, which strengthens to sustainability of the team 2 ability to obtain funding for their research has noticeably improved over the last few years and reaches 2.5 million euros including European FEDER projects, ANRs, INCA, Labex and IdEx. Team 2 has recently published in high impact journals like Nucleic Acid Research and Sci Adv, showing their capacity to carry out high-quality research at the international level. Team 2 shows exceptional strength since the two recent relocations have not slowed down the scientific success.

Weaknesses and risks linked to the context

Team 2 has trained fifteen PhD students and employed thirteen postdocs over the reviewed period and training such a high number of young scientists is an excellent achievement. One of the identified risk points for Team 2, however, are the issues related to the renewal of the team since achieving special expertise in structural bioinformatics are time-consuming and the skilled personnel has good opportunities to move toward industrial career path, special attention should be paid on aiming to the new recruitment for the trained PhD students and postdocs e.g. via tenure-track position and the career paths to keep them in the team on a more permanent basis.

Analysis of the team's trajectory

Team 2 has actively developed new methods and tools using modern computational AI-based methodologies and created databases available on websites, which shows a forward-looking initiative and mindset for delivering the outcome of research in accordance with open science principles. The team currently has a good balance between methods development, applying the developed methods for scientific research and working in collaboration with other teams and research groups. The two distant sites (Paris and Saint-Denis de la Réunion) have established fruitful means to carry out collaborative projects remotely as demonstrated by three joint FEDER projects with eight postdocs in Reunion Island and nine joint publications. The publication forums or the research outcome has improved over the years and this development could be further enhanced. The team has good connections to industry. EUR, an education program in bioinformatics and genomics of human health and disease to meet the challenges of personalised medicine, is a significant and important effort initiated by team 2. The staff resources have improved due to significantly increased external funding. The external funding is mainly for short-term staff and there is a risk of reduced permanent staff when the current staff retires or if the non-permanent highly skilled staff seeks for permanent positions elsewhere in academia or industry and this point would benefit from a risk management plan.

RECOMMENDATIONS TO THE TEAM

Team 2 has recently published in scientific journals like Nucleic Acid Research and Sci Adv, which shows the potential of the team and, thus, the team should continue wider multidisciplinary studies in collaboration with other research groups to achieve impactful research results that can be published in high impact journals (as they did in Nat Microbiol and ACS Catalysis). Furthermore, the team could seek for equal authorship position in the publications for the authors with equal contribution to the workload. Team 2 has improved the amount of scientific research funding to the level suitable for their activities and outcome and, thus, should aim to keep the research funding at the constant level in the future. The team interacts well with industry but could encourage the PhD students to attend international meetings abroad more actively. Dedicated strategic planning on how to maintain and attract skilled personnel in future for example by aiming to create career paths for PhD students and postdocs should be carried out as part of future vision of team 2.

Team 3: Pathogenesis of severe malaria

Name of the supervisor: Benoit Gamain

THEMES OF THE TEAM

The Severe Malaria Pathogenesis team's research focuses on understanding the molecular determinants of the sequestration of *Plasmodium*-infected erythrocytes (IEs) in the vascular system which are associated with severe forms of malaria such as placental malaria (PM) and cerebral malaria (CM). Specifically, the team has four axes of research:

1) Study of ligand-receptor interactions in the context of parasite adhesion to placental and cerebral epithelia.
2) Identification of molecular mechanisms underlying homing and the persistence of *P. falciparum* in the bone marrow.
3) Development of both current (PRIMVAC) and new vaccines against placental malaria.
4) Development of new immunotherapeutic approaches to reduce parasite burden and transmission.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Only minor recommendations had been noted in the previous HCERES report and the team has taken them into account. For instance, one recommendation was to work on the recruitment of new early career scientists and the team has succeeded in the recruitment of an INSERM CRCN in 2021.

Another recommendation was an increase in the volume of trainees. Accordingly, in the 2017–2022 period, the team hosted several visiting junior scientists (3 PhD students and 1 postdoc) from other laboratories, in the context of collaborations and trained four PhD students (including 1 who defended), three postdocs and 6 Master 2 students. In addition, the newly recruited CRCN obtained his HDR diploma which will in turn allow the team to increase the number of PhD students and consequently team size and productivity. Finally, a recommendation to intensify cooperation within the unit and contribution to common seminars and/or meetings, has also been addressed with not only the creation of new collaborative projects but also the new role of the newly recruited researcher as a board member of the Unit scientific communication committee (COSU) from 2018 to 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	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**6**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	1
Post-doctorants	0
Doctorants	3
Sous-total personnels non permanents en activité	**4**
Total personnels	**10**

EVALUATION

Overall assessment of the team

Team 3 is an excellent to outstanding team. It has an excellent track record with some outstanding publications in generalist and specialised journals such as Science advances, Lancet Inf Diseases and Cell Host Microbe (2023).
The Team has a distinctive expertise in basic research with strong translational potential. In particular, they pioneered the first placental malaria vaccine (undergoing clinical trials) and have patented a novel immunotherapeutic approach. The valorisation potential of the Team is therefore outstanding.
Team3 attractiveness is also outstanding: the Team has an outstanding capacity to attract funding (7.2M). The recent recruitment of a CRCN enhanced the fund-raising abilities of the team and increased their capacity to train graduate students.

Strengths and possibilities linked to the context

In the period 2017–2022, team 3 exhibited a great publication output with a total of 32 publications, in both generalist and specialised journals. Most of the publications are open access and several are in highly reputable journals (Science advances, Cell Host and Microbe, Lancet Infectious Diseases). The translational potential of their research has enabled them to not only pioneer the first placental malaria vaccine – currently entering phase II trials, but also, they have patented a novel immunotherapeutic approach with potential to tackle a variety of diseases. Additionally, the team demonstrated an exceptional ability to attract funding, securing a substantial 7.2 million euros in the evaluation period which included both national (coordinator of 3 ANR/4) and EU-funded sources (Advance-VAC4PM and PRIMAVALC) and foundation FRM (Equipe labelisée and contract). National and international visibility is ensured by the frequent presence of the team in the press as well as by participation in conferences and other scientific events. The team is also a member of two different labEx networks and has recently recruited an INSERM CRCN scientist.

Weaknesses and risks linked to the context

While this team enjoys a high profile, enhancing certain aspects, such as addressing the absence of dedicated personnel for managing grants and ongoing clinical trials, along with expanding the number of researchers in the team (including students and postdocs), would potentially have a positive impact on productivity and efficiency.

Analysis of the team's trajectory

Since its establishment, the team has consistently produced outstanding scientific work. Substantial funds have been secured to finance ambitious projects. Work developed by the team is on track to produce the first pregnancy malaria vaccine, a ground-breaking initiative with the potential for a significant impact in endemic settings. The team leader is highly involved in the dissemination of scientific results, reaching both fellow scientists and the general public. The team has also established multiple fruitful collaborations with other national and international teams. Over time, the team has grown in size and is anticipated to expand further with the acquisition of the second HDR.

RECOMMENDATIONS TO THE TEAM

The success of this team during the 2017–2022 period is undeniable. The team has an outstanding capacity to attract funding both at national and international level. The next recommended step would be the consolidation of industry partnerships for the continuing development of the malaria vaccines. Strategic planning of the move into the new institution will be required to ensure smooth integration of the team without loss of productivity or disruption of the ongoing projects. A plan for interaction with teams in the new host environment should also be envisaged. The recruitment of a (CDI) research assistant even part-time to handle the bureaucracies associated with the clinical trial management is desirable to ensure the PIs can be effective in the scientific management of the various projects.

Team 4: Tissular biology of the red cell

Name of the supervisor: Pierre Buffet

THEMES OF THE TEAM

This team explores the interaction between red blood cells and the spleen with the broad dual objective of better understanding physiology/pathophysiology and delivering optimised medical interventions, such as tests and drugs. Specifically, the team aims at:

(1) clarifying the protective and pathogenic roles of the spleen during a malaria infection;
(2) determine the mechanisms of red blood cell clearance by the spleen following transfusion
(3) and clarify the pathogenesis of spleen-related complications in inherited RBC diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has effectively addressed most recommendations outlined in the previous report.
For instance, one of the recommendations was to incorporate *in vivo* models in their research programmes to better address the physiological relevance of the *in vitro* conclusions. The team has taken steps which have facilitated access to *in vivo* models such as setting up collaborations with other institutes, the recruitment of a CRCN with direct access to *in vivo* models and also the move to the new Necker site which has animal facilities. Another recommendation suggested expanding the team and increasing the number of HDRs to enhance the team's capacity to recruit PhD students. In line with this, permanent personal was increased to six people and a new HDR was obtained in 2022, with a second one being expected in 2023.

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	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**4**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	4
Post-doctorants	1
Doctorants	2
Sous-total personnels non permanents en activité	**8**
Total personnels	**12**

EVALUATION

Overall assessment of the team

This is an outstanding team, with a distinctive expertise combining basic with clinical research. Despite the complexity of the systems used, the team has an outstanding track record and capacity to attract funding. The five permanent members have published 49 manuscripts during the evaluation period, fifteen in high tier journals. Examples of publications in journals with a high scientific impact are Am. J Hematol 2018&2022, New England J Med 2021&022, Nature Communications 2023, Blood 2021, Clinical Infectious Diseases 2021, PNAS 2023. Nat protocols 2018, EBioMedicine 2022.
All PhD students (5 during the evaluation period) and postdocs who finished their training co-authored at least one publication. The team size has gradually increased which has not only enhanced its fund-raising abilities but also increased the capacity of the team to train graduate students.
The valorisation and clinical innovation activities are outstanding with three patents, development of a unique technology to mimic RBC filtration by the spleen, 4 industrial contracts and identification of new therapeutic compounds to treat malaria.

Strengths and possibilities linked to the context

In the period 2017–2022, team 4 exhibited an outstanding publication output with a total of 49 manuscripts, of which 24 were signed as main authors (First, last or corresponding). National and international visibility is ensured not only by a high number of participations in conferences but also through the involvement in scientific boards of multiple institutions/funding bodies and through the various collaborations at national and international level (IRD, National Institutes of Health (Bethesda, MD, USA), the Menzies University (Darwin, Northern Territories, Australia), the University of Columbia (New York, NY, USA), the university of Oxford (UK), Brown University, Providence, USA; Massachusetts Institute of Technology, Boston, USA, European LeishMan Network…). During the evaluation period the team has also trained a reasonable number of researchers. Additionally, the team demonstrated a great ability to attract funding, acquiring nearly 3M€ in this period from both national (ANR (4 contracts; 2 as coordinators), DIM "Ile de France" (Thérapie Génique and MalInf), GREX LabEx) and international (Bill & Melinda Gates Foundation (PI), 2 NIH R01) sources. Notably the team has also registered three patents and four industrial collaborations (NHS, Cerus…). Finally, the team is a member of a labEx network which facilitates the recruitment of PhD students.
The team has also participated in actions toward the Public with three interviews in medical or general Journals (le quotidien du médecin, le monde, le monde Afrique) and one video (LabRoom Des Globules rouges contre le paludisme, 18 Septembre 2018).

Weaknesses and risks linked to the context

Absence of a project manager who would handle the bureaucracy associated with the management of the various projects. This is particularly relevant in a team where most of the staff has heavy loads of either teaching or clinical duties.

Analysis of the team's trajectory

Team 4 has consistently produced scientific work of high quality. The team has gained international recognition thanks to its publications and international conferences. Abundant (national and international) funds have been obtained to finance the various projects. Work developed by the team has led to the filling of three patents and funds from the private sector have also been acquired to further develop these projects. Over time the team size has increased and gender balance as well as career mentoring strategies are in place.

RECOMMENDATIONS TO THE TEAM

The number of interactions with the general public is adequate and may be expanded to include other media outside TV and radio. Recruitment of a project manager would be desirable to relieve the PIs from these duties. This is particularly relevant given the load of teaching and clinical duties accumulated by the PIs.

CONDUCT OF THE INTERVIEWS

Date

Start: 08 décembre 2023 à 8 h 30

End : 08 décembre 2023 à 18 h 30

Interview conducted : on-site

INTERVIEW SCHEDULE

Matinée : Auditorium du bâtiment Laennec

8:30 a.m.-8:45 a.m. Presentation of the committee

8:45 a.m.-9:15 a.m. Highlights of the Unit (10 min) and trajectory (5 min) by the Director
(15 min presentation, 15 min questions)
9:15 a.m.-9:50 a.m. Team 1: Normal and pathological red cell physiology (Le Van Kim/Azouzi)
(20 min presentation, 15 min questions)
9:50 a.m.-10:10 a.m. A new team for the future (Gouya)
(10 min presentation, 10 min questions)

10:10 a.m.-10:40 a.m. Closed-door meeting of the committee + coffee

10:40 a.m.-11:10 a.m. Team 2: Dynamic of structures and interaction of macromolecules in biology (de Brevern)
(15 min presentation, 15 min questions)
11:10 a.m.-11:30 a.m. Team 3: Pathogenesis of severe malaria (Gamain)
(10 min presentation, 10 min questions)
11:30 a.m.-12 h Team 4: Tissular biology of the red cell (Buffet)
(15 min presentation, 15 min questions)

12h-1:30 p.m. Closed-door meeting of the committee + lunch (Auditorium Laennec)

1:30 p.m.-2:10 p.m. Meeting with 1) technicians and administrative staff (salle Robert Debré); 2) PhDs and postdocs (salle Pasteur Lavoisier); 3) researchers not team leaders (auditorium Laennec), in three parallel sessions

Suite de l'après-midi : Auditorium Laennec

2:15 p.m.-2:45 p.m. Meeting with the representatives of the local institutions

2:45 p.m.-3:15 p.m. Closed-door meeting of the committee + coffee

3:15 p.m.-3:45 p.m. Meeting with the Directors (present and future)

16h-6:30 p.m. Closed-door meeting of the committee

PARTICULAR POINT TO BE MENTIONED

No point to be mentioned.

GENERAL OBSERVATIONS OF THE SUPERVISORS

Université Paris Cité

Le Président

Paris, le 4 mars 2024

HCERES
2 rue Albert Einstein
75013 Paris

Objet : Rapport d'évaluation de l'unité **DER-PUR250024206 – BIGR – Biologie Intégrée du Globule Rouge**

Madame, Monsieur,

L'université Paris Cité (UPCité) a pris connaissance du rapport d'évaluation de l'Unité de Recherche **BIGR – Biologie intégrée du globule rouge.**

Ce rapport a été lu avec attention par la direction de l'unité qui signale des erreurs factuelles à corriger (cf courrier joint), la vice-doyenne Recherche et le doyen de la Faculté des Sciences d'UPCité (cf courrier du doyen Cazayous), par le vice-doyen et le doyen de la Faculté de Santé, par la vice-présidente Recherche d'UPCité et par moi-même.

J'adresse mes remerciements au comité HCERES pour la qualité du rapport d'évaluation, ainsi que pour ces remarques, et vous indique ne pas avoir d'observations de portée générale à apporter.

Je vous prie d'agréer, Madame, Monsieur, l'expression de ma considération distinguée.

Édouard Kaminski

Présidence

Référence
Pr/DGDRIVE/2023

Affaire suivie par
Christine Debydeal - DGDRIVE

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MC/NE/EB/2024-018

Faculté des Sciences
Université Paris Cité
5 rue Thomas Mann
75013 Paris

Objet : DER-PUR250024206 - Évaluation HCERES de l'UMR-S 1134 BIGR – Retour Tutelle Université Paris Cité

Chères et Chers Collègues,

Nous souhaitons par ce courrier remercier les membres du comité de visite pour le temps qu'ils ont consacré à l'évaluation de BIGR, ainsi que pour leur écoute et le travail considérable qu'ils ont accompli.

La Faculté des Sciences est fière de compter BIGR parmi ses unités de recherche et rappelle la grande qualité de la recherche menée par tous les membres du laboratoire.

Après lecture du rapport provisoire d'évaluation de l'UMR-S 1134 BIGR, la Faculté des Sciences ne souhaite ajouter ni remarques générales, ni remarques factuelles.

En vous priant, chères et chers collègues, d'accepter nos chaleureuses salutations.

Maximilien CAZAYOUS
Doyen
Faculté des Sciences
Université Paris Cité

Nathalie EISENBAUM
Vice-Doyenne recherche Faculté des Sciences
Université Paris Cité

Observations générales

Il n'y a pas de commentaires particuliers sur le rapport, ni d'erreurs relevées ou de problèmes d'interprétations.

Au nom de l'unité, je tiens à remercier, le comité HCERES présidé par le Dr Eric Soler.

Le rapport du comité est clair et très bien rédigé, avec très peu d'erreurs factuelles.

Il reflète parfaitement bien la situation de l'Unité, ses qualités et ses points à améliorer et points de vigilance pour le futur. Nul doute que ce rapport remplit son rôle d'aide pour la trajectoire et l'avenir de l'Unité au sein du campus Necker.

Caroline Le Van Kim
Professeur Université Paris Cité

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