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

Department for the evaluation of research units

AERES report on unit:

Integrated Red Blood Cell Biology

Under the supervision of the following institutions and research bodies:

Institut National de la Santé et de la Recherche Médicale

Université Paris 7 - Denis Diderot

Université des Antilles et de la Guyane

Université de la Réunion

January 2013

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

Research Units Department

President of AERES

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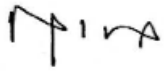
Research Units Department

Department Head



Pierre Glaudes

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

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).
This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.
NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

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

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

- Grading table of the unit: Integrated Red Blood Cell Biology

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

- Grading table of the team: Normal and Pathological Red Blood Cell Physiology

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

- Grading table of the team: Structural dynamics of the multi-molecular complexes of macro bio molecules

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

- Grading table of the team: Pathogenesis of severe malaria

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

Evaluation report

Unit name:	Integrated Red Blood Cell Biology
Unit acronym:	
Label requested:	UMR
Present no.:	UMR_665
Name of Director (2012-2013):	Mr Yves COLIN ARONOVICZ
Name of Project Leader (2014-2018):	Mr Yves COLIN ARONOVICZ

Expert committee members

Chair:

Ms Geneviève MILON, Institut Pasteur

Experts:

Ms Cécile DENIS, INSERM (representative of INSERM CSS)

Ms Valérie GUILLET, CNRS

Mr Joao LAVINHA, INSA, Portugal

Mr James STURGIS, Université d'Aix-Marseille

Mr Serge THOMAS, CNRS

Mr Francesco TURRINI, Université de Turin, Italie

Mr Michel VIDAL, CNRS

Scientific delegate representing the AERES:

Mr Hubert LEVEZIEL

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

Ms Chantal LASSERRE, INSERM

Mr Marc MAIER, Université Paris 7 – Denis Diderot, UFR SDV

1 • Introduction

History and geographical location of the unit

The research unit under review was created in 2005, and re-created in 2009 post some constructive remodeling. In 2011 the unit Head was inviting the members of unit UMR_763- to join the UMR_665.

- The Team 1 co-headed by Ms Caroline LE VAN KIM and Mr Yves COLIN is structured around Scientific Working Groups (SWG) the leaders of which are addressing distinct though otherwise integrated research topics. Indeed, whatever the SWG, there are all linked by their common interest for

i) the circulating human reticulocytes,

ii) the circulating human red blood cells

iii) the (a) three heterogeneous human cell lineages – mononuclear phagocytess, (b) vascular beds- lining endothelial cells, (c) the litttoral cells that line the unique human spleen red pulp sinusoids - ,

iv) the basement membrane as well as spleen red pulp extracellular matrix molecules with which interact the erythroid cells more or less transiently or irreveresibly.

- The Team 2 headed by Ms Catherine ETCHEBEST is bringing the relevant skills and expertise for each of the wet/ex silico research topics. Whether located in Paris or in Saint Denis de la Réunion, the numerous outputs of this well-structured team have been exemplified by studies on many red blood cell molecules such as the fascinating Duffy Antigen Receptor for Chemokines / DARC molecule.

- The team 3 headed by Mr Benoit GAMAIN, an ATIP Avenir Grantee, is exploring and characterizing the pathogenesis of severe human Plasmodium falciparum-driven malaria

Historically, a major focal point of the unit members activities has been on characterizing, biochemically, the molecules the human red blood cells i) are displaying at their plasma membrane, a special attention being given to the molecules supporting the so called “blood group antigens” ; ii) that concur to the unique RBC submembranous cortical cytoskeleton.

In addition to the main location-in the building of Institut National de Transfusion Sanguine (INTS), the other locations are in Paris (Paris Diderot University), Point à Pitre (University of the French West Indies and Guiana) and Saint Denis de la Réunion (University of Reunion Island). Of note, the unit members localized in the dedicated spaces provided by the two latter universities benefit from functional visioconference equipments that allow, regular discussions in real time.

Management team

Upstream the three teams-based UMR_665, its director, Mr Yves COLIN ARONOVICZ, generated and sustains an outstanding collegial framework by progressively incorporating i) the team 2 members, ii) the ATIP-Avenir Grantee and his collaborators iii) the ex-UMR_ 763 2 members.

AERES nomenclature

LS- 4, LS-6

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	10	10	9
N2: Permanent researchers from Institutions and similar positions	11	8	8
N3: Other permanent staff (without research duties)	10	9	9
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	2		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	6	6	6
N6: Other contractual staff (without research duties)	1	1	1
TOTAL N1 to N6	40	34	33

Percentage of producers	***97 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	15	
Theses defended	25	
Postdoctoral students having spent at least 12 months in the unit*	6	
Number of Research Supervisor Qualifications (HDR) taken	6	
Qualified research supervisors (with an HDR) or similar positions	19	16

2 • Assessment of the unit

The unit members know that all the molecular and cellular processes accounting for i) late erythropoiesis and ii) tightly coordinated functions of erythroid cells, are proceeding within distinct tissues - ranging from bone marrow, blood vascular bed lumen, spleen red pulp, to the placenta inter-villus spaces, in pregnant women. Therefore, they not only incorporate the unique features of each of these distinct compartments where reside or navigate the erythroid cells but they are designing the most advanced and accurate readout assays for properly characterizing distinct erythroid populations such as i) the otherwise neglected circulating reticulocyte population and ii) the circulating mature red blood cells as well as their late ascendants.

The unit members were and are actively exploring and characterizing, in depth, the cellular, sub-cellular and molecular features that account for the adhesive and rheological properties of abnormal human reticulocytes or abnormal human red blood cells, anomalies that prevent them to circulate within the blood vascular beds and to navigate through the human spleen red pulp parenchyma. Such exploration relies upon accurate though still incomplete knowledge of both the endothelial cells of micro-vessels and the abluminal basement membrane on which these endothelial cells reside.

Moreover they are now ready to explore whether abnormal developmental program of late human erythroid progenitors, upstream the circulating reticulocytes and mature red blood cells, could reflect transient or more or less prolonged disruption of the human bone marrow steady state, a special attention being given to the bone marrow erythroblastic islands. In order to optimally set up these novel research topics, all the Members are incorporating the solid knowledge on:

- the structural and functional features of the bone marrow, the native milieu where the late erythropoiesis does proceed within the erythroblastic islands briefly introduced above,

- the structural and functional features of the spleen red pulp, the native milieu where mature red blood cells are repeatedly probed for their structural and functional integrity, where red blood experiencing physiologically senescence are cleared by the red pulp macrophages through a-phlogistic processes,

- the red blood cells experiencing accelerated senescence whatever the origin of these otherwise diverse processes- SCD, asexual development of *P. falciparum*

- the unique features of the extracellular matrix components of the basement membrane - interrupted or not – on which reside either i) endothelial cell lining the capillaries and the post capillary microvessels ii) or the littoral cells lining the spleen red pulp venous sinusoids,

- the fundamental properties of the syncytiotrophoblasts - one of the two placental trophoblast populations of pregnant women - to which maturing *Plasmodium falciparum*- hosting red blood cells are adhering,

- the low normoxia values that mark the steady state bone marrow parenchyma and spleen red pulp or the hypoxia that marks tissues that experience repetitive vaso occlusions.

Each of the members of the former and present Unit did integrate these tissues's contextual features when they identified and are identifying the research areas that need to be consolidated, expanded or created. Therefore while extending the conceptual frame of their bio-medically sound investigations, the Unit members:

i) rapidly adapt state of the art methods - multi-parametric flow cytometry- the high content data sets being processed through and in house generated softwares conceived by Team2 -,

ii) generate innovative reagents -;e.g., nanobodies - they carefully validate,

iii) design and renew relevant bio-computional approaches, a strong emphasis being put on in silico modeling and molecular dynamics of single protein or multi-molecular complexes exported to the red blood cell membrane, the ones specified by Plasmodium falciparum included,

iv) co-design and validate innovative devices complemented with carefully selected and refined visualization and/or analysis methods.

Over the past years promoting their own well thought research choices, the Unit Members have focused and are focusing increasingly on human erythroid cells and their late ascendants. They do so within the context of very well organized clinical settings. Not only, all the members of the three teams are focusing on the fascinating red blood cell lineage and the four major cell lineages - endothelial cells lining the blood vascular bed, littoral cells of the spleen venous sinus , mononuclear phagocytes and syncytiotrophoblasts - they interact with, but they are in the unique position to reach optimal integration of clinical investigation, clinically relevant bench research and bio-computing activities.

By breaking down traditional barriers between disciplines, they identify the programmes to discontinue and the ones to either initiate or to further consolidate by welcoming an ATIP CNRS INSERM grantee.

Notably, the emphasis placed on normal and abnormal human erythroid cells and their immediate ascendants has allowed and will allow original contributions to be made at the intersection between cell biology, computational biology, as well as mechano-biology/rheology, three topics that are too rarely assembled within a unique entity of reasonable size. In addition such research is benefiting from unique human red blood cell repositories /resources, the INTS Members have generated and will continue to generate.

Strengths and opportunities

All the investigations are aimed to provide an integrative picture of the systemic and /or local human diseases

i) initiated by abnormal erythroid cells – included the potential RBC anomalies generated during blood storage-

ii) and more or less rapidly sustained and progressive disruption of the late developmental processes accounting for the late erythropoiesis, a phase of the erythroid cell lineage known to take place within the erythroblastic islands/niches.

as well as the disruption of the complex circulatory beds through which navigate the long lived human red blood cells

Also of particular interest, is the capacity to co-design microfluidic devices and to image interactions of erythroid cells with any cells they could be retained to, in dedicated and fully mastered facilities, the aim being to gain insight into the disease mechanisms at the molecular, cellular and partially reconstructed tissue levels.

Moreover the team 3's integrative vision will impact, increasingly, on human health by deciphering what are the earliest processes that could disrupt the human body steady state more or less severely.

Well thought approaches are rooted to carefully selected and renewed equipments. Both the wet and in silico components of the optimally positioned Unit benefited from funding resources that range from the INSERM, INTS, and Universities as well as successful applications to highly competitive research programme calls originated from national and international agencies or private companies.

All the Unit members put their efforts to unveil and characterize the local and systemic damages driven by human red blood cells displaying mutations or subverted as hosting cells by *Plasmodium falciparum.*

It is clear that the broad range of investigatory approaches mastered and renewed by the unit Members reflects not only the sustained willingness of collegiality but also the impact of integrated analysis, from the human body levels to the single cell and molecular levels.

Weaknesses and threats

Both the Unit Head and the three team Heads were pro-active to prevent weaknesses to occur and/or to unfold by :

- ending projects that have proved their full scientific and biomedical value, moving ahead with exciting and biologically and bio-medically sound research projects aimed to focus on human erythroid cells in both steady and non steady state

- anticipating any potential threats such as the flat budget or budget constraints or the transient uncertainties of the missions of the INTS structure.

Recommendations

Taking into consideration the complementary missions of its supporting bodies, the unit members did remarkably build on their synergies with the goal of strengthening the existing excellent research core they let progressively emerge on human erythroid cells, a lineage they always explore within the context of steady or non steady state human body. The site visit committee members appreciated that all the missions of these funding bodies were very well fulfilled and they all anticipate that they will be even more remarkably fulfilled in the future.

The site visit committee members highlights that the unit members have demonstrated their reactivity in grasping and developing the most relevant concepts - the ones to which is rooted the computational biology included – a reactivity which reflects their collegial strategy to build and renew a very well structured Unit. This structured unit will allow extending the in depth characterization of biologically sound features of the human erythroid cells whether the latter are normal, abnormal or remodelled as Plasmodium falciparum -hosting cells. Moreover, it is too rarely appreciated that the placenta, by virtue of its critical structural and functional roles, is a key link in the chain of events that lead to intra-uterine programming of post natal and adult health.

The unit members are combining oustanding activities that provide a more comprehensive and coherent picture of complex questions to which bringing bio-medically relevant answers. Moreover, while, through bona fide interdisciplinarity, the unit members are combining clinical data, data from *in vitro* models fuelled by powerful new technologies, as well as computation-based data, they fit the intrinsic features of research that both the normal and abnormal human erythroid cells do require.

3 • Detailed assessments

Assessment of scientific quality and outputs

The high quality data sets generated-within the unit were introduced, displayed and discussed in high quality and high impact publications that are deeply appreciated resources for other groups, many serving as core knowledge on which rooting further in depth exploration of the normal and abnormal mature human red blood cells and their late ascendants, known to develop in the post natal human bone marrow. Over the 2007-2012 period, in addition to the 250 publications in peer-reviewed journals, the committee members are pleased to mention patents such as the one that highlights the combination of mastered multi parametric flow cytometry data sets and innovative bioinformatics skills.

Assessment of the unit's academic reputation and appeal

Of note, while the highly valuable insights provided by team 1 and team 3 members reflect the soundness and rapid impact of wet research questions and strategies, the equally highly valuable insights provided by team 2 members reflect the soundness and the impact of their innovative computational skills and tools.

Such highly valuable outputs have been achieved because questions and strategies are rooted to accurate clinical and biological data collected within the frame of internationnaly recognized teams of dedicated clinicians and experimentalists located in either Paris or in Point à Pitre and, very soon, in Brazil.

The visiting committee highlights illustrative examples of (a) regional (b) national and (c) international funding: (a)-two through SESAME-Ile de France (drépanocytose, modélisation), (b1) one through ANR maladies rares - drépanocytose-, (b2) two through ANR Biologie Structurale et Chimie, (c) one through Primalvac. , Per year, these grants provide three fold the amount of the recurrent funding amount.

A core facility that reflects the impact of the unit's academic outputs, within the INTS perimeter,the BioFACy-lity platform, proposes the expertise and the innovative equipment to guarantee the support and the development aid of scientific projects exploiting the biophotonic imaging, the microfluidic and the flow cytometry. The up-to-date flow cell adhesion platform is perfectly suited to screen anti-adhesive therapeutic molecules. As far as the flow cytometry component is concerned, an "in house" software generated by Team 2 members provides the optimal way to acquire store and extract the multiparametric datasets.

As far as the Unit attractiveness is concerned, one should highlight that not only two constituted INSERM teams and one ATIP -Avenir Team but also both junior and senior investigators were recruited as permanent staff members (1 PR , 1CR, 1MCU, three Engineers).

Of note, in addition to the regular collaboration between the team 2 members located in Saint Denis de la Reunion and a Bengalore located team, the team 1 members promoted the exciting concept and succeeded to extend their Sickle Cell Disease topics through a collaboration agreement with teams in Brazil.

Moreover, the excellence of the scientific achievements of both senior and junior scientists is reflected not only by the numerous awards and prizes they received but also by their attractiveness for renowned Scientist such as the Vice President for Research, Head of the Red blood Cell Physiology Lab (New-York, USA)-who was welcome for a sabbatical leave.

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

It was appreciated that the unit members were/are not only coping very well with advancing technologies, their principles included, but they rapidly share this mastered skills within the context of either training in house workhops, international conferences that are highly attractive for professionals in charge of safe blood transfusion, as well as for clinicians and non clinician scientists who are curious to better capture the unique features of these organelles-free long-lived cells.

Moreover In the period under review, they were also successful by either benefiting from partnership with private sector or contributing to renew bioscience clusters by transforming the concept of directed molecular evolution to an early biotech company that is "offering "predictive *in silico* solutions for molecular evolution", one output being to improve therapeutic peptides and small proteins that emerged through the proof of concept experimental step. Briefly developed by Founders of Peaccel at la Reunion University, the computer models can predict effects of combining single-point mutations on various biological properties and help to design novel proteins/peptides. They do so through a bioinformatics platform that is operational both in France and Cambridge (Massachusetts).

Moreover they will benefit from the expertise of those who are structuring The Technology Transfer Company Ile de France Innov or SATT (Société d'Accélération et de Transfert de Technologie) Idf Innov, an entity expected to manage the overall valorization strategy of two out of the 4 WP of the Labex GR-Ex, to promote and support the creation of relationships with the private sector in order to develop, protect, transfer and make available research results for the public benefit.

Assessment of the unit's organisation and life

Whether unit, team or future Scientific Working Group/SWG leaders, they are all setting clear, ambitious but realistic goals for individual researchers and create an atmosphere of collaboration and intellectual rigour by organizing regular meetings to present and discuss research progress. They also encourage participation of students and post-docs in various transferable skills courses that will prepare and are preparing them for being " attractive" to those search committee members who launch calls aimed to provide space and funding to independent group leaders.

These achievements reflect the coherent agenda and actions of the Unit Council that comprises each team leader, the "Hygiene and Safety" representative, the elected representative of the administrative personnel, research technicians/engineers and students. During each of the unit council's meeting are addressed and discussed questions that range from unit budget, equipment, recruitment of trainees, engineers technicians as well as any collaborations with external teams, any new projects being expected to insure further transversal programs between the different unit teams' members. Both the unit council meetings and the general assemblies held twice yearly are benefiting from the unit scientific meetings that are organized every two months as well as from the team scientific meetings – research progress reports .

Each of the new collaborations that recently emerged within the INTS site- eg collaboration with the Platelet Immunology unit - reflects the soundness of having the three team heads located in this entity which keenly dedicates its efforts to both basic and translational research. Within such a context, the members of the Unit under appreciation take part in the teaching programs developed at the INTS, the vocational training of medical and technical personnel from French transfusion centers of the Etablissement Français du Sang (EFS), and teaching/training of medical students and interns. The unit members do participate in the scientific exchanges at INTS by contributing to the organization of diverse scientific events, i.e., weekly seminars, yearly Séances d'Actualité Transfusionnelle, Annual Congress of the French Society for Blood Transfusion, which is presided by the General Director of INTS, the two international congresses, which gathered the most famous international experts in red blood cel physiology developmental programs , on endothelial cells.

Since 2012 and with the fusion with Inserm U763 team, the Unit is also integrated by agreement to the University of the French West Indies and Guiana. This team has largely participated to the acquisition and development of the "molecular biology platform", dedicated to diagnosis and research at the Centre Hospitalier et Universitaire of Pointe à Pitre. In addition, this team provided an Hemorheology platform (viscosimeter, Lorrca ektacytometer, collaboration with the UAG Faculty of Sports Sciences - STAPS) and a Center for Biological Resources (CRB) for DNA and other sample collections (both joint-use facilities open to the University Hospital),

Considering the soundness of the proposal of the future unit, it is also important to re-emphasize how an internal Unit meeting, held as a well prepared retreat at the "Station biologique de Roscoff", allowed complementary commitment of dedicated clinicians, junior or seniors experimentalists, computation scientists, engineers, technicians, Administrative Assistant and Secretary to be translated in a coherent Unit structured around three teams each of the three being internationally recognized as tenured entities, to act as key partners of the construction of the outstanding Labex "Gr-Ex".

The visiting committee also notice that the personnel insuring the administrative components enjoy contributing daily to team's vibrant enthusiasm dedication and internationally appreciated achievements.

Assessment of the unit's involvement in training through research

The unit contributed to the training of 50 PhD students, with 37 defended between 2007 and 2012, the collaboration between teams allowing master students and post-doctoral fellows to be jointly trained.

The involvement in training through research was extended progressively when two Universities – Universities of the French West Indies and Guiana and of Reunion Island - were invited to join the one – Paris Diderot- that was a key co-founder of the Unit. The 12 dedicated University Professors/Assistant Professors- 2 out these 12 being teams 1 and 2 leaders- are actively involved in the teaching in BScs, Master degrees, PhDs and though the disciplines they cover are unfolded as Biochemistry, Genetics Cell biology, Bio-informatics, they all pay attention to put this disciplines within the broader scope of life sciences *per se* highlighting how is it essential to incorporate the data generated within the disciplines named i) Developmental Biology, ii) Mammal Physiology, mammals being a term that designates both (a) model laboratory rodents and (b)humans.

The number of (a) PhDs (41, 23 being completed) (b) Master degrees (50) BSc degrees (30) reflects the outstanding inputs of a research entity where training is a full mission/responsibility of its members – whether they are official supervisors, mentors, engineers, technical staff members, secretaries.The optimal ratio value (~1) of senior to junior investigators allows optimal mentoring included portraying i) the solid knowledge as well as ii) gaps in our understanding of the full biology and physiology of the the post natal human red blood cell lineage, while attracting, at soon as possible, the attention on fragile data that prevailed, at times, over caution and rigor. The junior trainees are guided daily to know how to design and conduct research – the hypothesis-driven research included the acquisition of these skills reflecting mentoring and "protected time".

Assessment of the five-year plan and strategy

The ambitious proposed research program will unfold through leadership of the unit head and teams' heads, encompassing basic as well as translational research on abnormal human erythroid cells using the normal erythroid cells as the referent cells. The human red blood cells cannot anymore be the only cells under investigation when a diverse range of diseases that reflect their pathogenic features need therapies. Despite the many important advances made, substantial uncertainties about mutant red blood cells, aged red blood cells or *P. falciparum* –hosting red blood cells there is an urgent need to know more on the upstream developmental stage within the erythroblastic islands in both steady and non steady state.

Grasping the unique nature of the human erythroid cell lineage in both steady and non steady state, the unit members have indeed collegially set up new and sound methods rooted to a broad range of sound concepts that open new avenues for capturing the unique features of the ascendants of the reticulocytes and red blood cells. Moreover, the notion of specific remedies for specific disease mechanisms is at the heart of their demanding approaches, assessing their sound approach of what should be contemporary medicine. Departing from loose set of criteria as well as from biologically unsound readout assays, the unit members were and are rooting their program within the frame of solid data sets, avoiding to let prevail applicative over caution and rigor: indeed they are aware that any damages exerted by circulating reticulocytes or red blood cells occur in defined contexts of tissue physiology or disrupted physiology.

Careful consideration of the inherent specific biology of erythroid cells within the erythroid islands (their three-dimensional nature, the stromal macrophage features to which they are bound) will be studied at all the scales, the molecular one whenever possible. Such a prerequisite will impact the understanding of organ and body physiology and the way in which individual diseases can be thought of or modeled mechanistically.

The future unit will not only benefit from the strengths of the collegial structure but also from collaborations with colleagues building on available technology platforms - the ones offered within the Labex GR-EX included and establishment of close links with IRD/INSERM overseas units in malaria endemic regions where prospective immuno-epidemiology studies will be undertaken before any validation of preventive or therapeutic interventions.

The committee members deeply appreciated the breadth of the research planned for the next five years across the unit.

4 ● Team-by-team analysis

Team 1 : Normal and Pathological Red Blood Cell Physiology

Name of team leader: Ms Caroline LE VAN KIM/Mr Yves COLIN ARONOVICZ

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	5	5	4
N2: Permanent EPST or EPIC researchers and similar positions	8	5	5
N3: Other permanent staff (without research duties)	4	3	3
N4: Other professors (PREM, ECC, etc.)	1		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1	1
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	19	14	13

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	8	
Theses defended	16	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	13	10

• Detailed assessments

Assessment of scientific quality and outputs

Over the 2007-2012 period the team 1 entitled "Membrane proteins of erythroid and epithelial cells involved in transport and cellular adhesion activities" was first enriched by:

- a group who brought expertise on the spectrins-based cortical cytoskeleton in different biological processes (cell proliferation, apoptosis and motility) as well as the unique plasticity of the human red bood cells: 8 publications illustrating the range of spectrin properties in distinct cell lineages assess the solid knowledge provided by this internationally renown team.

- the Inserm Unit 763 - Pathophysiology and pharmacogenomics of sickle cell disease/SCD treatment-, (between 2007 and 2012, 80 publications illustrate the achievements from this team in Journal of Biochemistry, Biochem J, Blood, British Journal of Haematology, Haematologica Clin Hemorheol Microcirc, Blood Cells Mol Dis, Am J Physiol Heart Circ Physiol……).

Designated as a public health priority by the French Ministry of Health (2004), UNESCO (2005), WHO (2006) and the UN (2008) the biological processes that account for SCD Vaso Occlusive Crisis/VOC were deciphered with a flow adhesion platform that allow mimicking the vascular microcirculation: it was established that upon exposure of reticulocytes and RBCs to epinephrine, the Lu/BCAM is phosphorylated and displayed adhesive properties for laminin α 5 that dominates the basement membrane on which reside the endothelial cells. Moreover, another ligand- counter ligand couple, namely the RBC and monocyte α4ß1 integrin was shown to account for RBC adhesion to the Lu/BCAM expressed on endothelial cells and RBC respectively (16 publications). Using a cytomic and pharmacogenomic approach, they were able to demonstrate that hydroxicarbamide HC displays a range of activities: not only it interferes with the expression of adhesion molecules on SS-RBC (Sickle red blood cells) both *in vivo* and *in vitro* reducing SS-RBC adhesion to endothelial cells in flow conditions and lowering cAMP and Lu/BCAM phosphorylation but also by preventing the endothelial to produce pro-inflammatory cytokines and of endothelin-1 thereby modulating the endothelial activation status and the "vasoconstrictive stress" observed in SCD patients. In addition they identified GATA2 and GATA6 as intermediates of the HC-induced signalling pathway(s) that lead to an altered endothelial expression of HC-target genes.

One of the main focuses of Pointe-à-Pître group – former Inserm 763 unit - were /are to extract biomarkers that could reflect progression to the most severe clinical manifestations of SCD: they showed that SS-RBC activation by inflammatory cytokines (IL-8 and RANTES) could promote vasoocclusive crisis through RBC dehydration and increased RBC adhesion propensity to endothelial cells. This study was one of the projects of SCADHESION (ANR 2008-2011) and constituted part of two PhD projects: In SS children, it was possible to establish that not only there is an inverse relationship between microvesicle/MV concentration and fetal hemoglobin level but also that in HydroxyCarbamide/HC-treated children, there is a lower concentration of MVs shed by RBCs endothelial cells and platelets. Moreover based on their mastered skills to monitor a range of hemorheological parameters -blood viscosity, RBC deformability, and aggregation and disaggregation- they compared the full blood rheological profile of SS and SC (sickle cell-hemoglobin C) children according to the rate of vaso occlusivecrisis and acute splenic sequestration. They were also able to monitor parameters of the autonomic nervous system in these very well built cohorts.

The generation of human red cell surface proteins/glycoproteins-binding nanobodies allowed both outstanding fundamental knowledge to be completed as well as unique reagents to be proposed for diagnosis purposes. Indeed, among the RBC targets of the generated nanobodies are i) the fascinating DARC molecule and ii) the abundant glycophorin A, two molecules also recognized by *Plasmodium/P. vivax* and *P. falciparum* merozoites at the onset of the invasion of the reticulocytes and RBCs they respectively remodel as niches where to generat their asexual and sexual progenies.

Over the 2007- 2012 period many new biological functions of transport and adhesion were assigned to several proteins displayed at the plasma membrane of the red blood cells. The Rh proteins were shown to display gas transport activities in both RBCs and epithelial cells and also structurally characterized (5 major publications).

The team developed genotyping tests for the different blood group systems setting up a kit for the non invasive prenatal diagnosis of RhD hemolytic disease of the fetus (one key publication as well as exclusive license for Europe with the Jacques Boy institute and the BioRad company in 2011). It also explored pathogenesis of other hematological diseases such as spherocytosis, polycythemia vera as well as non nonhemotological diseases such as central retinal vein occlusion and Gaucher disease.

While characterizing; in depth, structurally and functionnaly, both the minor population of human reticulocytes – known to transiently navigate in the circulatory beds- and the dominant population of human long lived red blood cells, the team1 members remarkably worked at extending their international place and outputs This is reflected through their first order and regular publications, the number of junior trainees who defended their PhD thesis, the number of well trained PhD students who have been recruited in prestigious laboratories abroad, these multiple successes reflecting the range of national international grant applications that were funded.

SWG1 members, who are exploring the pathophysiology of SCD, published 124 articles. 0ver the last five years, they built or renewed collaborations with both academic – 7 national 5 international- entities- and industrial partners (2)

SWG2 members, who are exploring erythroid cell adhesive properties in diseases other than SCD, published 5 articles - 3 in Blood, one in British Journal of Hematology, 1 in J. Thromb Haemost, and filed 2 patents.. They built collaborations with both clinicians and researchers in Paris or in Amsterdam

The emerging SWG3 aims at characterizing the cell interactions during terminal erythropoiesis, a project that benefits from recurrent operational budget as well as external funding ITMO. Of note between 2007 and 2012 the 15 publications – 5 in Blood , 1 in journal of Biological Chemistry- - of the SWG3 leader assessed his outstanding achievements.

SWG4 members, who are exploring red blood cell transporters, published 10 articles. They built strong internal, national, and international collaborations as well as they develop a kit for the non invasive diagnosis of RhD hemolytic disease of the newborn – this kit is available through J Boy Institute

Assessment of the team's academic reputation and appeal

The team 1 attracts both junior and senior scientists as well as many national and international collaborations : one Professor was invited for a very fruitful sabbatical leave, another one was invited to lead the 5th SWG, for detecting and characterizing any potential abnormal features the red blood cells could acquire over the storage. In addition to prizes awarded to both senior and junior scientists, team 1 members communicate their solid data as invited speakers within the context of many international conferences.

In addition to the Labex GR-EX – the most recent assessment of a novel scientific structure benefiting from an outstanding Scientfic Advisory Board, team1 members develop an outstanding ability to create networks such as the CAREST – which stands for CAribean NETwork of Researchers on Sickle cell disease and Thalassaemia or the GSCDN –which stands for Global SCD Network, an entity within the Program to Global Pediatric Research.

The International Associated Laboratory of Haematology aimed to address not only SCD pinpointing two distinct though related issues, namely-- modifiers genes and haematopoietic stem cell transplantation. It assesses the comitmment of Academic structures in Brazil - University of Sao Paulo, the National Center for Cell therapy at USP Medical School Ribeiro Preto and in France – INSERM UMR 665 UMR 940 as well as the " Laboratoire Eurocord EA 3815-

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

This is reflected by (a) many distinct precious and appreciated initiatives which benefit to i) either national or international professionals or ii) Patients' Associations (b) as well as by interventions for the general public- Fête de la Science, radio as well as TV programs- . Their interventions allow improving public awareness and patient 'collaboration. Considering the substantial challenges intrinsic to such a setting it is remarkable that they do succeed to reach the point where reciprocity operates as the core organizing principle.

Among the actions for professionals: in addition to several training initiatives, standardization of laboratory techniques and diagnostic algorithms, scientific back-up for the Paris and Antilles Guyane National SCD Reference Centers, let us also highlight the development of methods and/or reagents for prenatal diagnosis of Rh disease, nanobodies for the blood group antigen detection/ characterization as well as novel concepts for therapy of disease such Central Retinal Vein Occlusion/ CRVO. The quality of their outputs is such that Team 1 members are invited to provide reports commissioned by public policy makers at both the national and international level: the content – SCD, blood transfusion, international networking.- of the reports assess the range of scientific and biomedically oriented projects of the Team 1 members. Considering the roots of their scientific vision, it is no surprise that they engage with the global community in promoting education to and sharing information with those afflicted with Sickle Cell Disease : they do so at both national and international level. The cohort coverage of sickle cell disease patients is extended to Brazil and biomarkers of early damages will be actively searched.

Last but not least, out of the tight link between Institut National de Transfusion Sanguine/INTS and INSERM the research and long life education ones have also allowed to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of diseases and conditions. In addition by making available small compound libraries, more and more non academic partners are interacting at the earliest stage with academic researchers.

Assessment of the team's organisation and life

In order to further extend the already remarkable collaboration within the team 1 members, many team meetings as well as visio-conferences have been set up. The shared objectives of the team 1 being to contribute filling the gaps in the understanding of the onset of the human erythroid cells-dependant-damaging processes, it is appreciated that their sustained and collegial efforts through prospective multicenter studies are warranted to define the most appropriate recognition of markers expected to improve the quality of surveillance and data collected globally. In such a demanding context, their success in meeting their research objectives is coming not from isolated individuals but from broad and integrated approaches collegially discussed. It is remarkable that they succeed creating a niche that shares the structural and functional features of the erythroblastic islands located in the post natal bone marrow parenchyma. Though, -time, scope and cost-competing constraints are known to influence any team' organization and life, they succeed creating and maintaining high quality production as objective assessment of the outstanding team's and unit organization.

Assessment of the team's involvement in training through research

Whatever the sites of their training the students and junior fellows express their satisfaction, commenting the quality of the guidance the care to facilitate the access to the world of employment in their chosen field. The tutoring, a process through which a more advanced scientist is accompanying a new arriving student/fellow helps revealing her/his creativity, is used. It also prepares the students/fellows for interdisciplinary work based on the particular competencies of each person. The junior trainees are guided daily to know how to design and conduct research- the hypothesis-driven research included- the acquisition of these skills reflecting mentoring and "protected time". The commitment, passion of junior investigators did assess the range of qualities of the mentoring.

Assessment of the five-year plan and strategy

The research team1 interest stems from their previous outstanding data on human erythroid cells, a cell lineage they will continue to soundly explore in both steady and non steady state. Whatever the physiological traits- -transporters channels, biomechanical features, aging- of both circulating reticulocytes and red blood cells and whatever the disease - Sickle Cell Disease/SCD, Central Retinal Vein Occlusion (CRVO), Gaucher disease, Polycythemia vera- , under investigations, their ambitious though realist objectives are to fill gaps in our knowledge about this fascinating hematopoietic cell lineage and to translate this basic knowledge in sound interventions that will benefit to those who carry mutations such as HbS, the $JAK2^{V617F}$ ……. Together with the unit head and team 1 head, the SWG leaders do co-assemble a unique and outstanding working force, an approach that augurs well for a deepening in our understanding of the earliest processes that account for steady state disruptive damages, those that do not benefit from endogenous repair mechanisms. Such articulations put the Unit Members at the forefront of developments that will benefit to human populations at high risk of severe diseases.

By being attractive for scientifically demanding international research bodies, by generating sound technology transfer at an early stage, the private company members will have no other choice than designing the safest targeted drugs.

Conclusion

All the members of the team 1 are dedicating their biologically sound research efforts within the otpimal clinical and bench settings they co-construct and they will re-adjust where and whenever necessary.

- Strengths and opportunities:

All SWG heads or scientists invited to lead a SWG have demonstrated their unique reactivity in grasping and developing the most relevangt concepts which reflects their collegial strategy to arrange a well structured team that will allow extending the in depth characterization of biologically sound features of human erythroid cells.

The team is well articulated with the two other teams and focused on the missions of the funding bodies. It is successful in attracting extramural funding and it is involved in the Labex GR-EX.

- Weaknesses and threats:

No specific weakness was noticed.

- Recommendations:

The visiting committee members encourage Team 1 to continue along these research lines, providing a more comprehensive and coherent picture of complex questions about the human erythroid cells to which they are bringing bio-medically relevant answers.

Team 2 :

Structural dynamics of the multi-molecular complexes of macro bio molecules

Name of team leader:

Ms Catherine ETCHEBEST

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	5	5	5
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)	2	2	2
N4: Other professors (PREM, ECC, etc.)	1		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	12	11	11

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs

Each of the team 2' Members

- designed and renewed relevant bio-computional approaches, a strong emphasis being put on *in silico* modeling and molecular dynamics of single protein or multi-molecular complexes exported to the human red blood cell membrane, included the ones specified by the eukaryotic parasite *Plasmodium falciparum* during its asexual developmental program ;

- generates in house softwares that allow the optimal processing of high content data sets,-the Cytomic software being one bright illustration of these outputs among many others.

The first order quality of what was achieved by this team is best illustrated by their in depth modeling studies of the fascinating DARC molecule displayed by erythroid cells, whether the latter-was analyzed:

as the interacting molecule of the Duffy-binding alleles of *Plasmodium vivax* isolates

or as an atypical chemokine receptor within the context of the Sickle Cell Disease or within the context of subversion of humans by the HIV lentiviruses.

Since the long-term scientific objectives of Team 2 Members are to elucidate the mechanisms governing important functions of endogenous or exogenous – eg plasmodial - proteins displayed at the human RBC plasma membrane or at the submembranous cortical cytoskeleton, their expertise in structural bioinformatics and molecular simulations enables them to tackle both aspects by combining the prediction of 3D protein structures and exploring their dynamics. It is now established that it is possible to use a 3D protein structural template to build the 3D structure of a protein displaying a homologous sequence. Though the number of templates of membrane proteins is extremely small, the team has accumulated the expertise to provide experimentally testable predictions while incorporating their versatile lipid environment. Indeed, whether it is the complex RBC plasma membrane or there are the neo-organelles that are generated in *P. falciparum*-hosting RBCs, there is more and more evidence on the role of lipid composition in the regulation of membrane protein sorting/dynamics and functioning. While the membrane proteins do optimally perform their function when in the appropriate membrane environment, it is still difficult to study experimentally the structure, dynamics and functioning of membrane proteins in their native membrane environment. Thus the molecular simulations mastered by team 2 Members is providing and will continue providing testable predictions on human erythroid cell membrane systems.

Briefly, the methodologies they develop and will develop do allow predicting structural and functional properties of membrane proteins from sequence and at elucidating dynamics and thermodynamics properties starting from 3D structures, the long term objectives being to design drugs able to interfere with the disease mechanisms under study in teams 1 and 3: they are in the position to do so for membrane proteins of the red blood cell – transporters, channels , integrins,…..- otherwise known to belong to protein families.

Their publication list -120 referenced in PubMed -reflects the regular diffusion of original and solid data as well as of "state of the art" reviews: of note the latter are written with the objectives to be comprehended by biologists who were not trained as bio-computation scientists. Moreover in addition to software on protein engineering, many web services are operational (iPBA, PredyFlexy, mulPBA, PP3D, PB-kPRED, PB-SVindex) as well as databases (Mitogen,PB-PENTAdb, PB-SAdb) available at http://www.dsimb.inserm.fr and http://bioinformatics.univ-reunion.fr/.

Assessment of the team's academic reputation and appeal

In addition to the sustained funded connection with biocomputation-driven scientists in Bangalore- India-, the other objective components of their international visibility are reflected by the regular citation of their original publications as well as their regular invitations to conferences covering their fields of expertise as well as conferences others than those dedicated to *in silico* biology and computational tools.

As illustrations of team 2 attractiveness and reputation:

- recruitment of 2 MCU, 1 CR and 2 engineers ;

- two Unesco-L'Oréal prizes « Pour les femmes et la science » for two PhD students.

- Prix « Maurice Nicloux »

- Organization of the Fifth Indo-French Bioinformatics Meeting (IFBM, 2011) Hyderabad (India) ;

- Co-organization of the International Symposium entitled "The role of blood group antigens and associated molecules in red cell biology: from molecular approaches to clinical applications" in 2010 ;

- Co-chair of the Scientific Council of the "International Biotech Business Conference China Reunion".

- Invitations to participate and or chair sessions of many international meetings or seminar in universities abroad

Moreover, in addition to the successful application to Sésame Ile de France (2009) « Development of computational prediction of the structure of membrane proteins », the Team 2 members were partners within two funded ANR projects.

Team members were also ANR SVSE5 member (2008-2011), ANR Emergence member (2012) and members of the 16 and 44 sections of the CNRS National committee as well as members within the boards of three distinct societies -Société Française de Biophysique, Société Française de Biochimie et de Biologie Moléculaire/SFBBM , Société Française de Bioinformatique.

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

The team 2 members were also successful either benefiting from partnership with private sector or contributing to renew bioscience clusters by transforming the concept of directed molecular evolution to an early biotech company that is "offering predictive *in silico* solutions for molecular evolution", one output being to improve therapeutic peptides and small proteins that emerged through the proof of concept experimental step. Briefly developed by Founders of Peaccel at la Reunion University, the computer models can predict effects of combining single-point mutations on various biological properties and help to design novel proteins/peptides. They do so through a bioinformatics platform that is operational both in France and Cambridge (Massachusetts).

The robustness of the rationale and completion of their computational approaches to predict novel drugs, to reposition potential small compounds candidates is also illustrated by an active participation in the MEDIT-SA scientific council

Assessment of the team's organisation and life

Structured along two Scientific Working Groups, each team 2 member does contribute to renew in silico approaches for research questions, the most complex ones included. Indeed are covered all the scales from the multi-molecular complexes within the membrane environment the single molecules - the translational modification(s) of some of their domains include-, to the atomic level. They are interacting, daily, with biologists who enjoy creating and benefiting from multidisciplinary approaches that involve individuals with diverse and complementary areas of expertise such as the one mastered and renewed by team 2 members.

Assessment of the team's involvement in training through research

The junior trainees are guided daily to know how to design and conduct their research project. The acquisition and mastering of their skills do reflect the high quality of the mentoring and the will to shape "protected time". The commitment, passion of junior investigators did assess the range of qualities of the mentoring team. Team members are also very active and interactive within the context of pre-PhD-teaching phases, the doctoral schools (iVIV, B3MI) or the post university trainings – Formation continue at Paris 7, Workshops.

Assessment of the five-year plan and strategy

Since both the RBC membrane and cortical cytoskeleton sense and process a range of signaling agonists, emerge the hypothesis that some of their constituents are substrates of a number of kinases and phosphatases. In addition, the recent high-content mass spectrometry data generated for human RBC membrane and cytoskeleton proteins - whether they are abundant or rare - as well as the data about RBC membrane lipids became unique repositories for demanding computational biologists generating in silico models and who enjoy discussions with biologists.

The computational data of team 2 members have provided and will provide further solid ground for experimentalists who are addressing the questions of the molecular and cellular basis of the unique structural and functional plasticity of human red blood cells that are known to experience over their life time a large range of physiological or pathological conditions - such as the sickle cell disease and polycytemia vera -. New comprehensive, high content and sound computational approaches reflect renewed efforts by team 2 members and will provide new information on RBC membrane protein structure and functions within their native milieu or disruptive conditions. The committee members are convinced that the structural changes associated with protein-protein "complexation" will be properly investigated using structural measures and Protein Block description as well as other tools engineered by Team 2. All the tools designed by team 2 to pre-compute multiple sequence alignments of most likely interacting proteins within the context of the unique erythroid cell plasma membrane and its submenbranous cortical cytoskeleton will allow richer databases to be re-interrogated.

In order to avoid approaches known to generate fragmented pictures of the complex molecular environments where are operating the many molecules diplayed by circulating reticulocyte and mature red blood cell molecules, the team 2 members are renewing oustanding and sound research efforts to get comprehensive pictures of multimolecular complexes they model on the basis of data they mined through the most advanced informatics and processed through astute computations. From such unique registries, repositories of data, they do and will generate models reflecting the most demanding and accurate conceptual frame and bench generated data. Of note the Team 3 is extending their interest for plasmodial molecules that are exported to the red blood cell membrane post the invasion process: this bilateral collaboration will benefit to the general unit research project.

Conclusion

The team 2 is built on exceptional grounds, explaining why the team members did already fill important gaps and are in the position to contributing to fill many of the bench-to-bedside gaps:

while co-interrogating multiparametric data sets generated by either physicians or biologists, with the most advanced computational tools.

while exploring and characterizing what determines the structural dynamics of either the single molecules or the molecular complexes that concur to physiolgiocal functions or dysfunctions of the human erythroid cells.

- Strengths and opportunities:

The site visit committee members highlighted:

- a unique reactivity in grasping and developing the most relevant concepts which reflects their collegial strategy
- strengths of the articulations with the two other teams

- Weaknesses and threats:

No specific weakness was noticed.

- Recommendations:

By generating comprehensive and coherent model of the structural dynamics of the proteins that concur to the unique human erythroid cell plasticity, all the team members do bring sound answers to the sound questions they generate while collaborating with the team 1 and 3 members and their partners in Bangalore. Moreover, a better understanding of origins and factors leading to disease onset and persistence is opening new doors for both erythroid cells-dependant damage prevention and treatment as well as interactions with other blood cells such as the platelets.

Team 3 : Pathogenesis of severe malaria

Name of team leader: Mr Benoit GAMAIN

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

P. falciparum, is the eukaryotic single celled parasite remarkably studied by the ATIP grantee otherwise known to be acting as bona fide Team 3 head : not only this Grantee was successful to build a motivated and solid team while focusing on the trafficking and positioning to the RBC surface, of a protein called *Plasmodium falciparum* Erythrocyte Membrane Protein 1 (PfEMP1), but he has attracted much attention, since this multi-domain plasmodial protein accounts for the Pf-hosting RBC binding to receptors on the surface of micro-vessel endothelial cells as well as to syncythiotrophoblasts displayed by the placenta of pregnant women. Thus the otherwise circulating RBCs are prevented to freely circulate as soon as the *P. falciparum* ring developmental stage is progressing to the trophozoite and schizont developmental stage onward.

For following the in depth characterization of the remodeling of the human red blood cells as *Plasmodium falciparum*- hosting cells,the team leader and his collaborators did choose to do so in a too rare scientific environment where special attention is given :

to the structural and functional features of the bone marrow, the native milieu where the late erythropoiesis does proceed within the erythroblastic island,

to the structural and functional features of the spleen red pulp, the native milieu where mature red blood cells are repeatedly probed for their structural and functional integrity,

the unique features of the extracellular matrix components of the basement membrane- interrupted or not – on which reside either i) endothelial cell lining the capillaries and the post capillary microvessels ii) or the littoral cells lining the sinusoids of organs such as the bone marrow, the liver and the spleen,

the low normoxia values that mark the bone marrow parenchyma and spleen red pulp.

where it is possible to explore, in depth and in biologically and structurally sound conditions, each of the stepwise processes accounting, in pregnant women, for the adhesion of the Plasmodium falciparum-hosting red blood cells to the syncytiotrophoblasts - one of the two placental trophoblast populations.

Both mastered reverse-genetic approaches and mastered biochemical approaches as well as approaches that provide structural features allowed Team 3 to

i) establish that var2CSA is a key molecule displayed at the surface of Pf- hosting RBC that contribute to their sequestration to the placenta,

ii) to map the CSA-binding domains of var2CSA.

Though research about some of the P. falciparum var gene family members led to major discoveries, what has been achieved by this young team 3 on the P. falciparum var gene member encoding the var2 CSA protein is outstanding. Not only it reflects mastered skills for generating full length recombinant protein or domains of this multidomain protein, but also mastered skills to design the proper readout assays that allow the complex stepwise processes accounting for the adhesion of Pf-hosting RBCs to the human placenta syncitiotrophoblasts to be delineated and deciphered.

The publication list highlights the first order achievements and it is easy to anticipate the next original publications will display similar first order ranking. : four publications in peer-reviewed journals since the arrival at the UMR-S 665 are completing the 31 previous publications in peer-reviewed journals.

Assessment of the team's academic reputation and appeal

The original novel and solid insights provided on the Var2CSA molecule displayed at the surface of *Pf*-hosting RBCS known to accumulate along the syncitiotrophoblasts reflects the high level of excellence of this team leader and his young team members; these achievements were recognized as more than promising ones by the international bodies known to fund the 10% applications they received and processed through very selective evaluation processes.

Of note , the workpackage WP3 of the Labex GR-EX entitled "Sickle Cell Disease – Malaria" is co –driven by the Team 1 head - and the Team 3 head. This work package focuses on two human diseases affecting the circulating reticulocytes and mature RBCs.

Moreover , as one of the pioneering investigators addressing the key issue of the structural features of the multidomain protein encoded by the var gene family, the Team 3 head generated an outstanding core of original data that put him among the few who fully mastered this important topics born less than 20 years ago

Post his nomination for the CNRS bronze medal in 2008, the team 3 leader was successful to many competitive applications : Scientific Director of the FP7 funded collaborative project « PreMalStruct » 2008-2011, an ATIP-Avenir laureate 2009 onwards, 2012: European Vaccine Initiative (EVI) funding to initiate a placental malaria vaccine development program (PRIMALVAC project), a project co-funded by the German Bundes Ministerium für Bildung und Forschung (BMBF).

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

Taking into consideration the complementary missions of its supporting bodies- INTS, the academic institutes, the universities- as well as the missions of the United Nations and of the World health organization/WHO which recognize two of the diseases they are exploring, namely the sickle cell disease and *P. falciparum*-malaria as global health problem-, the team 3 members did remarkably build on their synergies with the goal of strengthening the existing excellent research core they were welcome to join. The site visit committee members appreciated that all the missions of these funding bodies were very well fulfilled and they all anticipate that they will be even more remarkably fulfilled in the future: indeed *P. falciparum* perpetuates in tropical area where also perpetuates its second host population namely *Anopheles*. In addition to closed links with the former colleagues he collaborated with, at NIH during his productive post doctoral fellowship, the team 3 head is connected through IRD to teams located in endemic area : one of those IRD unit is also driven by another pioneer in the field of pregnancy associated malaria/PAM. All these elements are appealing for any phase II trial of an original vaccine aimed to prevent pregnancy associated malaria as well as to re-address the questions of the processes that account for the other severe malaria outcomes. Last but not least, a private partner is contributing within the ATIP Avenir contract in addition to the academic institutions

Assessment of the team's organisation and life

By setting clear, ambitious but realistic goals for each member, the team leader creates and maintains an atmosphere of strong collaboration and intellectual rigor. This team is appreciated by junior investigators who see this entity as a first option to i) consolidate their skills ii) extend their scientific curiosity and iii) prepare the next step, namely iv) conduct their independent research.

Assessment of the team's involvement in training through research

By adhering to the ambitious research program of Team 3, not only the junior trainees - post doctoral fellows and PhD students - but also the engineer, the techinician rapidly acquire new skills and they are invited on a daily basis and on bi-week basis – within the frame of the unit –not only to present and discuss their ongoing investigations but also to capture and criticize any strong and fragile conceptual frames respectively. A training program- aimed to ensure a sustained level of competence in the diagnostics and management of abnormal human red blood-driven pathologies- has been tailored as the European Red Cell School within the Labex GR-EX: not only it will be benefit from the outstanding guiding and mentoring expertise of the heads of team 1,2 and 3 involved, but it will enable the trainees to fully benefit from the GR-Ex community.

Assessment of the five-year plan and strategy

Whatever the topics – i) structure function analysis of the parasite and host molecules accouting for the adhesive properties of *Pf*-RBC to the placental syncitiotrophoblasts ii) the PAM preventing innovative vaccine iii) the sickle cell disease- malaria, the future program plan and strategy is straightforward and very well constructed.

While further deciphering the molecular basis of adhesive properties of *Pf*-hosting RBCs to the placental syncitiotrophoblasts, the Team 3 members will extend their investigations by exploring other couples of parasite and host molecules displayed respectively on the RBC surface and on the placental syncitiotrophoblasts. Moreover they will also explore whether post translational modification (PMT) of var2CSA as well as PMT of the syncitiotrophoblasts CSA- displaying molecules could also be contributing to the sequestration of *Pf*-hosting RBC to the placental syncititrophoblasts: if so, the data are expected to open new avenues for desiging readout assays for screening adjunct therapies that block sequestration. As mentionned in the unit and team 2 sections, it is easy to anticipate the promising outputs of collaboration with team 2 members.

The in depth knowledge of red blood cell biochemical metabolic and mechanical plasticity as well as the molecular mechanisms that *Plasmodium falciparum* deploys to circumvent the immune functions of human organisms do represent a solid and fertile ground on which to renew vaccine strategy. It should be perceived as one of the biologically soundest approach of the Team 3 head who is acting at the earliest step of the vaccine strategy pipeline.

Conclusion:

The ambitious research program proposed by team 3 will unfold through his excellent leadership encompassing basic as well as translational research on *P. falciparum*- hosting red blood cells. Indeed a cohesive set of concepts and sound and mastered methodologies that tackle key and well formulated questions are not only translatable into vaccine strategy but will also be translated into invaluable chemotherapeutics, the target populations being a unique population of pregnant women. The team head and collaborators are in the optimal position to identify and characterize couple of molecules whatever the severe forms of malaria. Once moving up the scale, from single molecule to *Pf*-hosting red blood cells adhering to syncitiotrophoblasts, both data on refined structural features of var2CSA and models generated by team 2, are expected to allow them imaging at the proper resolution, the impact of the cellular environment of the *Pf* –hosting RBC maintained in either static or dynamic conditions. Of note one SWG leader, within Team 1, is in the optimal position to collaborate at this step of the project.

- Strengths and opportunities:

There is an urgent need to know more on the upstream developmental stage within the erythroblastic islands in both steady and non steady state.

The notion of specific remedies for specific disease mechanisms is at the heart of their demanding approaches.

The team members were and are rooting their program within the frame of solid data sets.

It is also appreciated that the team head is actively establishing close links with IRD overseas units in malaria endemic regions where prospective immuno-epidemiology studies will be undertaken before any validation of preventive or therapeutic interventions.

- Weaknesses and threats:

No specific weakness was noticed.

- Recommendations:

All site visit committee members did highlight that the team head has demonstrated his creativity as an independent team leader in developing the most relevant readout assays - the ones to which is rooted the computational biology included – a creativity which is translated in outstanding datasets appreciated by the other co-pioneering investigators who are also actively unveiling the structural features of the *var* gene family members. This well structured team will allow extending the in depth characterization of biologically sound features of the human *P. falciparum* –hosting red blood cells. Both the ATIP contract and the welcoming unit allowed outstanding extension of the team head independence and full visibility of his leadership. He brought in both new idea and substantial synergistic interest that bridge common themes with others. In the future, the team 3 will be in the optimal conditions to extend the in depth characterization of the molecular mechanisms that underlie the *Pf*-hosting RBC dependent damaging processes in pregnant women.

5 • Conduct of the visit

Visit dates:

Start: 24 january 2013, at 8:45

End: 25 january 2013, at 17:00

Visit site: Paris

Institution: INTS

Address: 6 rue Alexande Cabanel ; 75015 Paris

Conduct or programme of visit:

Day one – 24 january 2013

8:45 **Welcome & Closed-door Meeting of Visiting Committee with AERES Scientific Advisor**
9:30 **Introduction of Plenary Session:** AERES Role & Procedures: AERES Scientific Advisor
9:45 **General Presentation of UMR 665 & Discussion** (30' presentation, 30' discussion) ; Director of the Unit

10:45 *Coffee Break*

11:00 **Presentation of Research Team 1** (60' presentation, 45' discussion) **;** Team Leader

12:45 *Lunch (buffet)*

14:00 **Presentation of Research Team 2** (30' presentation, 30' discussion) **;** Team Leader
15:00 **Presentation of Research Team 3** (25' presentation, 20' discussion) **;** Team Leader

16:00 *Coffee Break*

16:15 **Closed-door meeting of the Visiting Committee** (in presence of AERES Scientific Advisor)
17:15 **Meetings of Visiting Committee with personnel:**
Discussion with students and post-docs (by videoconference with students from the Guadeloupe)
18:15 **Closed-door meeting of the Visiting Committee** (in presence of AERES Scientific Advisor)

Day two – 25 january 2013

8:30 **Meetings of Visiting Committee with personnel:**
Discussion with engineers, technicians, administrative staff
9:15 **Meetings of Visiting Committee with personnel:**
Discussion with staff scientists (excluding management staff)
10:00 **Closed-door Discussion of the Visiting Committee with Representatives of the Managing Bodies** (in presence of AERES Scientific Advisor)

11:00 *Coffee Break*

11:15 **Closed-door meeting of the Visiting Committee** (in presence of AERES Scientific Advisor)
12:00 **Discussion of the Visiting Committee with the Director of the Unit** (in presence of AERES Scientific Advisor)

12:45 Lunch (committee only)

13:45 **Closed-door meeting of the Visiting Committee** (in presence of AERES Scientific Advisor)
17:00 **End of the visit**

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

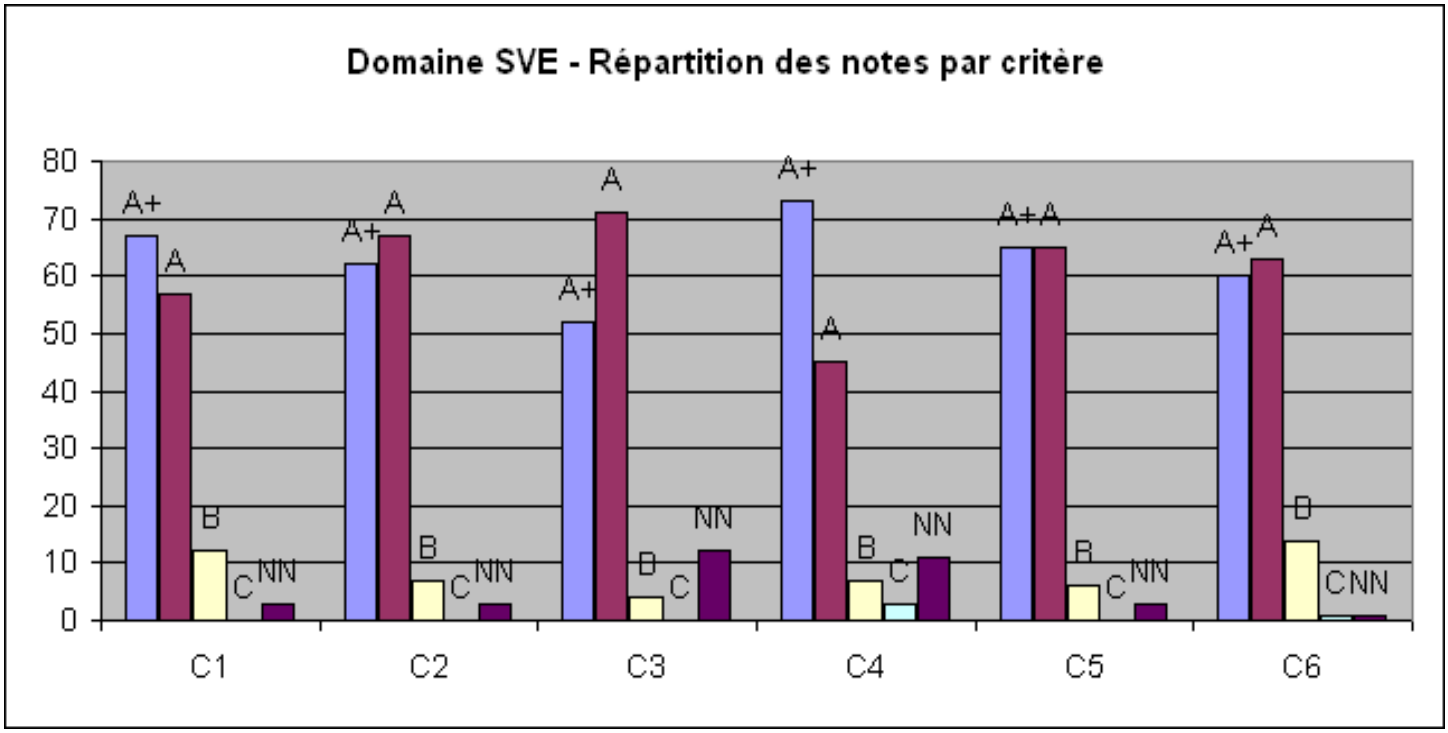
Grades

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

Percentages

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

Histogram



7 • Supervising bodies' general comments

Le Président

P/VB/RL/QG/YM – 2013 - 160
Paris, le 06 juin 2013

M. Pierre Glaudes
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

S2PUR140006321 - PROTÉINES DE LA MEMBRANE ÉRYTHROCYTAIRE ET HOMOLOGUES NON ÉRYTHROÏDES - 0751723R

Monsieur le Directeur,

Je tiens en premier lieu à remercier les membres du comité de visite de l'AERES pour la production du rapport sur la situation de l'UMR 665 « Protéines de la membrane érythrocytaire et homologues non érythroïdes» dirigée par Mr Yves COLIN ARONOVICZ. Le rapport très élogieux souligne l'excellente qualité de la recherche qui y est produite, attestée par le haut niveau qualitatif et quantitatif des publications et sa capacité à développer des sujets de recherche originaux dans un cadre pluridisciplinaire.

L'Université réfléchira aux moyens à mettre en place avec ses partenaires institutionnels (INSERM, INTS, Université de la Réunion, Université Antilles Guyane) pour conforter, dans la mesure de ses moyens, ce haut potentiel de recherche.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de toute ma considération.

Vincent Bergeron

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