HITh - Hemostase, Inflammation, Thrombose

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on interdisciplinary unit:

Hémostase-Inflammation-Thrombose

HITh

Under the supervision of the following institutions and research bodies:

Université Paris-Sud

Institut National de la Santé et de la Recherche Médicale - INSERM

December 2013

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Ms Véronique REGNAULT, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the experts committee,the composition of which is specified below.

The assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Hémostase-Inflammation-Thrombose
Unit acronym:	HITh
Label requested:	UMR_S
Present no.:	UMR_S 770
Name of Director (2013-2014):	Ms Cécile DENIS
Name of Project Leader (2015-2019):	Ms Cécile DENIS

Expert committee members

Chair:	Ms Véronique REGNAULT, Université de Lorraine
Experts:	Ms Marie-Christine ALESSI, Université de Marseille (representative of CSS INSERM)
	Mr Bernard PAYRASTRE, Université de Toulouse
	Mr Pierre SIÉ (representative of CNU)
	Mr Denis VIVIEN, Université de Caen
	Mr Jan VOORBERG, University of Amsterdam, The Netherlands

Scientific delegate representing the AERES:

Mr Patrick LACOLLEY

Representatives of the unit's supervising institutions and bodies:

Mr Etienne AUGE, Université Paris-Sud

Ms Chantal LASSERRE, Institut National de la Santé Et de la Recherche Médicale

1• Introduction

History and geographical location of the unit

The Inserm unit U770 entitled *Hemostasis and vascular cell dynamics* was created in 2006 under the direction of Mr Jean-Marie FREYSSINET and is linked with the Université Paris 11. This unit was a continuation of the Inserm unit 143 *Hemostasis and thrombosis* created in 1987 under the direction of Ms Dominique MEYER. It is currently under the direction of Ms Cécile DENIS since September 2010 and is organized into two teams: team 1, devoted to *Structure-function relations and regulation of hemostatic proteins* (Ms Cécile DENIS), and team 2 focused on *Cellular Physiopathology of Hemostasis* (Mr Jean-Philippe ROSA).

The unit is located on the ground floor of the Gregory Pincus Inserm building in Bicêtre Hospital and has a surface of 995 m^2. An additional 35 m^2 is allocated to a L2 laboratory for tissue culture and 10 m^2 to a radiation-safety laboratory, both on the third floor of the building. A common Institut Fédératif de Recherche (IFR 93) animal facility is located in the basement of the building.

The team EA4531 *Engineering of hemostasis protein with therapeutical potential* was created in 2010 under the direction of Ms Delphine BORGEL. This team is located at the Faculty of Pharmacy of the Université Paris 11 in Chatenay Malabry and has slowly grown between 2010 and 2013 to reach its current composition.

The team led by Ms Delphine BORGEL will join the Inserm unit U770 in January 2015 in the Gregory Pincus Inserm building (Bicêtre Hospital). The proposed new research unit entitled *Hemostasis-Inflammation-Thrombosis* will be directed by Ms Cécile DENIS and is the result of a complete re-organization of current research groups leading to the proposal of two new research teams. The future team 1, *Integrative hemostasis: from fundamental aspects to hemorrhagic disorders* (Ms Cécile DENIS), will encompass current U770 team 1 and part of current U770 team 2. The future team 2, *Thrombosis and inflammation: from pathophysiology to therapeutics* (Ms Delphine BORGEL) will be formed by the fusion of EA4531 and part of the current U770 team 2.

Management team

The management committee comprises all permanent researchers and one elected representative of each of the following categories of personnel, administrative, research technicians and engineers, students and post-docs. The committee meets at least once a year to discuss the budget, and more frequently if required.

There is no formal management committee for EA4531 given the small size of the team and the main decisions are discussed with all members.

Individual teams and the U770 unit have weekly meetings to discuss scientific results with all personnel. Every year a general health and safety meeting is organized by the risk prevention assistant.

AERES nomenclature

SVE1_LS4

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	4 (1,4)	6 (3)
N2: Permanent researchers from Institutions and similar positions	8	7
N3: Other permanent staff (without research duties)	12 (8,6)	12 (8,8)
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1 (0,1)	1 (0,1)
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	5	5
N6: Other contractual staff (without research duties)	2	1
TOTAL N1 to N6	**32 (25,1)**	**32 (24,9)**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit*	14	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	8	8

2 • Overall assessment of the interdisciplinary unit

The Inserm unit U770 has a long standing experience in the field of hemostasis and thrombosis with a strong implication in von Willebrand (vWF) related diseases and hemophilia. The scientific output of the unit is excellent and the published work has clearly advanced the field, in particular on vWF structure-function analysis and clearance as well as on the physiopathology of platelets. The unit benefits from a strong national leadership and was able to maintain an excellent international reputation over time by developing both original and competitive basic research and useful clinical applications (diagnosis/prognosis tools and therapeutic interventions). Despite the fact that EA4531 is a relatively young team, the strong orientation to translational research has produced important achievements transferable to medicine, in particular modified antithrombins as antidotes active against heparin derivatives. Altogether, the new combined unit will take a place of excellence in the field of hemostasis and thrombosis.

Strengths and opportunities related to the context

The scientific production is excellent, considering the impact factors of the publications, the citations and medical impact of the discoveries in the field of hemostasis and thrombosis.

The complementarity between the two teams of the Inserm U770 group is remarkable and is strenghtened by constant re-organization to favor the emergence of new themes while keeping a strong focus on structure-function relationships and regulation of hemostasis and cellular physiopathology of hemostasis.

The unit has been able to attract and recruit 1 foreign senior researcher and 1 young full time researcher, as well as one new group leader by the arrival of the team 4531 for the next contract.

The academic reputation is emphasized by regular invitations of several members of the unit to major national and international conferences and active participation in national groups and to the prestigious International Society on Thrombosis and Haemostasis.

The unit has developed an excellent level of international academic collaboration and strong interactions with companies, giving the unit an excellent efficiency to raise external funding.

The unit is involved in two national reference centers for rare diseases, and in patient's organizations.

There is a very good balance between the different research axes as well as a good balance between experimental and clinical research and this is supported by a highly efficient management. The director deserves encouragement in her leadership as regards the definition of priorities and the balance between authority and delegation of responsibilities and in her availability for all personnel.

The unit actively participates in the training of PhD students and the recruitment of post-doctoral fellows is impressive.

The new organization is interesting and coherent. The projects are solid, original and well-focused. The unit will be composed of two well-balanced and complementary teams and the reorganization proposed to integrate the team EA4531 has been well prepared. The future strategy is defined by paying attention to maintain an excellent interaction between experimental and clinical research and to further improve the competitiveness of the unit through the next contract.

Weaknesses and threats related to the context

As mentioned in the strengths of the Inserm unit U770, the recruitment of post-doctoral fellows is excellent but few PhD students have completed their theses so far. The retirement of experienced technicians and engineers during the next contract may also participate to weaken the teams.

Despite important investments to obtain expensive equipment and access to outside platforms, some difficulties to develop state-of-the art technology in imaging and analysis of transgenic animals remain. Such ambitious platforms may be shared with the Federative Research Institute.

Recommendations

Given the ability of the unit to develop external collaborations and connections with international groups, the establishment of international networks leading to collaborative publications in top general journals and european funding should be considered.

Diversity of the research themes may be a concern, especially because projects of future team 1 are very solid and successful and projects of future team 2 are original and more risky. It would appear essential that team 2 have a huge benefit of reciprocal interactions with team 1 to more clearly identify and focus on competitive projects, in particular clearance of natural anticoagulants and implication of platelets in vascular permeablity and sepsis.

3 • Detailed assessments

Assessment of scientific quality and outputs

The main research scope of the unit is to identify new molecular mechanisms involved (I) in the biology of the vWF/factor VIII complex, (II) in the cellular physiology and pathology of hemostasis focusing on platelets, and (III) in the relation between structure and function of main inhibitors of the coagulation system. Although the search for molecular mechanisms of hemostasis is a very competitive and busy field today, the projects are very original mainly because of the development of appropriate relevant animal models and the opening up of basic research discoveries towards new specific therapeutic strategies in hemophilia, von Willebrand diseases, platelet-related diseases, heparin therapy and severe sepsis.

The scientific production is excellent, with a total of 193 publications and 9 book chapters. In accordance with the aim to privilege quality over quantity, 34 original articles have been published in journals with IF>9 (including 13 articles with members in leading positions) and around half of the articles are published in journals with IF>5. Among these papers, some publications merit being highlighted based on their originality, methodological breakthroughs and impact: the association of type 2B von Willebrand disease with thrombocytopathy (J Clin Invest 2013), identification of LRP1 as a clearance receptor for vWF under flow (Blood, 2012), development of mouse models for type 2B von Willebrand diseases using hydrodynamic gene transfer (Blood 2010 and Blood 2013), identification of new mutations inducing quantitative and qualitative defects in vWF (Blood 2013), development of a recombinant antithrombin with a potent antidocte activity to heparin derivatives (Blood 2011).

Remarkably, the high level of research published in top hematology journals is evenly balanced between the different groups.

Assessment of the unit's academic reputation and appeal

Members of the EA4531 team participated in two Leducq transatlantic research networks and the team is partner to an ERC advanced grant.

The attractiveness of the research groups is excellent: 16 post-doctoral fellows and 3 visiting scientists have been hosted since 2008. The Inserm unit U770 has succeeded in recruiting two full time researchers, one high level foreign senior scientist and one young scientist. The arrival of the EA4531 group from the faculty of Université Paris-Sud for the next 5-year contract also illustrates the attractiveness of this unit.

All team leaders and several collaborators are regularly invited worldwide to give scientific seminars, with 22 national and 29 international conferences including one plenary lecture at the World Federation of Hemophilia, two state-of-the-art lectures and two symposium lectures at the International Society on Thrombosis and Haemostasis (ISTH) and one symposium lecture at the American Society of Hematology.

Several scientists from the unit have obtained prizes and distinction awards.

The head of the unit is a member of a specialized scientific committee at Inserm and co-chair of the subcommittee of the ISTH on animal models. A team leader is also a member of the board of the ISTH.

The scientists from the unit have developed a network of collaborations with all research groups in France in the field of hemostasis and thrombosis, and internationnaly with prestigious academic research groups and companies, leading to a high number of collaborative publications in high ranking journals in the field.

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

Four European patents have been filed during the past contract, and 5 international patents have been published, among which one has been licensed to a major pharmaceutical company.

Many recent discoveries have clear potential for medical impact, e.g. the development of a modified factor X molecule as a bypassing agent in hemophilia A and B with inhibitors, the demonstration of the negative regulatory role of apelin on platelet reactivity, and the development of a recombinant antithrombin as an antidote for all heparin derivatives.

Several members are involved in patients' organizations which are very important in the field of hemophilia and in rare disorders. The fact that the unit is associated with two national reference centers for rare diseases, the reference center for von Willebrand disease and the reference center for thrombotic microangiopathies, is of major interest for the development of clinical projects.

The fund raising is excellent (around 750 000 euros/year). There is a long lasting collaboration with biotech and pharmaceutical companies (18 contracts during the period 2008-2013, among which 2 CIFRE Contracts for PhD students).

Assessment of the unit's organisation and life

The unit benefits from a highly efficient management. The unit has experienced important changes during the past contract due to relocation of several members and recruitment of permenant Inserm researchers. Organizational transitions have occurred swiftly to successfully preserve a competitive, productive and well organized unit concerned with coherent, focused and highly connected projects. There is a good equilibrium between the different research axes and the level of interaction between groups within the unit is excellent as demonstrated by high level joint publications.

The personal interactions appear also very good and are favored by the group discussions with the students/post doctoral fellows and technicians. The unit has made the strategic choice to organize itself into groups focused on a research axis with their dedicated technicians to ensure the continuity of essential and specific know how. Although a potentially unfavorable approach for the development of ambitious platforms with new state-of-the-art technologies, it provides a good, friendly and collegial atmosphere between each of these key players.

A strong point of the unit is that it houses a genetically-modified animal facility and it has access to unique cohort of patients, thus providing adequate resources for the integration and interaction of basic and clinical research initiatives.

The financial rules are clear in terms of distribution of recurrent funding between transverse activities and between teams, and established at the level of the management committee.

Assessment of the unit's involvement in training through research

During the past contract, the unit hosted 15 PhD students, over 10 have defended their thesis so far, and 34 master students were trained. PhD students are affiliated to the doctoral school *Innovation thérapeutique: du fondamental à l'appliqué* (ED 425) or *Signalisation des réseaux intégratifs en biologie* (ED 419, BIOSIGNE). The unit has successful access to different sources for post doctoral fellows (16 since 2008) and PhD students.

The meeting with the students revealed a high satisfaction regarding the unit, its organization and their position. Their guidance is favored by the organization of weekly meetings with all members, and group discussions with their supervisors.

The impact of the unit on academic appointments is excellent as demonstrated by the recruitment of an Inserm researcher in 2011 and identification of 2 motivated and talented young scientists for future recruitments.

The involvement of the unit at various levels in teaching and in international training networks is remarkable. Several members of the unit are involved in the coordination and/or teaching of the specialities *Biologie Vasculaire, Athérosclérose, Thrombose, Hémostase* and *Biologie, Physiologie et Pharmacologie de la Circulation et de la Respiration* in the Master *Biologie Cellulaire Physiologie et Pathologies* (BCPP) at Paris Descartes/Paris Diderot. The unit has created a teaching module *Initiation à la Biologie vasculaire* (UEM 95H) in the Master *Médicaments et autres produits de santé* at Paris-Sud. The unit is also partner of the Princeton International Internship Program.

Assessment of the strategy and the five-year plan

Convergence of the scientific interests of the U770 Inserm unit and the EA4531 and the wish to foster research within the field of hemostasis and thrombosis in France have primarily driven the proposal for a new merged research unit composed of two complementary teams with a definitely original, important and ambitious project. This dynamic appears evident and timely, and complementary inputs should provide synergy and cross-fertilization to respond to a strong international competition.

The unit will be composed of two complementary teams, one focused on the pathophysiological aspects of hemostasis, particularly hemorrhagic disorders related to coagulation and platelet defects and the other on the reciprocal interactions between inflammation and coagulation in vascular diseases such as sepsis and ischemia-reperfusion. The unit proposes a strategy well balanced between the pursuit of ongoing, validated and solid projects, and riskier innovative and challenging projects, with a genuine attention being given to the translational aspects, interaction between experimental and clinical research and valorization of the findings.

General feasibility is high and secured by the past year's achievements of the unit in terms of reaching the proposed goals and raising funding from several agencies and private companies. Feasibility and overall quality of the projects are also well supported by existing technical facilities, in particular for genetically modified animal models and by a growing network of external collaborations for new technologies, and access to patients. The planned research has thus the potential to deliver pivotal results and breakthroughs in the next 5 years. The projects will be developed by internationally recognized leaders, but an expansion of the currently limited human resources in terms of PhD students and technicians should be pursued.

The SWOT analysis is extensive and adequate. The unit has shown that it can adapt to the evolution of the research in its field to maintain its leading international position.

4 • Team-by-team analysis

Team 1: Hémostase intégrative : des aspects fondamentaux aux maladies hémorragiqque

Name of team leader: Ms Cécile DENIS

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2 (0,6)	2 (1)
N2: Permanent EPST or EPIC researchers and similar positions	3	5
N3: Other permanent staff (without research duties)	3 (2,5)	7 (4,8)
N4: Other professors (PREM, ECC, etc.)	1 (0,1)	1 (0,1)
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	5
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	**15 (12,2)**	**21 (16,9)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	11	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	5	6

• Detailed assessments

Assessment of scientific quality and outputs

The team has a long standing expertise in the field of hemostasis and is internationally renowned in the search for molecular mechanisms of hemorrhagic disorders related to vWF/factor VIII proteins and platelet defects, with projects ranging from basic in vitro and in vivo approaches to human applications.

The research has produced major breakthroughs and led to the emergence of inventive concepts and tools for experimental models and therapeutic strategies. The most innovative findings include:

1) The opening of the hydrodynamic gene transfer technique towards the development of mouse models for type 2B von Willebrand disease (1 Blood in 2010 and 2 Blood in 2013). Such methodological research has paved the way for the in vivo analysis of vWF function.

2) The demonstration that the von Willebrand disease type 2B mutation p.V1316M alters platelet signaling through inactivation of Rap1 small G protein and inhibition of the inside-out activation of the ¤IIb¤3 integrin (J Clin Invest 2013).

3) The identification of the protective role of N-glycosylations in the activation peptide of factor X on rapid clearance (PloS ONE 2012), of the involvement of Siglec-5 in the catabolism of factor VIII/vWF complex (Haematologica 2012) and of LRP1 as a clearance receptor for vWF under flow (Blood 2012).

4) The identification of new mutations in the A3 domain inducing quantitative and qualitative defects in vWF (Blood 2013) and the construction of a human-murine chimeric vWF to evaluate the anti-thrombotic potential of monoclonal antibodies to vWF (Blood 2012).

5) The development of a thrombin-activatable factor X protein with a long half-life for hemophilia A and B treatments (international patent with exclusive license).

The elucidation of the key role of the JNK1 signaling pathway in platelet secretion and thrombus formation (Blood 2010) and the analysis of platelet morphological (macrothrombocytopenia and abnormal granule distribution) and functional (altered adhesive and secretory properties) anomalies in filaminopathy A (Blood 2011 and Arterioscler Thromb Vasc Biol 2013).

The output is very stable at a high level and the recent paper in J Clin Invest illustrates the ambition of the team. The reports include 119 original articles (28 in journals with IF>9 and 50 in journals with IF>5). Members of the team are first/last authors of 47 papers, including 9 in Blood and 1 in J Clin Invest. In addition, results have been communicated at several top international meetings.

Assessment of the unit's academic reputation and appeal

The senior scientists are all opinion leaders at the international level in their respective research fields and they have set up a large number of pertinent national (20) and international collaborations (15), in basic science and also in clinical investigation. The team leader co-chairs the Scientific and Standardization Committee *Animal, Cellular and Molecular Models* of the International Society of Thrombosis and Hemostasis (ISTH). Another team scientist is member of the ISTH council and chairs the World Health Organization (WHO) – ISTH Standards Liaison Group. A third team scientist is member of the organizing committee of the Groupe d'Etude sur l'Hémostase et la Thrombose (GEHT) and member of the organizing committee of the Société Française d'Hématologie (SFH).

Members of the team have been invited to give 19 conferences at national meetings and 28 lectures or conferences at international congresses of prestigious societies, the ISTH (2 state-of-the-art lectures, 2 symposium lectures and 3 conferences at the Scientific and Standardization Committees), the World Federation of Hemophilia (1 plenary lecture and 1 symposium lecture), the American Society of hematology (1 symposium lecture), the International Society for laboratory Hematology (1 symposium lecture) and the Bari International Conference (3 plenary lectures and one conference). Members of the team have received 9 inter(national) awards for the quality of their research and presentations including the Prize Danièle Hermann de la Fondation de Recherche Cardiovasculaire, the valorization prize of the Université Paris-Sud, 1 young investigator award from the ISTH and 3 young investigator prizes of the GEHT.

The quality of the work has also been highlighted by a high rate of success in getting funded by excellent and highly visible agencies. Members of the team have been or are coordinators of 5 ANR grants (2 ANR Blanc, 1 ANR Emergence Bio, 1 ANR chaire d'Excellence and 1 ANR Programme Cardiovasculaire, obésité et diabète (COD)).

The team leader is a member of the CCS4 Inserm committee and is a member of the ethical committee for animal experimentation n°26. Two scientists are manager and member respectively of the animal facility committee of the IFR 93. Another scientist of the team is member of the pilot committee of l'institut thématique multiorganisme (ITMO) Immunology-Hematology-Pneumology. Members of the team have been working as reviewer of grants or experts for several national and international institutions (ANR, AERES, health ministry, …).

The team was able to attract and recruit a high-level full-time foreign researcher and a French young scientist (the latter will joint team 2 for the next contract) and is very appealing for post doctoral fellows (14 since 2007). In the period 2012-2013 the team also welcomed 3 visiting foreign scientists for one or two months.

In the period 2009-2013, the team authored 31 reviews in qualified international journals and 9 book chapters. A team member is also an academic editor of PloS ONE. All senior scientists act as reviewers for several internationalscientific journals.

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

Their research has led to 8 patents:

- The work on the thrombin-activatable factor X protein for the treatment of blood coagulation disorders has been used to generate an international patent that has been licensed to a major pharmaceutical company and a phase I clinical trial is scheduled for the end of 2014 or at the beginning of 2015.

- The team is the inventor in 3 European patents that are focused on anti-vWF antibodies exhibiting antithrombotic potential.

- Two international patents related to polypeptides as apelin inhibitors and an apelin receptor agonist for preventing platelet aggregation respectively have been filed in 2012.

- The 2 last inventions relate to furin as a marker for rheumatoid arthritis and the quantitation of cell-derived microparticles.

The research of this team has had strong impact on the clinical and public health environment. The coordination of the French Reference Center for von Willebrand disease and of the national laboratory for ADAMTS13 investigation of the Reference Center for Thrombotic Microangiopathies (National Plan for Rare diseases supported by the French Ministry of Health) allowed a privilieged access to a wide range of patients' data and thereby (I) the validation of a new commercial ELISA for the diagnosis of type 2N von Willebrand disease, (II) the identification of vWF mutations and (III) the establishment of a predictive score of ADAMTS13 severe deficiency and of a predictive model for death in patients with thrombotic thrombocytopenic purpura linked to a severe ADAMTS13 deficiency. The work on microparticles has led to the development of an enzymatic assay to measure blood-borne tissue factor activity, licensed to Hyphen Biomed.

The team is involved in 5 clinical studies focused on inflammation and dysregulation of hemostasis, and Postpartum hemorrhage and is affiliated to the DHU (Département Hospitalo-Universitaire) TORINO (Thorax Innovation).

Five members of the team are involved in the "Association Française des Hémophiles". The team has also interactions with the association "Vaincre la Mucoviscidose" and the association ADIRAL.

The team had 7 contracts during the period 2009-2012 with LFB Biomédicaments and 8 contracts with other non-academic partners. These connections with industrial partners represent a substantial financial support for the team without unbalancing the research activity.

The fact that several members of the team are respected as international leaders in the field of hemostasis and thrombosis is of major importance for the development of proficient national and international collaborations, also providing academic fund raising.

Assessment of the unit's organisation and life

The team is well organized into coherent and logical scientific objectives and benefits from distinct experience that are shared among the subgroups. For the future contract, the team will result from the merging of former U770 team 1, highly focused on von Willebrand disease and hemophilia, and two members of former U770 team 2 who are specialists in platelet physiopathology and signaling. The principal scientists of the previous teams are developing different but highly connected projects. Thus, the scientific potential and complementary inputs are great as well as the promises for medical impact and valorization.

Recruitment of young researchers is actively addressed. The number of PhD students (1 full time and 1 half time) is low for five full time senior researchers.

Interactions with non-permanent young investigators are based on regular group meetings together with individual discussions. A weekly meeting gathers all the staff of the team in which ongoing work and future research are presented either by students or post-docs and discussed by everyone.

Assessment of the unit's involvement in training through research

The team is affiliated to the doctoral schools ED 425 (*Innovation thérapeutique: du fondamental à l'appliqué*) and ED 419 (*Signalisation des réseaux intégratifs en biologie)*. Seven PhD theses have been completed between 2008 and 2013.

The team has trained 13 post-doctoral fellows over the past years. One of them has been recruited as an Inserm researcher in 2011, another has been presented for recruitment at Inserm in 2013 and his ranking is promising, finally a third one has been identified for future recruitment and is now in a research laboratory in the USA to expand her expertises.

Looking at the list of PhD students and post-doctoral fellows, it seems that few of them are of foreign countries. The team has the infrastructure and competence to host foreign researchers in the future.

The team is fully involved in young student training. Twelve 2nd year Masters students, 3 first year Masters students and 4 3rd year License students have been hosted over the past years. Three bachelor students coming from Princeton University have been trained during the summers of 2010-2012.

Several researchers actively participate in teaching tasks in different Masters and "Diplôme d'Université" (DU) courses. The team leader coordinates the speciality *Biologie Vasculaire, Athérosclérose, Thrombose et Hémostase* in the Master *Biologie Cellulaire Physiologie et Pathologies* (BCPP) at Paris Descartes/Paris Diderot and a member of the team organized a module *Biologie cellulaire et moléculaire des plaquettes* in this speciality (M2 level). All members of the team also actively participate in the courses of this Master. The unit has created a teaching module *Initiation à la Biologie vasculaire* (UEM 95H) in the Master *Médicaments et autres produits de santé* (M1 level) at Paris-Sud. A member of the team also coordinates a DU dedicated to Hematology (120 hours a year including 70 hours focused on hemostasis) at the Medical School of the Université Paris Sud.

Assessment of the strategy and the five-year plan

The new team now entitled *Integrative hemostasis: from fundamental aspects to hemorrhagic disorders* maintains a focus on hemorrhagic disorders related to coagulation and platelet defects and the translational aspect is very important. The merging of the current U770 team 1 and part of current U770 team 2 will lead to the formation of an ideal platform of expertises on factor VIII/vWF complex, vitamin K-dependent proteins and platelets. The five-year plan is built on strong existing track records and the proposal is thus appealing and competitive at the international level.

The scientific project has four major axis:

1) The pathogenesis of congenital or acquired von Willebrand disease: one of the main objectives is to further examine the effect of VWF-type 2B mutants on megakaryocytopoiesis and thrombocytopoiesis as well as on platelet function, and thereby to design novel strategies against the bleeding tendency; a second translational objective is to identify new mutations in von Willebrand disease and their impact on functional assays; the two last main objectives are to unravel the role of LRP1 in vWF clearance, and to propose therapeutic approaches for patients with excessive vWF degradation.

2) The pathogenesis of hemophilia. The objectives are focused on the mechanisms of clearance of factor X or factor VIIa, and the expression of factor VIII variants in factor VIII-deficient mice to evaluate their hemostatic potential in bleeding and thrombosis models.

3) The pathogenesis of inherited platelet disorders. The objectives are derived from previous work and encompass the analysis of platelet function and signaling in patients with mutations in the FLNA gene, the genotype-phenotype relationship of mutations in the NBEAL2 gene in the gray syndrome platelet, the molecular analysis of the impaired activation of the small GTPase Rap1 in the von Willebrand disease type 2B with the mutation p.V1316M, the functional impact of the deletion in the Ca^{2}+-activated anion transporter involved in anionic phospholipid scrambling associated with the Scott syndrome and the identification of platelet signaling and secretion defects in patients with unknown thrombopathies.

4) The role of von Willebrand factor beyond hemostasis. The aim is to invetigate the absence of vWF-induced apoptosis of tumor cells via the generation of genetically modified animals, and to examine the role of the interaction between vWF and osteoprotegerin in bone protection.

The project is straightforward and ambitious but also realistic and feasible. The team will benefit from original methodologies or technologies running in the laboratory such as the hydrodynamic gene transfer approach to the development of relevant in house animal models, an efficient network of local, national and international collaborations, and direct access to patients through internal interactions with physicians. The project shows high feasibility in terms of financial resources since the team has raised funding from several agencies and industrial partners. The project has great potential considering the preliminary data already obtained. So all the conditions are gathered to search for breakthroughs.

The team leader identified clearly the potential and limitations of the project and proposes some solutions in the SWOT analysis.

Conclusion

- **Strengths and opportunities:**

Research team internationally recognized for its high standards and long-standing experience in the field of hemostasis and thrombosis.

Substantial contribution to knowledge and strong implications for treatment of von Willebrand disease and hemophilia.

Highly focused, original and translational research with molecular, cellular, animal and clinical approaches.

Very effective leadership and organization of the team as indicated by the national and international network of collaborations and the excellent training of post-docs leading to recruitment of young researchers.

Important valorization of research and interactions with non academic partners.

Excellent level of external funding.

- **Weaknesses and threats:**

Limited support by permanent technical staff due to the retirement of experienced technicians and engineers may be a danger for research continuity.

Crucial requirement for animal experimentation in a context where animal handling will become more and more controlled and restricted.

Relative lack of state-of-the art new technologies platforms on site.

- **Recommendations:**

The team deserves encouragement in its strategy to recruit young researchers.

Attention should be paid to the application for European grants through the network of international collaborations.

An additional effort needs to be made to reinforce the team with PhD students.

The team may start thinking about the creation of a start-up given the number of patents issued by team leaders.

Team 2:

Thrombose et inflammation : de la physiopathologie à la thérapeutique

Name of team leader: Ms Delphine BORGEL

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	5 (2,1)	4 (2)
N2: Permanent EPST or EPIC researchers and similar positions		2
N3: Other permanent staff (without research duties)	1	3 (2,2)
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**7 (4,1)**	**10 (7,2)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	2

• Detailed assessments

Assessment of scientific quality and outputs

During the past contract, the team has developed very well with translational projects focused on coagulation inhibitors, the protein C/protein S pathway and antithrombin, to address important questions on the relations between inflammation, hemostasis and thrombosis.

The research has generated original findings disclosing the role of protein S deficiency and Gas6 in pathology and highlighting the therapeutic potential of antithrombin-derived variants. The major contributions are:

1) The identification of protein S gene mutations (Human Genet 2009 and 2010) and viral infection (AIDS 2009) as mechanisms of protein S deficiency and the generation of the first protein S conditional deficient mice (Blood 2009).

2) Evidence of an anti-atherogenic role of Gas6 through the reduction of the pro-inflammatory phenotype of vascular smooth muscle cells (Thromb Haemost 2012).

3) The demonstration of extensive vascular damage with multifaceted prothrombotic local imbalance and bacterial pathogen adherence at sites of maximal damage in adult purpura fulminans (Am J Respir Crit Care Med 2013).

4) The production of modified antithrombins devoid of intrinsic anticoagulant activity and with increased heparin affinity as specific antagonists of heparin analogs (Blood 2011 and J Thromb Haemost 2013).

In the period 2008-2013, the team published 35 original research articles (7 in journals with IF>9 and 9 in journals with IF>5). Members of the team are first/last authors of 11 papers, including 2 in Blood and 1 in Am J Respir Crit Care Med.

Assessment of the unit's academic reputation and appeal

Several members of the team have international connections in their field. The team participated in two transatlantic networks, the Leducq Transatlantic Network of Excellence on Atherothrombosis Research (LENA) and the Leducq International Network Against Thrombosis (LINAT) both including 3 European and 3 American teams. The team was also invited to participate in an ERC advanced grant TERNANOMED (Terpenoylation: an original concept for the discovery of new nanomedicines). The team leader is member of the committee *Pharmacology and therapeutics* of the GEHT.

Members of the team have been invited as speakers in national (3) and international congresses (3). The team leader has been the organizer of the Annual Scientific Meeting of the European Society for Clinical Investigation (2008) of the GEHT Meeting in March 2013.

Members of the team have received distinctions for their innovative research (prize from the Fondation SGAM pour l'innovation thérapeutique and the valorization prize of the Université Paris-Sud) and the quality of their presentations (2 young investigator awards of the ISTH).

The team leader is coordinator of an ANR project (RPIB grant; recherches partenariales et innovations médicales). She is also a reviewer of grants for the ANRT.

A team member is the manager of the gestion committee of the L2 facility of the IFR 93 and a member of the regional and national committee for health, security and working conditions. The team leader and another scientist of the team are members of different councils or committees of the Université Paris-Sud.

The team has published 4 reviews in the evaluated period. Several members are reviewers of internationalscientific journals in the field of hemostasis (Blood, J Thromb Haemost, Arterioscler Thromb Vasc Biol).

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

Three patents have been filed in the past 5 years: the inventions related to mutated antithrombins has led to 2 international patents and the work focused on nanoparticles based on bioconjugate of glycosaminoglycans has been submitted to the European office in 2012.

The follow-up studies for the patent on mutated antithrombins for treating or preventing coagulation disorders are supported by a partnership with industry (LFB Biotechnologies) together with an ANR grant (RPIB) to generate recombinant antithrombin-derived variants. The team has a contract also with another non-academic partner. Most of the funding of the team is provided through these interactions.

The team leader is a senior consultant for a pharmaceutical company since 2011 (pharmacology of rivaroxaban) and for LFB (Protein C and severe sepsis).

A professor, who joined the team in September 2012, is vice-president of the foundation Martine Midy (for cancer research).

Assessment of the unit's organisation and life

The team is led by the former team leader of EA4531 and is well balanced in terms of staff composition. The team has coherent scientific objectives, with complementary research projects focused on coagulation inhibitors and the interaction between inflammation and hemostasis in the pathogenesis of severe sepsis and ischemia/reperfusion injuries.

The team is going to experience changes for the next contract due to the relocation of two young researchers of former U770 team 2. It is anticipated that this alliance will work very well and allow the emergence of new research directions based on their current research themes and/or their expertise on platelets.

Given the small size of the team, the main decisions are discussed by all members.

A weekly meeting with all the staff is organized for the presentation and discussion of ongoing work and future plans either by senior scientists or by students.

Assessment of the unit's involvement in training through research

The team is affiliated to the doctoral school ED 419 (*Signalisation des réseaux intégratifs en biologie)*. The team has trained 2 post-doctoral fellows and 5 PhD students. These are excellent results given the small number (2) of effective PhD student supervisors. Therefore it would be important for the young full time researchers to obtain their "*Habilitation à diriger des recherches*".

The team is fully involved in young student training. Six 2nd year Masters students, 13 first year Masters students and 1 3rd year License student have been trained over the past years.

The team leader actively participates in teaching tasks. She is responsible of the Chair of Hematology at the Faculty of Pharmacy of the Université Paris Sud. All the members of the team participate actively in the teaching of hematology (more than 750 hours a year). They also participate in the teaching of different courses (M2 level) of the specialities *Biologie Vasculaire, Athérosclérose, Thrombose, Hémostase* and *Biologie, Physiologie et Pharmacologie de la Circulation et de la Respiration* in the Master *Biologie Cellulaire Physiologie et Pathologies* (BCPP) at ParisDescartes/Paris Diderot.

Assessment of the strategy and the five-year plan

The team entitled *Thrombosis and inflammation: from pathophysiology to therapeutics* will benefit from the reorganization of the unit and the relocation of two young motivated full time researchers to propose an original and challenging project from the molecular scale to the development of diagnosis and therapeutic approaches.

The project reveals a relatively broad scope including four main axis, taking advantage of genetically modified animals and of the clinical activity of members of the team:

1) The role of endothelial sarco-endoplasmic Ca^{2+}-ATPase SERCA3 in severe sepsis and ischemia/reperfusion. This part of the project aims at characterizing the regulation by SERCA proteins of calcium dependent pathways involved in endothelial cell dysfunction, and is based on an *in vitro* cellular approach along with an *in vivo* approach with mice invalidated for SERCA3.

2) The second axis goes in line with the previous work of the team on antithrombin and is focused on the identification of the molecular network responsible for the protective role of antithrombin on endothelial glycocalyx and the characterization of the ability of recombinant antithrombin-derived variants to increase this cytoprotective effect. Another objective is to evaluate whether neutrophil extracellular traps modulate the concentration and/or activity of antithrombin and thereby coagulation in sepsis and inflammation.

3) The third axis consists of deciphering the role of the protein Z/protein Z-dependent protease inhibitor system on the endothelial glycocalyx and as a modulator of the thrombogenic potential of neutrophil extracellular traps.

4) The last axis is devoted to exploring the role of platelet heparanase in platelet adhesion and in vascular permeability and glycocalyx integrity during inflammatory responses.

The project shows high feasibility in terms of financial resources. The team will benefit from academic and non-academic funding and is a member of an IDEX (*Initiative d'Excellence*). The only problem is to assess the feasibility of maintaining all new research lines simultaneously while remaining well positioned in international competition. However, the team leader has a very good capacity for adaptation and change in strategic directions in response to results of ongoing research and for managing the team's expansion.

Some potential problems and limitations have been well identified in the SWOT analysis. It is emphasized that a significant part of the project is new, ambitious and highly competitive.

Conclusion

- **Strengths and opportunities:**

Important contributions in the field of coagulation inhibitors.

Strong interactions with physician scientists whose clinical responsabilities are critical for the translational nature of the research.

Timely reorganization to take advantage of close collaboration with top full time researchers of team 1 and their expertise in animal models and platelets.

Important valorization of research.

Excellent fund raising.

- **Weaknesses and threats:**

The projects on endothelial glycocalyx and neutrophil extracellular traps are original and ambitious but may be considered as being of a high risk since they are currently based on limited preliminary data.

The number of different projects is elevated given the relatively small size of the team.

High competition in the field so that the objectives could be out-dated when they are reached.

- **Recommendations:**

It is important for the team to better establish the priorities of the projects considering the critical mass of researchers in the team.

A strong interaction with team 1 and other international leaders in the field of inflammation and thrombosis should help reaching the fixed obejctives in a context of high international competition.

The team should aim at attracting post-docs.

The team is advised to reinforce its international position.

5 • Conduct of the visit

Visit date:

Start: Thursday, 12th December 2013, at 09.00 am

End: Thursday, 12th December 2013, at 05.00 pm

Visit site: UMR_S 770, Hôpital Bicêtre, Paris

Institution: INSERM

Address : 80 rue du Général Leclerc – 94276 Le Kremlin-Bicêtre Cedex

Conduct or programme of visit:

09.00 to 09.30 am	Welcome and coffee
09.30 to 10.00 am	Door-closed meeting: Committee members and scientifique delegate of the AERES (DS)
10.00 to 11.00 am	Unit 770 Activity report: Ms Cécile DENIS
11.00 to 11.45 am	EA4531 Activity report: Ms Delphine BORGEL
11.45 to 12.30 pm	New organization of UMR_S770: Ms Cécile DENIS Team 1 Projects: Ms Cécile DENIS and Mr Jean-Philippe ROSA
12.30 to 12.45 pm	Door-closed meeting: Committee members, DS, university and INSERM representatives
Lunch	
01.45 to 02.15 pm	Team 2 Projects: Ms Delphine BORGEL
02.15 to 03.00 pm	Simultaneous meetings: • Meeting with PhD students and postdoctoral fellows • Meeting with engineers, technicians and administrative assistants Meeting with researchers (excluding team leaders)
03.00 to 05.00 pm	Door-closed meeting: committee members and DS

6 • Supervising bodies' general comments

UNIVERSITÉ PARIS SUD

Comprendre le monde, construire l'avenir®

Le Président de l'Université Paris-Sud

à

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
AERES
20, rue Vivienne
75002 Paris

Orsay, le 12 mars 2014

N/Réf. : 45/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007501

Monsieur le Directeur,

Vous m'avez transmis le 26 février dernier, le rapport d'évaluation de l'unité de recherche – Hémostase – Inflammation - Thrombose - n° S2PUR150007501 et je vous en remercie.

L'université se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions.

Les points à améliorer seront discutés avec le directeur d'unité dans un esprit constructif pour l'avenir de la recherche à l'université.

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

Jacques BITTOUN
Président

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