ICAN - Unité de recherche sur les maladies cardiovasculaires, du métabolisme et de la nutrition

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Institut de recherche sur les maladies cardiovasculaires, du métabolisme et de la nutrition

UMR-ICAN

Under the supervision of the following institutions and research bodies:

Institut national de la santé et de la recherche médicale

Université Paris 6 - Pierre et Marie Curie

February 2013

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

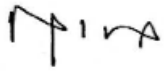
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

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

Grading

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

This score (A+, A, B, C) concerned each of the six criteria defined by the AERES and was given along with an overall assessment. NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

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

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

- Grading table of the unit: Institut de recherche sur les maladies cardiovasculaires, du métabolisme et de la nutrition

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

- Grading table of the team: Human genomics and genetics of cardiovascular diseases

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

- Grading table of the team: Biology and pharmacology of cardiovascular remodelling

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

- Grading table of the team: Pathophysiology of cellular excitability

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

- Grading table of the team: Dyslipidemia, Inflammation and atherosclerosis

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

- Grading table of the team: Stem cell biology

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

- Grading table of the team: Nutriomics: Nutrition and obesity

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

Evaluation report

Unit name:	Institut de recherche sur les maladies cardiovasculaires, du métabolisme et de la nutrition
Unit acronym:	UMR-ICAN
Label requested:	UMR_S
Present no.:	Fusion of INSERM-UPMC research units UMRS 787 (Team 1) + 872 (Team 7 and part of Team 3) + 937 + 939 + 956
Name of Director (2012-2013):	N/A
Name of Project Leader (2014-2018):	Mr Stéphane HATEM

Expert committee members

Chair:

Mr Rodolphe FISCHMEISTER, University Paris-Sud

Experts:

Mr Jacques BARHANIN, University Nice Sophia Antipolis

Mr Rémy BURCELIN, University Toulouse 3 Paul Sabatier

Ms. Giulia CHINETTI, University Lille 2

Mr Emilio HIRSCH, University Torino, Italy

Mr Frank LEZOUALC'H, Université Paul Sabatier Toulouse, CSS INSERM representative

Mr Jean-Jacques SCHOTT, University Nantes

Ms. Angélique VETILLARD, University Toulouse, CNU representative

Mr Kai C. WOLLERT, Medizinische Hochschule Hannover, Germany

Scientific delegate representing the AERES:

Mr Jean GIRARD

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

Mr Paul INDELICATO, University Pierre and Marie Curie

Ms Chantal LASSERRE, INSERM

1 • Introduction

History and geographical location of the unit

The project UMR-ICAN has emerged from the fusion of several INSERM/UPMC Units or teams. Eventually, all these groups will be localized in the same building at the Faculty of Medecine of the UPMC at Pitié-Salpêtrière Hospital, over 3 floors totalizing ~2500 m² of lab and office space. Three current INSERM-UPMC units (UMRS 937, 939, 956) and one team (UMRS 787/Team 1) are already located at Pitié-Salpêtrière Hospital, but in different buildings. One team from UMRS 872 (Team 7) and a small part of another team from the same unit (Team 3) are currently located at the Institut des Cordeliers and will relocate to the Pitié-Salpêtrière Hospital.

Altogether, the 6 teams of the UMR-ICAN project have been assembled as follows: Team 1 encompasses the whole UMRS 937 unit plus former team 1 of UMRS 956 and is led by a new team leader; Team 2 is the former team 2 of UMRS 956, but the team leader has changed; Team 3 is the former team 3 from UMRS 956 joinded by a small group coming from UMRS 872 (Team 3). The team leader is the director of the UMR-ICAN project; Team 4 is composed of the entire UMRS 939 and is led by its former Director; Team 5 is the former Team 1 from UMRS 787, and is led by the same team leader; and Team 6 is currently team 7 from UMRS 872, and is led by the Director of the IHU ICAN.

Even though each team has a long history of research within INSERM and UPMC, this project is an entirely new project, which brings together 136 persons. Most of the teams that compose this new research unit are part of the IFR14 which has been instrumental in the building of a number of technological platforms (genomics, human tissue biobanks, animal & experimental core facility, etc.) and provided a common scientific and cultural core.

Management team

Composed of the Director, all team leaders and a laboratory manager (to be recruited, position available). Each team will maintain its own administrative management.

AERES nomenclature

SVE1_LS2 - SVE1_LS4 - SVE1_LS7

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		19	
N2: Permanent researchers from Institutions and similar positions		38	
N3: Other permanent staff (without research duties)		39	
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		5	
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)		2	
N6: Other contractual staff (without research duties)		16	
TOTAL N1 to N6		119	

Percentage of producers	**100%**

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	38	
Theses defended	46	
Postdoctoral students having spent at least 12 months in the unit*	28	
Number of Research Supervisor Qualifications (HDR) taken	5	
Qualified research supervisors (with an HDR) or similar positions	49	

2 • Assessment of the unit

Strengths and opportunities

• Ambitious project with a number of excellent groups.

• The director has a strong scientific credibility and great merit for having managed to gather these different units and teams into a single unit.

• The IHU ICAN and the clinical investigation center provide an excellent environment, and ensures strong links between fundamental and clinical research.

• The UMR-ICAN project is timely for the reorganisation of the cardiovascular research laboratories at the Pitié-Salpêtrière Hospital.

Weaknesses and threats

• So far, each team develops an independent project and strategy and this still needs to be better integrated into a joint project.

• Hence, the level of interaction between the teams is suboptimal.

• Some concerns were raised about possible conflict of interests between the governance of the IHU-ICAN and that of UMR-ICAN, with the leader of Team 6 being also the Director of the IHU.

Recommendations

• Develop more interactions between the teams to increase the added value of this consortium.

• Governance still needs to be improved and conflict of interest issues sorted out.

• Recruit new high-profile researchers to replace departing PIs.

3 • Detailed assessments

Assessment of scientific quality and outputs

The scientific quality of the UMR-ICAN project is excellent when judged by the sum of the individual teams that contribute to its construction. But the project still needs to evolve in order to generate added value beyond the sum of its parts.

Assessment of the unit's academic reputation and appeal

All team leaders and many of the older PIs have a high international recognition. Several teams participate in Leducq transatlantic networks. Team 2 is associated with a New York laboratory within a transatlantic cardiovascular research center. All teams have strong international collaborations.

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

This is very high in about every team. Several PIs contribute to multicenter clinical trials, coordinate national reference centers or participate in national and international scientific committees. Industrial partnership and technology transfer is very good, with many patents filed, and with each team contributing to this effort. Several biotech companies have been generated. The capacity of the individual teams to generate income through various national and international calls is very high. Finally, a strong effort is developed for public dissemination of the scientific activities, in particular towards the young public.

Assessment of the unit's organisation and life

Discussions of the committee members with the researchers, the technical staff and the PhD students and postdocs revealed a strong commitment of all members of the UMR-ICAN project to this new integrated laboratory which is perceived as a unique opportunity to increase the visibility of the Pitié-Salpêtrière campus in the international cardiovascular and metabolic research arena. Although at this stage there is not yet a real unit's life, the UMR-ICAN project appears to have been generated from a bottom-up process and the common enthusiasm of its members, both junior and senior, warrants the success of this enterprise.

Assessment of the unit's involvement in training through research

Participation in teaching is high in each team, and altogether over 60 PhD students and postdocs have been trained over the last 5-year period.

Assessment of the five-year plan and strategy

The UMR-ICAN project represents an ambitious effort to organize and coordinate the biomedical research dedicated to cardiovascular and metabolic diseases, which constitutes one of the "research arms" of the IHU-ICAN. Many high profile and internationally recognized PIs share complementary expertise in genetics, genomics, biostatistics, bioinformatics, molecular and cell biology, physiology and pharmacology. The projects of the 6 teams, with half of them led by PIs in their early 40's, encompass a large spectrum of topics, from cellular remodeling in response to injury, regenerative biology, pathophysiological mechanisms controlling heart rhythm or homeostatic functions, to the exploration of the molecular and functional elements of the genome that predispose to disease. The project appears today as the sum of its individual parts rather than a real integrated project, but this is likely to evolve over the years, in particular when all the teams will be located in the same building.

4 • Team-by-team analysis

Team 1: Human genomics and genetics of cardiovascular diseases

Name of team leader: Mr David TREGOUET

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	3	
N2: Permanent EPST or EPIC researchers and similar positions	9	10	
N3: Other permanent staff (without research duties)	29	13	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	8	1	
N6: Other contractual staff (without research duties)	2	2	
TOTAL N1 to N6	53	29	0

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	8	
Theses defended	11	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	16	

• Detailed assessments

Assessment of scientific quality and outputs

The proposed team builds on two previous distinct research groups, INSERM UMRS 956/team 1 and INSERM UMRS 937. Both teams are recognized as world experts in their field. Using state of the art genomic approaches they made major scientific contributions in generating new concepts in cardiovascular diseases (CVDs).

For each team the output is excellent, both scientifically and quantitatively.

➢ Former Team 1 –Genetics of hereditary cardiac diseases- in unit UMRS 956, research mostly focuses on the identification of genetic bases of rare CVDs, cardiomyopathies and cardiac arrhythmias (major and modulator genes). The group made major advances in the field: (i) identified rare (*but also common*) variants in *MYPN, ANKRD1, BAG3* and *MOG1* leading to dilated cardiomyopathies and cardiac arrhythmias; (ii) performed phenotype-genotype analyses in hypertrophic and dilated cardiomyopathies as well as in familial arrhythmogenic right ventricular cardiomyopathy; (iii) functionally investigated the expression of the recently identified selenoprotein-N during mouse development.

Altogether the team published 107 original articles (24 of them with IF>10 & 20 with 5<IF<10), out of which 31 were either with first or senior authorship (Eur Heart J, Ann Neurol, Cardiovasc Res, etc.).

➢ Inserm UMRS 937 comprises 3 teams. They aimed to characterize the genetic predisposition to common CVDs and to understand the underlying gene-environment interactions, with strong emphasis on coronary artery disease and venous thromboembolism.

Among over a dozen of major findings, the group performed large GWAS and meta analysis studies and identified: (i) >43 novel CHD-associated loci; (ii) 2 novel dilated cardiomyopathy-associated loci, HSPB7 and BAG3 (in collaboration with other groups);

(iii) a new locus on chromosome 11 for idiopathic pulmonary arterial hypertension (in collaboration); (iv) 4 novel susceptibility genes for venous thrombosis, *HIVEP1*, *KNG1* (first two GWASs performed so far on venous thromboembolism).

They also established the two largest resources of transcriptomic data in key cells for coronary artery disease (monocytes, macrophages) and conducted a comprehensive characterization of the genetic and non-genetic factors that influence monocyte gene expression and their impact on the development of disease.

Taken altogether the team published 400 original articles, out of which 152 were either with first or senior authorship, and many of them in major journals including Nature, Nature genetics, JAMA, JACC, Circulation, etc.

Assessment of the unit's academic reputation and appeal

This group benefits from worldwide recognition for the quality of their research allowing them to:

- integrate and play a major role in large international consortia including, 2 Leducq and FP6 networks. Such international recognition formalizes the research in these heavily structured networks,

- obtain additional research grants from major national funding agencies (Fondation pour la Recherche Médicale, ANR and PHRCs).

Academic reputation and appeal is also attested by:

- majors awards and leadership position (prix INSERM de Santé Publique and prix Jean-Paul Binet, CNRS scientific excellence award; presidence of the European Society of Cardiology),

- translational Research Contracts,

- large numbers of invited national or international conferences,

- Hosting of 12 post doctoral fellows and 7 visiting scientists.

The new team leader will certainly benefit from the strong visibility of his former PIs and, despite his relatively young age (40), has already a strong national and international scientific recognition.

The Team leader has published 97 articles in international peer-reviewed journals. Furthermore he belongs to the editorial board of 4 journals (*Arteriosclerosis Thrombosis and Vascular Biology*, *Human Genetics*, *Journal of Molecular Medicine* and *BMC Medical Genetics*). The Team leader is also co-director of the Genomics department of the Institute for Cardiometabolism and Nutrition (IHU-ICAN) and since autumn 2011 coordinates the bioinformatics group of the Post Genomic Platform of the Pitié-Salpêtrière Hospital (P3S).

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

- All PIs contributed to either a major European multicenter clinical trial, to European or National guidelines related to inherited cardiomyopathies, coordinate national reference center on hereditary cardiac diseases, or participate in national and international scientific committees.

- Team members participate actively to numerous public dissemination activities including, meetings with 'association des parents', writing article in a major newspapers (*le Monde*), etc.

- Two patents have been filed.

Assessment of the unit's organisation and life

The team leader will play a significant role within the new Inserm Unit and within the IHU-ICAN and benefit from a strong support of his former PIs.

Gouvernance & management:

- The team - Genomics & Pathophysiology of Cardiovascular Diseases- is large (5 DR; 1 CR; 3 PU-PH; 2 MCU-PH; 1 MCF; 3 IR; 5 PH; 3 IE; 1 AI; 2 TR; 4 PhD and 6 PostDoc) and is subdivided into 5 complementary subgroups.

- All PIs including DAT have a strong track record in management. An open discussion with PhD students and Postdoctoral fellows revealed a very positive feedback both about their scientific environment and mentoring (Journal club, two day scientific annual retreat).

Assessment of the unit's involvement in training through research

The team is involved in teaching at the undergraduate and graduate levels (3PU-PH; 2 MCU-PH and 1 MCF and is affiliated to various doctoral schools: ED515- "Complexité du vivant"-Paris 6 and to several Masters (Paris 5, 6, 7 & Paris 11).

Altogether 19 PhD students and 12 Postdoctoral fellows have been trained in addition to over 15 Master and 'BTS' students.

Assessment of the five-year plan and strategy

The new team -Human genomics and genetics of cardiovascular diseases corresponds to a logical merge of the two previous distinct research groups focusing on rare and common forms of CVDs. The rationale for merging the two teams with complementary skills is very straightforward since, the sequencing of the human genome and the development of next-generation sequencing (NGS) has radically revolutionized the research landscape in the field of human disease genetics. It appears that the formal distinction between Mendelian and common forms of CVDs is no longer adequate since the same research strategies are now applied to common or rare diseases and that a gene may harbor both rare and common variants associated with the same CVD.

The current research program is based on high-throughput genomic and transcriptomic approaches using microarray and/or NGS technologies, followed by in-depth functional investigations of the genes/variants identified. The genomics tools used will generate high-dimensional complex data requiring strong expertise and novel tools for data management and bioinformatics/biostatistics analysis. The expertise of DAT in bioinformatics/biostatistics and the fact that a substantial part of his activity is devoted to new methodological research will greatly enhance the chances of success of the current projects.

The main CVDs targeted will be cardiomyopathies (dilated-DCM, hypertrophic-HCM, arrhythmogenic-ARVC), arrhythmias (long QT and Brugada syndromes, ventricular fibrillation), coronary artery disease (CAD) and venous thrombosis (VT). According to the state of knowledge for each disease, different strategies will be pursued:

✓Genome-wide association study (GWAS),

✓Meta-analysis of GWAS in the framework of large consortia,

✓Genome-wide expression study in monocytes in relation to CVD risk factors.

✓Whole-exome sequencing in patients and families presenting unresolved cardiomyopathies, arrhythmogenic disorders and inherited platelets-associated disorders,

✓Functional characterization of CVD-associated genes identified recently (BAG3 for DCM; DSG2 for ARVC; Navβ1 for Brugada syndrome; KCNQ1 for long QT syndrome; SASH1, GAS6, PPAP2B for CAD; HIVEP1 for VT).

Altogether the projects are innovative, well designed and achievable with a strong emphasis on translational research.

Conclusion

- Strengths and opportunities:

- Strong expertise in statistical/bioinformatics is key for the success of state-of-the-art genomic investigations,

- The scientific achievements are excellent and the rational and the proposed strategies to decipher the genetic background of major CVDs are sound. The projects are innovative and well designed,

- The team will benefit from an exceptional setting (UMR-ICAN) as well as from long lasting international and internal collaborations,

- The current team, by its new organization, has proven its "'superior' insight in the majors scientific challenges for the year to come and will, without a doubt, remain extremely productive and competitive.

- Weaknesses and threats:

- Despite his young age, the team leader has a strong track record (97 manuscripts). Furthermore within the coming years he will remain surrounded by highly experienced PIs,

- Despite the availability of funding there will be a clear need for additional financial support to develop all the proposed projects.

- Recommendations:

- To recruit new high-profile researchers to replace departing PIs,

- To develop expertise to investigate epigenetic marks such as DNA-methylation and Histone modifications.

Team 2: Biology and pharmacology of cardiovascular remodelling

Name of team leader: Mr Jean-Sébastien HULOT

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3	5	
N2: Permanent EPST or EPIC researchers and similar positions	3	3	
N3: Other permanent staff (without research duties)	3	4	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	1	
N6: Other contractual staff (without research duties)	2	2	
TOTAL N1 to N6	16	15	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	6	

• Detailed assessments

Assessment of scientific quality and outputs

The main goal of the team is to decipher new mechanisms involved in cardiac hypertrophy and failure and in vascular proliferative diseases (pulmonary hypertension and restenosis following angioplasty) in order to define new therapeutic approaches. During the last quadrienal period, the team reported several very interesting and original observations in the context of Ca^{2+} signaling in cardiovascular remodeling and pulmonary arterial hypertension (PAH) physiopathology. Specifically, the group showed that increasing SERCA2a expression or silencing STIM1 prevents cardiac hypertrophy and smooth muscle proliferation. This work is based on the use of relevant mouse animal models or innovative AAV-gene transfer approach. A clinical trial (AGENT-HF trial) for SERCA2a gene transfer in patients with heart failure in the Institute of cardiology from La Pitié-Salpêtrière is currently ongoing and witnesses the excellent translational activity of the group. The team is thus involved in the basic description of molecular mechanisms underlying cardiovascular diseases but is also part of future evaluation of therapies in patients. The team also identified MRP4 and a new BMP homologue as therapeutic target in CV remodelling and PAH. Finally, a genome wide association study was performed in a large cohort of PAH patients through an international collaboration, and a highly significant association was found on a locus on Chr 18.

The group is very active and productive with 69 original articles, out of which 25 were either with first or senior authorship, and many of them in major journals including 1 *Nat Genetics* in press, 2 *J Clin Invest*, 1 *Circulation*, 1 *Circ Res*, 2 *Aging Cell*, 1 *FASEB J*, etc. The team leader and members of the team are also authors of 9 reviews and co-authors of scientific papers in excellent journals (2 *Lancet*, 1 *J Pathol*, 1 *JAMA*, 1 *PNAS*, 1 *Blood*…).

Assessment of the unit's academic reputation and appeal

The team has strong international visibility as attested by the quality of the scientific production, the number of invited conferences and communications at national and international meetings. The group is very active and highly successful in obtaining grants from national and international agencies (in the last period the group coordinated 1 grant from the Leducq Foundation (Transatlantic network), 1 NIH, 3 ANR, and got various grants from charity fundations (2 AFM, 2 FDF, 2 FRM), UPMC-ICAN or PHRC and indutsrial partners. Many international collaborations are depicted in the report and the team is an associate laboratory of the Cardiovascular Research Center of Mount Sinai School of Medicine (New York). Of note, the team also developed local and national collaborations with different basic and clinical research teams.

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

The group has various on-going clinical investigation protocols (3 PHRC, CRC, contracts with biotechnology and pharmaceutical companies) and developped several industrial partnerships with biotechnology and pharmaceutical companies (Ectycell, Celladon, Bayer). The team has a strong capacity of development of innovative experimental models (Vectorization, cardio-vascular targeted gene transfer). Five patents have been filed by the group.

Assessment of the unit's organisation and life

Organization and management appear to be very strong for running research and training tasks. Many of the members have been working together for several years. The scientific project is very original with good complementarity between the researchers of the team and some of the other teams of the new unit.

Assessment of the unit's involvement in training through research

The team has well-established expertise and roles in different teaching activities (physiology, cardiovascular pharmacology and genetics) at the undergraduate and postgraduate levels. Team members have proven training abilities and skills, as also witnessed by the high numbers of PhD students and postdocs that attend the lab. Since 2007 the team trained 4 BTS, 8 Master 1, 6 Master 2 and 7 PhD defended their thesis during this period. The participation of team members to master courses (and other types of training activities) further expands the opportunities for recruiting good students.

Assessment of the five-year plan and strategy

The aim of the project is to understand the molecular and cellular mechanisms involved in different cardiovascular diseases with a focus on two different diseases namely heart failure and pulmonary arterial hypertension. Three themes will be developed: a) Targeted Molecular therapy for heart failure (Cardiac Ca^{2+} cycling and compartmentation); b) molecular and cellular determinants of vascular remodeling (molecular genetics of hereditary angiopathies, vascular progenitors recruitment and differentiation during PAH, targeted therapy in PAH); c) stress signal pathways and cardiovascular differentiation (molecular pathways driving differentiation of cardiac progenitors, microRNA and cardiovascular differentiation). The final objective of the project is to identify relevant targets to reverse the remodeling process or alternatively promote the tissue repair. Although the proposed studies focus on potential tools to modulate remodeling, an aim on the basic mechanisms of remodeling appears advisable. In addition, given the controversial role of adult stem cells in remodeling, careful planning of such endeavors is highly recommended. Nonetheless, the project is clearly attractive and very competitive at an international level.

Conclusion

- Strengths and opportunities:

- Multi-disciplinary skills in translational and basic research (physiopathology, pharmacology, cell biology and molecular biology), in clinical cardiology and genetics,

- Excellent track record of conducting innovative human therapy trials and translational research in humans. The connection with the hospital as well as the integration of on-site physicians in the team create great opportunities to carry out high-level translational studies,

- Very good international visibility as attested by the international associated laboratory, the participations in international research networks, by the number of invitations to congress, and publications in high impact journals,

- Highly Innovative research (identification of new targets for CV remodeling such as STIM1 and MRP4),

- Various Industrial partnerships.

- Weaknesses and threats:

- With respect to the size of the team, there is a high number of competitive projects developped.

- Recommendations:

- To recruit young researchers in basic science.

Team 3: Pathophysiology of cellular excitability

Name of team leader: Mr Stéphane HATEM

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	
N2: Permanent EPST or EPIC researchers and similar positions	4	5	
N3: Other permanent staff (without research duties)	2	1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	2	
N6: Other contractual staff (without research duties)	3	3	
TOTAL N1 to N6	17	16	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	8	
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	8	

• Detailed assessments

Assessment of scientific quality and outputs

Team 3 research was focused on the pathophysiology of atrial fibrillation (AF), the most frequent form of cardiac arrhythmia. Two main research axes have been developped: i) regulation of expression and activity of ion channels under normal and AF conditions; ii) atrial myocardium remodeling and formation of the AF substrate. The team also promoted translational research through clinical and industrial partnerships for development of new devices and preclinical models.

The group is leader in the field of ion channels in atrial fibrillation. Its expertise goes beyond the pure electrophysiology and extends to cell and tissue studies using sate-of-the art techniques of imaging and viral infection.

The publication track record is definetely high with 37 original articles, out of which 17 were either with first or senior authorship, inluding 3 with and IF>10 (1 *J Clin Invest*, 1 *Circulation*, 1 *Eur Heart J*), and 4 with IF>9 (3 *Circ Res*, 1 *PNAS*). The international recognition is also reinforced by the publication of a *Physiological Review* article by the team in 2012 (IF 28).

Among the major scientific breakthroughs:

The role of SAP27, a major anchoring protein, in the cardiac K^+ channels sorting and organization (*AJP 2008, Circ Res 2009)*; the discovery of separate subpopulations of Na^+ channels targeted to intercalated discs by SAP17 or to lateral membrane by the syntrophin-dystrophin complex (*Circ Res 2011*); the recruitment of Kv1.5 K^+ channel to plasma upon cholesterol depletion: the first description of channel exocitosis in cardiomycytes. (*PNAS 2009, Physiol Rev 2012*).

The description of novel mechanisms innvolved in the formation of the substrate of atrial fibrillation: down regulation of Ca^{2+} currents induced by the atrial hemodynamic overload (*Eur Heart J 2008*); the demonstartion that CRE is a major transcription factor involved in the formation of the AF substrate (*Int J Cardiol 2011*); the implication of thrombin in cardiovascular remodeling (*J Pharmacol & Exp Ther 2011*).

Assessment of the unit's academic reputation and appeal

The team leader is the vice director research of the IHU. IHU-ICAN is one of the 6 medical research institutes created in France in the frame of national "Grand Emprunt".

The team leader is also the director of the unit UMR-ICAN.

As director of the UMRS 956, the team leader is at the origin of the creation of an International Associated Laboratory with the cardiology research department of the medical faculty of Mont Sinaï, New York.

Team 3 participates in a Leducq TNE and in FP7 networks. In addition, the team has other national and international collaborations through networks (3 ANR with Institut du Thorax in Nantes and the University of Bern, 2 collaborations with Necker and CHU Bichat Claude Bernard). 5 other international and 1 national collaborations without networks.

The team members participate in several scientific societies.

22 invitations to give-lectures in international congresses, among them the Annual Congress of the European Society of Cardiology (2011), Heart failure Winter Meeting (2011), Gordon Conference (2012).

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

The team leader played a significant role in the creation of the IHU-ICAN.

3 patents have been filed and, remarquably, two of them are currently being developped; 1) a hand-held disposable analyzer to meseasure platelet activation (APOL); 2) a process for preserving blood platelets by zeodration.

Two industrial contracts are mentionned in the report (with Pierre Fabre and with Servier).

Team members participated in INSERM manifestations "L'Inserm fait son cinéma" and "Science à cœur".

Assesment of the unit's organisation and life

With the arrival of the “kidney group” from the "Institut des Cordeliers", the team is now pretty large with 7 permanent researchers (3 DR or CR, 4 PU or MCU), 6 PhD and postdoc, 3 technicians. The team is organized in 4 subgroups that develop independent research projects, yet linked to and cross-fertilized by each other. Each subgroup has its dedicated personal. In addition, cardiac and kidney physiology studies are well balanced, with two projects on each field.

Assessment of the unit's involvement in training through research

The team is directly involved in teaching at the undergraduate and graduate levels (4 PU and MCU). Since 2007, the team has trained 13 PhD students and about 20 master students (4 per year). The team has also trained 3 post-docs.

Assessment of the five-year plan and strategy

The future team 3 comprises the previous team led by the director of the unit and specialized in cardiac physiology and a novel group of 3 PI's coming from the Institut des Cordeliers in Paris and specialized in kidney physiology. Altogether, the team's investigators share a common interest in cellular electrophysiology. The association of heart and kidney physiology makes sense on the clinical point of view as many pathologies are cardio-renal pathologies.

Team 3 has four main objectives for the next 5 years:

1. Describe and understand the mechanisms of ion channel trafficking and cardiac plasticity under physiological and pathological conditions.

2. Understand the biology of the substrate of atrial fibrillation, with a particular interest for the role played by other cells than myocytes, paricularly cardiac adipocytes and endothelial cells.

3. Analyze the physiopathological roles of Kir K^+ channels complexes in the kidney.

4. Analyze the physiopathological roles and biophysics of chloride channels complexes in the kidney.

Team 3 participates in 2 integrative projects that are common to several teams:

- the project "resident adult stem cells and cardiovascular remodeling" in collaboration with teams 2, 5 and 6.

- the project "cardiac arrhythmias" in collaboration with team 1.

In conclusion, the team has shown to maintain a high level of expertise in its traditional discipline, electrophysiology, and to adapt to the evolution of the research by acquiring expertise in imaging and molecular biology state-of-the art technologies.

The projects are well designed, they aim at investigating basic biological questions with direct relationships with the clinic.

Conclusion

● Strengths and opportunities:

- The general feasability of the projects is high,

- The fundings are strong and,for most of them are already acquired for the next two years,

- The clinical and academic environment is optimum,

- The team participates in inter-teams integrative projects that provide the backbone of the scientific dynamic of the UMR-ICAN,

- The team benefits of performant core facilities, particularly in terms of omics, imaging and viral handling,

New mouse model of kidney pathologies are made available with the novel kidney component of the team that may be interesting to explore also for the cardiac phenotype.

● Weaknesses and threats:

The team expansion to the kidney physiology is certainly a strength, but is also a challenge to find the perfect cohesion and harmony between the two components.

Even though the publication track record is high and if the subjects of research are oriented toward important clinical problems, yet the team has difficulties to publish in the most famous journals such as Nature, Science, Cell or New England J Med.

● Recommendations:

The research performed in the team is mainly a continuation of what was done before, making the feasability of the projects high. Other more risky projects are certainly considered, but they are not really exposed in the report.

The kidney physiologists who are joining the team may envisage to open their interest to more cellular models, parituclarly iPS cells made available in the ICAN environment.

Relationships with the 5 other teams do exist, but still need to be reinforced.

Team 4: Dyslipidemia, Inflammation and atherosclerosis

Name of team leader: Mr Philippe LESNIK

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	2	3	
N2: Permanent EPST or EPIC researchers and similar positions	9	10	
N3: Other permanent staff (without research duties)	9	6	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	2	
N6: Other contractual staff (without research duties)	18	7	
TOTAL N1 to N6	43	28	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6	
Theses defended	15	
Postdoctoral students having spent at least 12 months in the unit	7	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	9	

• Detailed assessments

Assessment of scientific quality and outputs

This team derived from the previous Inserm UMRS 939 headed until september 2011 by J. Chapman. Following the director retirement, P. Lesnik has been nominated Unit Director. The team is characterized by a strong publication record. During the last 5 years more than 300 peer-reviewed articles have been published , out of which 121 were either with first or senior authorship, but only 7 of them in journals with IF>10 (1 *Lancet*, 1 *NEJM*, 2 *Circulation*, 2 *Eur Heart J*, 1 *Trends Mol Med*). Two patents have also been filed, although this can be considered as low regarding the size of the group. The number of national and international collaborations is also impressive. Members of this team have international leaderships in the field of HDL lipidomics and functions, post-prandial lipoprotein metabolism and atherosclerosis in relations to mononuclear cells. This research team hosts two platforms of the ICAN: one in lipidomics and the second in flow cytometry. The team is quite large and actually composed of 36 persons including 14 permanent research scientists (2 DR, 4 CR, 3 PU-PH and 4 MCU-PH, 1 MCU). Finally, the team is strongly supported by national and industrial grants.

Assessment of the unit's academic reputation and appeal

The group is well funded, particularly by national grants (ANR, FRM, local fundings) and by industrial partnerships. Members of the Unit also participate in a Transatlantic network funded by Leducq Foundation. The group has national and international collaborations assessed by commun publications with leading groups in Australia and Netherlands.

Appeal of the Unit is assessed by the presence of several foreign students and medical doctors that joined the team to complete/do their scientific training. The group has also welcomed several visiting scientists from USA, Australia and Argentina. In 2012 as well as in the near future (2014) new permanent scientists have joined and will join the team.

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

Two patents have been filed and several research contracts with industrial partners have been obtained. Members of the unit are involved in events such as the “Programme chercheurs en herbe”, a program welcoming teenagers (from 15 to 17 years) once a week to discover the research word. Young college students are also welcomed in the lab for short periods (1 week) for early immersion in research laboratory and medical services.

Assessment of the unit's organisation and life

The Unit is well organized. Beside management committee which meets every week and every month for functioning and strategic decisions, respectively, a scientific lab meeting is organized every week with the participation of scientists, post-docs, students and engineers/technicans. Interestingly, four seminars/year are organized as mini-symposium with 4 oral english presentations. Twice/year poster sessions are also organized during which PhD students discuss posters that they previously presented in national and international congresses. All these initiatives demonstrate the high dynamic potential of the team.

Assessment of the unit's involvement in training through research

The Unit is active in student training, PhD and Master 2 particularly. 15 PhD theses have been defended in the near past. 4 members of the Unit qualified as Research Supervisor (HDR). As indicated above, the Unit gives a particular importance to the management/training of students.

Assessment of the five-year plan and strategy

The research team focuses on a very important and competitive research area. The proposed project is based on 4 main axes:

1. lipidomics, functions and structure of HDL.

2. post-prandial state and lipoprotein metabolism.

3. epigenetic and genetics of dyslipidemia.

4. cellular lipids and immuno-inflammation.

Strategy and methodology are straightforward and the group has already a strong background in the field. Nevertheless, axis 3 merits some comments: this is a highly competitive field, especially those of epigenetics in cardiovascular disease. The Team is very ambitious since they want to develop and characterize several mouse models of tissue specific deletion of the the DNA methylase DNMT3A. The project is led by two MCU-PH with an equivalent 0.8 ETP in research. It is not very clear whether technical staff and students/Post-docs are associated to this group. This project is risky even with the help/support of animal facilities for mouse model generation/development and it is not clear whether it will be feasible in the next 5 years. Actually no previous results related to subject in specialized journals can support the competitiveness of this group in this field. Eventually, the theme 4 also appears to be risky and not properly addressed. It is wondered whether this team will be skilled enough to lead the project in collaboration with the microbiologists? Hiring a microbiologist could help. The skills required (microbiology, bioinformatic, biostatistics) might not be covered by the team. Furthermore, it is not clear what the team will be doing with the results from the microbiota analysis and how will the molecular crosstalk between the host and the microbiota be identified. This part needs to be reinforced.

Conclusion

- Strengths and opportunities:

The project in its globality is well thought and feasible. Team members already provided their capacity to raise fundings and to build up collaborations.

- Weaknesses and threats:

Some concerns may be raised on axis 3 of the project. As stated above, the structure of the group in charge of this part is not completely clear as well as the competitiveness. Particular attention should be payed to the study of mechanistic insights. Publications in high IF journals and raising of international funding are actually not optimal.

- Recommendations:

This is a group with high potential. In terms of scientific project, attention should be payed to the deciphering of mechanistic insights. Caution should be also taken for the epigenetics part. Particular efforts should be developed to improve IF of the publications as well as for the obtention of european/international grants. Recruitment of a resarcher specialized in microbiology is strongly encouraged.

Team 5: Stem cell biology

Name of team leader: Mr David SASSOON

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3	0	
N2: Permanent EPST or EPIC researchers and similar positions	7	2	
N3: Other permanent staff (without research duties)	4	3	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	12	1	
N6: Other contractual staff (without research duties)	4	2	
TOTAL N1 to N6	30	8	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	7	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	8	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	3	

• Detailed assessments

Assessment of scientific quality and outputs

This team is working on the role of adult stem cells in a number of tissues ranging from skeletal muscle to brain, and skin. Previous work of the team has led to the identification of a marker gene (Pw1/Peg3) that defines a novel population of stem cells in skeletal muscle and that can be used to identify stem cell niches in other tissues as well. This gene appears to play a crucial role in the response of stem cells to stress and inflammation. Moreover, Pw1 appears to enable a new approach to stem cell mobilisation. More recent original publications from this team (9 in total since 2008, with 5 authored at first or last position) include papers in EMBO Mol Med (2012), PNAS (2011), PloS One (2010), Nat Cell Biol (2010), and Development (2009), journals with intermediate to high IFs. Considering that The PI is heading a relatively small team that is involved mostly in basic research, the scientific output of the team is very good.

Assessment of the unit's academic reputation and appeal

The PI has a documented track record in the field of adult stem cell biology. His main focus in the past has been the role of stem cells in skeletal muscle. His expertise in the field is documented by his participitaton in two FP7 programs, one where he serves as the coordinator (EndoSTEM) and another one (OptiSTEM) where he is a work package leader. The PI has (co-)organised several international meetings. He is regularly invited to attend and speak at international conferences and meetings dedicated mostly to stem cell biology and skeletal muscle development and disease.

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

The team has filed several patent applications related to the use of the Pw1 reporter mouse as a tool to identify or isolate adult stem cells from various organs. Building on these patents, the team has established a spin-off company called AdSTEM. Currently, the company is supported by small grants from the UPMC, Oseo, and Agoranov. Eventually, 800.000 Euro will have to be raised for the company to become fully operational.

Assessment of the unit's organisation and life

Although the size of this team is smaller than other ICAN teams, the excellent research output indicates a successful organization. However, the team appears to be decreasing in size, which may ultimately jeopardise its abilty to address all of the ambitious themes outlined in the proposal and to interact with other ICAN teams that may have or develop an interest in adult stem cells in their future projects.

Assessment of the unit's involvement in training through research

In the period from 2007 to 2012, one PhD thesis has been completed, whereas 4 PhD students are still working on their thesis. Two foreign Postdocs and 5 visiting professors have been hosted by the team.

Assessment of the five-year plan and strategy

Several interesing research avenues were proposed, including a more detailed analysis of the mechanisms whereby Pw1 controls stem cell activation, fate, and self renewal during stress, after injury, and during aging. To this end, several transgenic mouse models have been developed by the team, including a Pw1 reporter mouse that allows to visualise Pw1 expressing (stem) cells in multiple tissues, possibly also the heart. Moreover, although not explained in greater detail, the group appears to have created a transgenic mouse line that allows to lineage-trace Pw1 expressing cells after injury, for example after myocardial injury. Building on the observation that Pw1 expression is epigenetically regulated, the team plans to identify regulators of stem cell epigenetic changes. Studies on the parental imprinting of Pw1 and other genes in stem cell biology appear a promising avenue for high impact outcomes.

Conclusion

● Strengths and opportunities:

- Track record in (basic) stem cell research, as demonstrated by publications and coordination/particpation in two EU projects on this subject.

- Team has developed transgenic mouse models that allow visualisation and (apparently also) lineage tracing of adult (stem) cells expressing the marker gene Pw1.

- There are important opportunities for interdisciplinary interactions within ICAN. This team conributes with their unique adult stem cell expertise.

● Weaknesses and threats:

- Work is focused to a large extent on a single molecule (Pw1).

- Team leader has no track record in cardiac (stem cell) pathobiology.

- A recent lineage-tracing study has shown that pre-existing cardiomyocytes (rather than stem cells) are the dominant source of cardiomyocyte replacement in normal mammalian myocardial homeostasis as well as after myocardial injury (Nature 2013). This threatens all potential future projects on adult cardiac stems cells in myocardial regeneration.

- Small team that may not have sufficient manpower to address all of the ambitious themes outlined in the proposal.

- Currently it is not planned that the team moves into the same building as the other ICAN teams which will impede interactions with the other teams on a daily basis.

● Recommendations:

- Team should try to identify additional molecules and mechanisms (e.g. epigenetic modifications) that play a role in stem cell biology and that may lead to the identification of regenerative therapeutics.

- Considering the questionable role of adult stem cells in the injured heart, the team may want to focus on the role of adult stem cells in other tissues studied in ICAN, including adipose tissue (may want to look at interactions with skeletal muscle in obesity), the kidneys, and the vasculature (atherosclerosis).

- Try to strengthen the interaction with the iPS cell core facility.

Team 6: Nutriomics: Nutrition and obesity

Name of team leader: Ms Karine CLEMENT

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	2	3	
N2: Permanent EPST or EPIC researchers and similar positions	9	8	
N3: Other permanent staff (without research duties)	5	3	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	0	
N6: Other contractual staff (without research duties)	6	2	
TOTAL N1 to N6	25	16	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	8	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	7	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	7	

• Detailed assessments

Assessment of scientific quality and outputs

The leader of this team has an excellent publication record, with 81 original publications since 2008, out of which 36 were either with first or senior authorship, and many of them in high IF journals (1 NEJM, 1 Nat Med, 2 Diabetes, 1 Circulation, 1 Hepatology, 2 J Hepatol, etc.). Several observations are of major importance; adipose tissue fibrosis and collagen load is noticeable, relationship with gut microbiota. The bioinformatic developments are original and online with the ongoing concept of personalized medicine.

This team can certainly centralize and coordinate numerous ambitious programs. It is a leader team in the field and in Europe.

Assessment of the unit's academic reputation and appeal

This team has an extensive collaborative and disseminating potential and is certainly extremely active in the field. It is clearly in France a major player in the field of obesity and metabolism.

The number of international and national lectures is impressive showing the importance of this team in the field.

This team has been in charge of the coordination of numerous research programs of quality in Europe and in France. These are major achievements.

It is noticeable that a lot of research programs and hence publications have been performed in collaboration where the principal investigator is not the leader of this team.

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

A major achievement concerns the founding of a biotech company Adipophyt and the establishment of numerous industrials partnerships.

Numerous book chapters and books have been written. The scientific informations has been largely disseminated.

Assessment of the unit's organisation and life

The governance of the team is strong and organized with numerous exchanges between researchers.

Assessment of the unit's involvement in training through research

This team has 5 HDR and is affiliated to doctoral school in physiology and pathophysiology, a master in nutrition. They ensure teaching and training in these school programs and in many other master programs.

They ensure monthly scientific meetings.

Assessment of the five-year plan and strategy

This team is developing researches from clinic to benchside and back to clinic. The approach is various but well coordinated. All proposed research projects are funded. They have established clinical cohorts suitable to performed the desired work. Cell biology and animal experimental concepts and facilities are available, and the team will collaborate to obtain the missing skills. The five year plan is certainly ambitious but the research team is now composed of several senior scientists who will be leading some of the topics. One noticeable aspect of this team, however, is that not enough new innovative themes are being developed. Even though adipose tissue fibrosis is an important topic, more innovation would be expected from such a large team with so many expertises.

Conclusion

● Strengths and opportunities:

A large group which is specialized in the study of obesity development and which has achieved numerous collaborative studies and scientific networking throughout the world.

This team leader is also the leader of the ICAN projet which is a major breakthrough in the field.

This team has an impressive number of publications.

The program is ambitious but achievable.

● Weaknesses and threats:

This team has too numerous collaborations and does not focus enough on its own research in order to publish major breakthroughs in the field. Hence, basic scientific innovation is not as outstanding as is should be regarding the size of the team, its expertise and the available fundings.

● Recommendations:

This team has all the concepts and skills to fulfill its goals but needs most likely to focus more on its own work in order to identify new mechanisms.

From a scientific point of view it could be recommended to consider obesity as a multiparametric disease which should be studied in subgroups. Certainly the identification of biomarkers will help. This might also lead to the identification of new original mechanisms which are so far lacking in this team.

5 • Conduct of the visit

Visit date: 12 February 2013

Start: Thursday, February 12th, 2013, at 8:15 AM

End: Thursday, February 12th, 2013, at 6:15 PM

Visit site: Faculté de Médecine, site de la Pitié Salpêtrière

Institution: Université Paris 6 - Pierre et Marie Curie

Address: 91 boulevard de l'hôpital, 75634 PARIS CEDEX 13

Specific premises visited: laboratories

Conduct or programme of visit:

8h15 – 8h30: Welcome (6th floor, room 616)

8h30 – 8h50: Door-closed meeting: Committee members and AERES representative (6th floor– room 602)

8h50 - 9h30: Past activity and future directions: Mr Stéphane HATEM

9h30-10h15: Team 1: Human genomics and genetics of cardiovascular diseases. *Mr* David TREGOUET

10h15-11h00: Team 2: Biology and pharmacology of cardiovascular remodelling. *Mr* Jean-Sébastien HULOT

11h00: **Coffee Break (3rd floor – Meeting room)**

11h15-12h00: Team 5: Stem cell biology. *Mr* David SASSOON

12h00-12h45: Team 3: Pathophysiology of cellular excitability. *Mr* Stéphane HATEM

12h45-13h45: **Lunch Break (7th floor – Library / Committee members and Team Leaders)**

13h45-14h30: Team 4: Dyslipidemia, Inflammation and atherosclerosis. *Mr* Philippe LESNIK

14h30-15h15: Team 6: Nutriomics: Nutrition and obesity. *Ms* Karine CLEMENT

15h15-15h30: **Coffee Break (3rd floor – meeting room)**

15h30-16h00: Meetings with personnel (6th floor – room 616/7th floor - Library)

- Meeting with PhD students and postdoctoral fellows
- Meeting with engineers, technicians and administrative assistants
- Meeting with researchers with permanent position

16h00 -16h30: Closed meeting with INSERM and UPMC representatives

16h30-18h00: Door-closed committee meeting

18h00: Departure

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

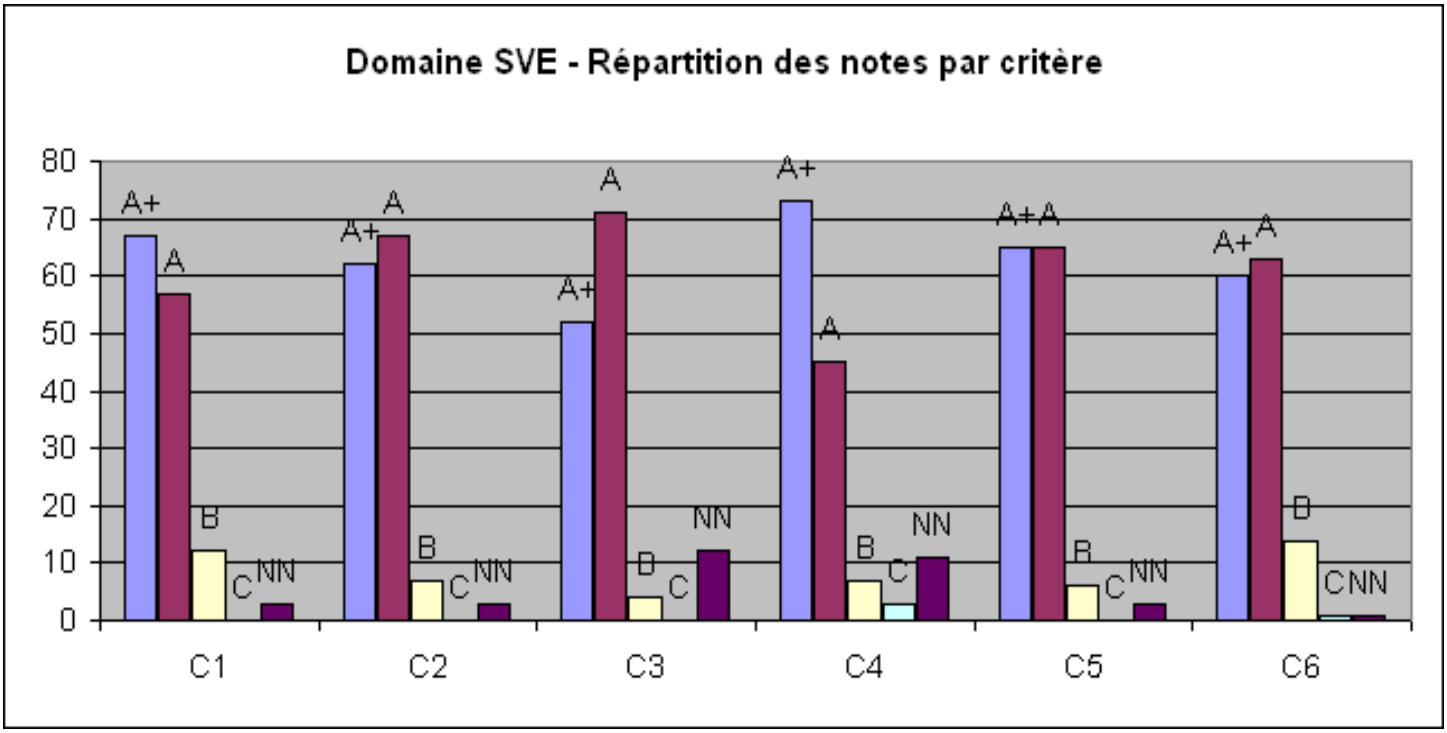
Grades

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

Institut de recherche sur les maladies cardiovasculaires, du métabolisme et de la nutrition

➢ Assessment of the Unit

We want to thank the commission for the time and the effort they spent to review our project and for all their positive and constructive comments. Below, we address the comments raised by the commission and have tried to clarify some of the points raised.

Weaknesses and threats and recommendation

• *"So far, each team develops an independent project and strategy and this still needs to be better integrated into a joint project".*

Answer:

We agree with the commission that a major challenge for the next few years is to reinforce and promote joint projects between the teams. At present, the main limitation is the geographic dispersion of the teams throughout the campus. However, extensive renovation of the building allocated to the unit is needed in order to unite the teams. With the support of the university, we have submitted to the Domaines d'intérêt Majeur "Ile de France" a funding request for 1.3 M€ to perform these renovations. In addition, the university is committed to help significantly to the restoration of the building in any case. It is planned that by 2014, the 6 teams will be united in these renovated laboratories.

• "*Some concerns were raised about possible conflict of interests between the governance of the IHU-ICAN and that of UMR-ICAN, with the leader of Team 6 being also the Director of the IHU*".

Answer:

The UMR-ICAN will have its own governance including an executive and strategic committees together with its own administration staff with a dedicated budget and financial support. In addition, INSERM had opened a position for an operative director of the UMR (engineer level). After a stringent selection, Ms. Hamon has been hired. She has a strong experience in the management of a research foundation (2008, PREMUP) and of Inserm research policy (department of partnerships with the industries and the regions 1993-2007). Her mission will be to manage the operational aspects of the UMR. She will be in charge of the relationship with the operational staff of the IHU-ICAN and the research foundation.

This concern of potential conflict of interest is been taken seriously by the director of the IHU, and for this reason, it is important to note that the governance of ICAN is includes a board of trustee, a science advisory board of international experts, an executive committee and a strategic committee. Research partner teams belong to 3 entities; UMR-ICAN (6 teams), Cordelier Research Center (3 teams), Saint-Antoine (3 teams). Each entity is represented at the strategic committee, where organization of core facilities and research

plans are discussed for the benefit of all partner teams. The composition and duties of these committees are defined with clear procedural rules ("*réglement intérieur*") signed by our institution boards and approved in March 2012 by the board of trustees, which is composed of our institution representative (INSERM, UPMC, APHP).

The issue potentially raised by the fact that that the director of ICAN is also leader of team 6 of the UMR-ICAN has been notified to UPMC and ICAN directory boards. Discussion with the UPMC research board has also been initiated. We would like to point out that it is not uncommon for a team leader to perform the function of a leader of a research center or of an initiative of excellence structure such as Labex, IHU, "cohort", or "platform" either in France or even in the USA. The directory board of INSERM reviewed recently our proposed governance (board of Wednesday 10, 2013) and apporoved this organization.

- **Specific feed-back team 1**

We thank the reviewers for highlighting the quality of the research led by our team as well as the relevance of merging into a single team the genomic and physiology expertise in both rare and common forms of cardiovascular diseases.
We are aware of the major issue that our team is facing: the immenant retirement of 4 PIs of the team. To anticipate these departures, we are already embarked into a strategy for attracting PhD and postdoc trainees that could serve as a source of further recruitment. 3 PhDs and 6 post doc trainees are currently working in our team.
As any research teams, fund raising is also a key point. Two Leducq projects , ~700K€ each, have been granted for the next five years and will support our projects on coronary artery disease and dilated cardiomyopathy. Team 1 members are coordinators or co-investigators of 13 projects that have applied for 2013 fundings (ANR (3), ANR_DGOS (3), ANR_BMBF (1), E-Rare (1), EFSD (1), FDF (1), IHU-ICAN (1), PHRC 2012 (1), SFC(1)), among which 4 are collaborative projects with other teams of the UMR_ICAN. Among these projects, two focus on epigenetic marks in relation to cardiovascular diseases.

- **Specific feed-back team 2**

We would like to thank the AERES committee for its positive feedback on our project. We agree with the committee's recommendation on our need to recruit young researchers in basic science. We have already started identifying candidates and we anticipate applications for recruitment in the near future.

We would also like to mention that our application (in collaboration with team 5) to the Leducq Foundation on "Cellular and molecular targets to promote therapeutic cardiac regeneration" has just been selected for funding. We believe that this will greatly help consolidation of our research axis on stem cells in cardiac remodeling and will further help attracting young talented researchers to our team. This effort, coordinated by the leader of Team 5 (Sassoon) will soon put out a call for young research fellows who will benefit from the unit expertises and the composition of an international consortium.

➢ **Specific feed-back team 3.**

- *"The team extension to the kidney physiology is strength but also a challenge…"*

-We thank the commission for their positive comments on our team and notably regarding the quality of our research. In the field of electrophysiology, major scientific breakthroughs and innovations come mainly from the capacity to set up new cutting-edge technologies and develop interdisciplinary research projects. Therefore, we believe that bringing together researchers from cardiac and kidney electrophysiology in a single team will favor the emergence of innovative projects. As a starting point forcollaborations, we have identified the role of anchoring proteins in the formation of ion channel in macromolecular complex and cross talk between atria and kidney to regulate blood volume.

- "..Publication track record is high but the team has difficulties to publish in the most famous journal Nature, Science, Cell"

-We will do our best to maintain the high productivity of the team as outlined by the jury and to publish in high ranking scientific journals. Our strategy is to develop more interdisciplinary and collaborative research projects notably in the frame of our international research networks.

➢ **Specific feed-back team 4**

We thank the members of the Review Committee and the Committee Chairman for their careful examination of our scientific project and for constructive comments. We are grateful for their positive evaluation of the overall quality of the project, the global strategy and the management of our Research team. Concerning the weaknesses and threats to the project developed in Axis 3, we would like to highlight several key points-

First, the epigenetic project represents a transversal collaboration that involves three teams of the proposed UMR-ICAN and two teams of the research centers « St Antoine » and « Les Cordeliers », founding Members of the IHU-ICAN. We propose that this project responds to two recommendations made by the committee, notably 1) "to develop expertise to investigate epigenetic marks such as DNA-methylation and histone modification", and 2) "to develop more interactions between the teams to increase the added value of this consortium".

Second, from the time of the project submission, several of the concerns raised by the committee have been addressed. The project was reviewed by an international committee whose report underlined a "true multidisciplinary effort to investigate the potential role of epigenetics in the mechanisms and phenotype of cardiovascular disease with the use of unbiased whole genome comparative approach". Furthermore, this project entitled "DeNoMatE" is financially supported both through collaborative teams' own funds and transversally using seeding funds. Finally, our emerging expertise in this field is further strengthened by a close collaboration with Dr R. Barres; CBMR, Denmark, an international recognized specialist in this field. Concerning the projects of Axis 4, we agree that the recruitment of a researcher specialized in microbiology would definitively strengthen our team in terms of exploring relationships between the microbiota and cholesterol homeostasis. We have already taken actions in this direction as attested by a recent recruitment of a post-doctoral microbiologist in our unit. Moreover, we have developed strong

interaction with research scientists at INRA who will perform analysis of microbiota data. In addition, we are currently concerting our efforts to develop bioinformatics and biostatistics analyses in close collaboration with Teams 1 & 6 of the UMRS-ICAN.

- **Specific feed-back team 5**

-We thank the committee for the favorable remarks regarding our productivity, team organization and involvement/visibility in the international stem cell community and for recognizing the fundamental (basic) research nature of this team. Among the concerns or potential weaknesses noted, there was the comment that the work of the team is too focused on a single molecule (Pw1). We are engaged in the examination of larger network of genes as well as have an established and ongoing effort on genes that mediate cell stress and regeneration (p53, inflammatory cytokines, DNA repair enzymes (Ku80), AKT, IGF, myostatin, Pax7/3 to name a few). Our presentation was focused upon the aspect of our work immediately relevant to our interactions within the context of the proposed UMR to avoid confusion of the various projects that are focused on other issues such as metastasis, general 'stem-cell biology' and parental imprinting (>20 genes of immediate interest).

The committee commented that the team (and team leader) is well recognized in the stem cell community and participates in and/or coordinates large EC consortiums (Sassoon is the coordinator of Endostem (FP7), participant in Optistem (FP7) and a participant in the LABEX-REVIVE), however they raised the comment that the team has no track record in cardiac (stem cell) pathobiology. Whilst this may present a challenge for the team, we have a long record of entering new fields and making important discoveries in those fields. During the presentation of the team and in the context of the unit, we had indicated that the team leader had recently submitted a grant to the Fondation Leducq (a highly competitive funding mechanism for heart research) with the team leader as the 'European Coordinator'. At the time of the presentation, our proposal had been 'pre-selected' and presently we have learned *that our proposal was selected* for funding. Related to this point was the concern that our specific project is reliant upon the assumption that the heart contains stem cells but that a recent study suggests that new heart tissue arises from de-differentiation of cardiomyocytes. We tried to make it clear that we have no bias regarding the role of stem cells versus de-differentiation and that to this end, we have one Leducq network partner (T. Braun, Germany) who favors the 'de-differentiation' hypothesis. At present, it would be premature to rule either hypothesis out as the heart shows meager regeneration at best in the adult mammal, thus no mechanism appears to be working optimally. We also know that the cells we are examining can form cardio-myocytes, vessels and smooth muscle, and we are not limiting our vision to any single lineage and will examine this not only in collaboration with expertise in the unit but also within the context of our consortium which includes opinion leaders in the field of heart regeneration. We presently have a paper in press addressing precisely this issue in skeletal muscle and are prepared to extend this line of investigation to the heart in light of recent observations by the team of S. Hatem (Team 3) and K. Clément (Team 6) on ectopic cardiac adipogenesis.

The commission remarked that team 5 is small by comparison to the other teams in the proposed unit. In contrast to the other teams, our team is not a result of the fusion of

previously existing teams. The team leader built a unit founded in 2006 and recruited 3 independent 'young' teams (Avenir) and these newly independent teams do not wish to be fused together in larger teams which is disadvantageous in basic research and their own visibility. This stated, we are deeply concerned about the lack of highly fundamental stem cell research teams within the proposed structure and we are concerned with the increasing pressure to recruit permanent posts into the team due to stringent regulations on temporary contracts in France. The profile of our team is consistent with that of Basic Research departments in the USA or teams in institutes such as the Curie or Pasteur that experience a higher turnover and are more student/postdoctoral fellow based. This complexion does require extensive external funding to pay the contracts that will remain a challenge but thus far has been met with success. This stated, we are recruiting 2 postdoctoral fellows to be selected from a very competitive group that responded to our recent call placed both nationally and internationally. Our team will consist of 4 postdoctoral fellows, research engineer and 3-4 Ph.D. students as well as 2 permanent INSERM researchers (total 10 persons).

The commission stated that currently it is not planned that the team moves into the same building as the other ICAN teams which will impede interactions with the other teams on a daily basis. We acknowledge this issue but a decision to be physically united with the unit rests with the university that has, at present, not made their intentions nor vision clear. This should be done in order to allow for a reasonable transition. Lastly, they raised the point that our team has created a spin-off that will require significant financial support. With the UPMC and SATT-Lutech (Technology transfer), we are engaged in discussion to provide this essential support. Three patents have been filed with the UPMC at present to support this effort.

- **Specific feed-back team 6**

We thank the AERES committee for their positive comments regarding the relevance and ambitious nature of our scientific program, the team position in Europe, particularly in coordinating a European new project (FP7-Metacardis), the publication record, as well as dynamic aspects regarding creation of a start-up and partnerships with industries. Also mentioned by the committee, networking collaborations have been an assumed politic of the team, which contributed to its national and international visibility.

The AERES committee suggested that there might be not enough "innovative" and "mechanistic" approaches in the team's program. The strategy of our team has been based primarily upon human investigation, tissue exploration and large-scale approaches, combining clinical and bioinformatic skills. As mentioned at the end of the AERES report, team members have indeed long considered obesity as a multiparametric and complex disease and, pioneered the field of ameliorated clinical stratification to develop the medicine of obesity. In this context, exploration of adipose tissue at the scale of transcriptomics to identify individual signatures and biomarkers is a major focus that is now extended in task 3 and 4 combining multiple signatures (environmental, metabolic and metagenomic). Driven by these large scale approaches, new mechanistic hypotheses have emerged. Specifically, the team has put forward the original concept of fibrotic adipose tissue, which is currently

investigated in depth at the molecular level regarding the consequences of mechanical constrains on adipocyte metabolic and inflammatory responses (ongoing ANR project Adipofib). Moreover, to reinforce mechanistic investigations, the team has recently recruited three fundamental researchers with skills in molecular biology and transcriptional regulation, immunology and cell biology. An INSERM CR1 was recruited in 2010 and a INSERM DR and a MCU in immunology have joined the team in 2012. We note that this has already been fruitful with high-impact publications, in JCI in early 2013 and 2 papers under review in Nature and J Exp Med. Moreover, ongoing research programs have already led to important discoveries, including defective autophagic flux in adipocytes and hitherto unidentified inflammatory cross-talk between macrophages and T cells in the adipose tissue of obese and diabetic subjects. These processes are explored at the cellular and molecular levels and in relation with obesity co-morbidities and potential treatment, thereby linking basic and clinical research in fitting with the team's strategy.

To summarize, the Nutriomic team is organized to undertake a mechanistic approach to address the biological research questions as well as to perform a systemic approach to address the mechanistic aspects from a broader perspective.