Institut de recherche en santé, environnement, travail

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

IRSET

Institut de Recherche Santé, Environnement & Travail

From the

Université de Rennes 1

INSERM

EHESP

November 2010

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

November 2010

Research Unit

Title: Institut de recherche Santé, Environnement & Travail

Requested label: UMR_S INSERM

N° in the case of renewal:

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Report

1 • Introduction

- Date and execution of the visit

All presentations and meetings were held on November 23th-25th, 2010 at the auditorium of Ecole des Hautes Etudes de Santé Publique (EHESP) in Rennes.

The panel included 10 members covering well all the scientific fields of this large research unit. The origin and general organization of IRSET was introduced by a 45 min lecture of its Director, in the presence of all members of the Institute. Then, the 10 teams all reported on their organization, results and perspectives in the form of 45 min. sessions, including a 25 min. presentation by the team leader + 20 min. questions from the committee. All team members, including students, were present during their specific sessions.

A complementary presentation of recent results was also organized as a poster session (3-4 posters for each team) during lunches and coffee breaks.

Although they were not formally in the evaluation process, the 4 platforms of IRSET were also presented by their Directors; 45 min. each for LERES (analytical chemistry) and PPB (Plateforme Protéomique-Biogenouest), 20 min for TERRA (toxicological models and methods), and within the talk of team 7 for the Genomics and Bioinformatics platform.

A one hour meeting was organized with the Presidents of University Rennes 1 and EHESP, the Directors of Pharmacy and Medicine Departments of Rennes 1, the Director of the Clinical Research Center of Rennes Hospitals, the Regional representative of Inserm, and the representative of Rennes Metropole.

The committee splitted into 3 sub-groups for short meetings with i) PhD students and postdoc fellows; ii) engineers, technicians and administrative assistants, iii) researchers with permanent positions.

The committee benefited from a sufficient time to share views and potential concerns during the three days of visit in Rennes.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

The Research Institute for Environmental and Occupational Health (Institut de Recherche Santé, Environnement & Travail, IRSET) was founded in 2009 as a collaborative initiative from several teams in Rennes. They came from established research units spread in 3 different locations : Campus de Villejean (Faculties of Medicine and Pharmacy), Campus de Beaulieu (Faculty of Sciences), and Ecole des Hautes Etudes de Santé Public (EHESP). The 210 collaborators of IRSET are yet spread but expect to gather in a single building by 2014. The future site will be located on the EHESP campus, in close vicinity of the Villejean campus.

The scientific mission of IRSET is to study biological processes and environmental factors that might influence human health in a risk assesment perspective. The considered agents range from chemicals to infectious agents, and also include physical stresses. They might be studied alone or as a combination. The ten teams at IRSET are able to characterize their impacts on several important functions, from immunity to reproduction, and from development to cancer. Three transversal domains have been identified to promote internal exchanges at IRSET : "Signaling and response to stress", "Endocrinology, reproductive and development health", and "Technology, research and development". The latter includes four technical platforms that provide research projects with an access to cutting edge methods in analytical chemistry, proteomics, genomics and proteomics.

IRSET is already jointly recognized by Université Rennes 1, EHESP and Université Antilles-Guyane. It also expects to be further granted as an Inserm joint research unit for the forthcoming period 2012-2016.

- Management team

The current elected board of IRSET includes Bernard JEGOU (DR Inserm), as the Director, and Dominique LAGADIC-GOSSMANN (DR CNRS) and Denis Zmirou-Navier (Dir. Dept. EHESP, Professor at University of Nancy), as deputy-directors. This compact team is directly advised by both an internal Council and an external international scientific advisory board (SAB), according to the Institute's internal rules. The Council includes the direction team, all team leaders, platform directors, and elected representatives of the three categories of personnels, including doctoral and post-doctoral fellows. The SAB is a 8 members high level committee that helps the director of IRSET in drawing its strategic perspective, and in selecting new teams or collaborators.

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	45	47
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	22	23
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	14	16
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	69	71
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	19	
N6: Number of Ph.D. students (Form 2.7 of the application file)	36	
N7: Number of staff members with a HDR or a similar grade	36	37

*Including the members of common services

2 • Overall appreciation on the research unit

- Summary

IRSET started in 2009 in the context of growing concerns about the impact on human health of an increasing number of environmental hazards. The Institute has been formed by the merging of 10 research teams and 4 technical platforms to reach the critical size required for such an ambitious and multifaceted goal. These teams collectively display a very good track record of publications and productions. It looked obvious to the committee that the creation of IRSET brings an added value to all of them. The meeting with local authorities confirmed the structuring role IRSET is aimed to play in Rennes. It clearly demonstrated the strong support to IRSET, in particular regarding the investment for the building, and for the recruitment of PhD students (about 15 grants per year out of 86 per year in Rennes University).

Teams and platforms contributing to IRSET come from many different albeit complementary backgrounds, i.e. from different campuses, from different cultural environments (clinical biology to analytical chemistry or epidemiology). In fact, this AERES meeting appeared as an important milestone for IRSET ; it corresponded to one of its first formal event involving all its collaborators. It apparently was an exciting opportunity for all of them to have a complete and comprehensive vision of IRSET's activities. The committee could feel an excellent atmosphere, with very open discussions between the members of IRSET and between them and the committee.

The committee was also very impressed by the dense network of scientific interactions that all teams were able to build in the recent months. It further demonstrated the shared expectations for this common venture. The

involvement of EHESP is also very interesting since it corresponds to an important evolution toward experimental research for this specialized higher education school.

Building the collective vision and cohesion within the diverse components of IRSET will be the major challenge to the management team. This compact team demonstrated a very effective leadership during the site visit.

- Strengths and opportunities

A major strength of IRSET is that its creation results from a collective process initiated by a motivated direction team and committed team leaders. The natural leadership of Bernard JEGOU also accounted in this initiative, taking advantage of his influence at both the regional and national levels.

The global project is based on very complementary research skills. We noticed that many papers in the period 2006-2010 were already co-signed by authors from different labs.

Ten teams might be difficult to coordinate but the organization of three scientific domains encompassing the competences of all IRSET's teams (signaling and stress response ; endocrinology, reproductive and developmental health ; technology) has been an efficient way for promoting internal actions. In addition, some dedicated working groups for the future have been implemented ; i.e. a clinical project around Kepone and biological effects, or around the genomic/proteomic methods.

Another strength of IRSET is its capacity to proceed fast and efficiently, as exemplified by the recent creation of an European Doctoral College on Health and Environment, by its ability to get the joint support of University, Rennes metropole and government of region Bretagne. These sponsors to the project have already permitted some targeted recruitments. The commitment of EHESP is a further bonus. It will reinforce the capability in analytical toxicology, and has assigned the ground for IRSET's building on its campus.

Last but not least, the high technical level of all platforms is another major asset. LERES is already accredited for many environmental analytical duties, and both CGB (Center for Genomics & Bioinformatics) and PPB are among the best at the national level.

- Weaknesses and threats

Unfortunately, IRSET is lacking an international orientation. For most teams, even for some with established reputation for long time, the international activity is restricted to publications, workshops or conferences. Fundings and collaborations are mostly at the national level. Very few foreign collaborators are currently hosted in IRSET's labs, with the exception of Primig's team that came from Basel, Switzerland. During the meeting with PhD students and postdocs, the committee was surprised by the small number of them willing to work abroad. This might be detrimental to them, and to the development of IRSET's international network, and finally to its attractiveness.

The large variety of competences were earlier described as an advantage, but they might also become a drawback considering the challenge of managing multidisciplinary research, and the risk of spreading resources over too many topics. Many members in the committee also alerted on the difficulty to get multidisciplinary projects funded apart from ANR. Furthermore, there is a risk of internal competitions for the fundings.

The overall number of researchers able to supervise doctoral work is good (22 HDR for 59 researchers), but a more detailed analysis revealed that three teams are fragile since they have a few, even just one, HDR-holding researcher. This might prevent their capacity to recruit high level undergraduates.

Availability of the new building has been announced by 2014. It is clear that any delay in this project would directly impact the development of IRSET. The gathering of teams in a unique location is a largely shared expectation.

- Recommendations

The AERES committee formulates the following recommendations to the direction team and to its Councils :

- increase the internal scientific animation of IRSET in order to strengthen the cohesion, the mutual core of knowledge, and thus, the ability to respond collectively to large calls. Many IRSET members met by the committee told it about their expectation for enhanced scientific exchanges. The creation of a dedicated Web site for IRSET might help ;

- organize a first meeting of the SAB as early as the first semester of 2011 in order to confirm the scientific orientations, and to identify the potential partners for external collaborations ;

- think more internationally ; the young French fellows we met in Rennes unfortunately seem to lack appetite for international careers. It may be a handicap for the Institute since incoming and outgoing researchers are key factors for the development of an international network. IRSET claims to be comparable to GSF in Munich or to IRAS in Utrecht. Have they been approached ? The committee suggests to establish bilateral agreements with such selected partners. Here again, the SAB might be helpful.

- address the issue of internal promotion versus external recruitment. We identified that several colleagues acting as assistant professors or "chargés de recherche" have not yet envisioned defending an "habilitation à diriger des recherches" (HDR). In the same time, targeted professorships and related positions have been announced by University authorities. The committee confirm they are more than necessary.

- clarify the connections between teams and platforms ; in particular the access for any researcher at IRSET and the access fees should be made clearer. The 2011 quotations for platforms should rapidly be distributed to all potential users. The concept of a joint offer for the models and competences in toxicology (TERRA platform) is attractive but its economical model should be clarified.

Finally, the committee recommends to further develop the strategic vision of IRSET. Beside individual projects in the various teams, the Institute should develop its collective vision for short, mid and long terms, and dynamically adapt it according to the actual support of host University. It was noticed that IRSET applied for several items in the "Investissements d'avenir" calls, including a Labex and two Equipex. The IRSET team leaders should also define the strategy for avoiding the internal competition for fundings. Applications to regional funds or to ANR could be organized in such a way that IRSET does not propose too many applications at the same calls, that would be detrimental to all.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	45
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	22
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	11
A5: Number of PhD granted during the past 4 years	30

3 • Specific comments

- Appreciation on the results

Environmental and occupational toxicology is an important issue for modern societies, and IRSET has the ambition of covering almost all areas from agricultural practices (e.g. Kepone) to habitat or workplace. The results obtained by the 10 teams of IRSET represent an excellent contribution to the field, with an interesting balance between basic and more clinically-oriented papers. The vast majority of IRSET's papers correspond to the characterization of molecular and cellular events that control the mode of action of several toxicants and related agents. The scientific production is also highly pertinent regarding physiology or epidemiology. Globally, in the period 2006-2010, IRSET researchers produced more than 400 papers in peer-reviewed journals*, delivered about 150 invited lectures, and filed 5 patents. The average yearly production ratio is then of about 1.7 considering 100 papers per year

for the 59 researchers (21 professors PU/DR + 38 MC/CR/PH, including part time collaborators). Noteworthy, the largest part of the production has been carried out by about 20 scientists publishing more than 3 papers a year. The results were largely published in journals with impact factors higher than 3. Several papers could have been submitted to journals with higher impacts since many of them were 2-3 fold more cited than the average for each respective journal.

The Institute has had an important function in the training of young toxicologists. The committee could not accurately calculate the number of PhD, MD or PharmD trained in IRSET's labs the period 2006-2010; a rough estimate was of about 50.

The teams display a pretty large list of partners from academic as well as industrial laboratories, and many of them were established in the period 2006-2010. The ongoing process of merging into IRSET will undoubtedly benefit the partnership policy by increasing the global offer and visibility.

** the sum of teams' papers is 440, but the actual number might be a bit lower considering co-authored papers by members of different teams.*

- ## Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners

While the scientific reputaton of IRSET is still to be built, the reputation of some of its teams and leaders is already satisfactory. Six researchers at IRSET exhibit an outstanding list of invitations to international conferences, demonstrating a solid reputation. The arrival of new teams with young internationally-connected leaders (teams 4 and 7) would be instrumental in expanding the range of collaborations.

The Institute has been very active at the national level and participates to major scientific networks in its field, such as the Ineris-sponsored Antiopes consortium for predictive toxicology. However, one may regret that collaborations result more from interpersonal relationships than from institutional partnerships. IRSET claims itself to be comparable to major environmental toxicology labs, such as GSF in Munich or IRAS in Utrecht. Formal agreements with such large multidisciplinary organizations might help for the out placement of doctoral fellows and for the selection of new teams.

The activity report demonstrates a good ability for all the 10 teams to raise funds in competitive calls. They have benefited from a large number of contracts in the tens to hundreds k€ range, from several agencies and from the regional government of Brittany. The scientific lines remain coherent and are not disturbed by the diversity and heterogeneity of funding mechanisms.

The Director is personally engaged in local entrepreneurship and is an ardent promoter of the regional economical development. However, few researchers are actually involved in high impact socio-economic activities. Methods and skills amenable to collaborations will be gathered in the TERRA platform of services. This initiative is interesting but its economical balance has yet to be demonstrated.

Consultancy is another important way for IRSET to deliver a socioeconomic return. Many scientists participate in high level expert groups or committees of Anses, InVs, HCSP or PNSE2. The formal creation of IRSET is likely to further increase this capability and its influence.

- ## Appreciation on the management and life of the research unit

The scientific management of IRSET is based on a compact and cohesive direction team, which is directly advised by both an internal council and an external international board. The current director and the two deputy directors are all recognized scientists representing well the various research fields studied in the Institute. The IRSET Council displays a conventional format and is well suited to the current situation.

The SAB was created in June 2010, and already comprises 8 high level members. It is expected to grow to 12 members. According to its implementation rules, its first formal meeting should be held "at the mid-point of each quadriennal term", i.e. by 2013. Considering the importance of initial orientations in the IRSET's project, the committee recommends to gather the SAB earlier, ideally before the end of 2011.

Recruitment of two managers is planned in the next future, one for the administration, the other for practical organization of laboratories and utilities. The committee supports these recruitments because this will help making the cohesion of IRSET.

In fact, IRSET is a very recent structure that has not really started working as an integrated unit. The teams are still spread over three locations and few opportunity exists for gathering all its collaborators. Nevertheless, team leaders meet rather frequently and wish to elaborate common scientific programs for the forthcoming years. At a more practical level, the committee was told that lab seminars are largelly advertised inside IRSET. This is a first approach towards a common culture.

The external communication is insufficient and IRSET lacks its direct web page. At the moment, the on line information can indirectly be found at the GERHM / Inserm U625 pages (www.u625.rennes.inserm.fr). Some seminars are reported on the IFR 140 website (IFR 140 Génétique Fonctionnelle, Agronomie et Santé is directed by a member of IRSET). The committee suggests to book the "irset.fr" internet domain name.

Members of IRSET largely contribute to teaching. This is not restricted to the many professors or assistant-professors working at the Institute, and many full time Inserm or CNRS staffs participate in advanced courses. Noteworthy, some of them are key persons for several PhD or master programs.

- Appreciation on the scientific strategy and the project

IRSET has been organized quite recently but has already proven it is a favorable place for developing ambitious projects, and for launching new independant teams (e.g. teams 4 and 7). The 10 teams and the 4 platforms have elaborated their own specific projects for the next four years (see below), but also largely exploit the competences and resources available in other teams. At that stage, the main function of the Institute is to build the environment for emergence of ambitious multidisciplinary projects. In this respect, the organization in three specialized domains is adequate. In parallel, IRSET as a research unit is expected to work at developing the quality of partnering and at increasing the attractiveness. The lesson from the past three years has been that Rennes can be attractive to young talents from abroad, who rapidly take local responsibilities as team leaders. A strong policy for the detection and selection of new teams is set up.

The internal rules of the Institute plan severe measures for building the operational budget of IRSET ; i.e. 30% of recurrent public budget, and 15% of grant income will be allocated to the Institute in order to build its scientific ambition.

Team projects are ambitious and generally excellent, but sometimes heterogeneous. The global project of IRSET should now evolve from a sum of exciting projects at each team levels, to a sum of well-coordinated at the IRSET level, in coherence with the necessity to access higher investments. The Institute is an essential actor in the large Labex project "Environmental and Health Sciences" that aims at gathering most of the biological research in the Rennes campus.

4 • Appreciation team by team

TEAM 1 : Environmental chemicals, immunity and inflammation

Team leader: M. Olivier FARDEL

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	4
N7: Number of staff members with a HDR or a similar grade	4

- Appreciation on the results

This team is proposed for a creation in the project of IRSET. It results from the division of a larger team in the former EA 4427 SeRAIC, co-directed by the proposed leader for team 1.

This group has analyzed the effects of environmental metal ions and organic compounds, towards human hematological cells, especially macrophages. The past work has demonstrated a number of very interesting signaling triggered in macrophages by most of these toxicants. For instance, they showed that arsenic alters macrophages phenotype by up-regulating NADPH oxidase activity and superoxide production. They also characterized the transcriptomic response of macrophages to polycyclic aromatic hydrocarbons and benzo(a)pyrene, using a pan microarrays. Team 1 has been involved in an important project of occupational medicine, the study of chronic obstructive bronco-pneumopathy in farmers, together with the pneumology department at the University hospital.

The team production (40 publications) has been published in very good specialty journals, with impact factors varying from 2.4 to 6. We noticed some very good toxicology papers for which the specific citation index was largely higher than the average for the journal.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader is highly experienced in term of management considering his former role in SeRAIC. The visibility of the team is very high among French toxicologists, in particular for its contribution to the field of immunotoxicology. However, the level of communications in meetings is low (4 international communications, 7 national communications) and invitations for lectures were mostly in France (7 invitations).

The integration of team 1 inside IRSET is very beneficial since studying effects of chemical contaminants in immune cells is very relevant in terms of public health.

The team is largely involved in teaching duties, and appears to be very attractive for predoctoral (8) and PhD students (8). Two HDR were obtained for team members during the period 2006-2010. Unfortunately, despite the solid production, the team does not host any postdoc fellow.

It was rather successful in raising funds (industrial contracts; public grants from INERIS, ANSES and ANR). This capacity should encourage the team to search for post-doctoral funding. The team has exclusively developed national collaborations (University of Paris-Sud, Plateforme metatool in Toulouse, Plateforme Cochin in Paris, and INERIS). The collaboration with international groups would help them to attract new researchers and would increase its access to high-ranking journals.

- Appreciation on the scientific strategy and the project

The strategy for the next four years is clear. Research projects of team 1 will focus on the characterization of the effects of environmental contaminants towards cells involved in inflammation and immunity (dendritic cells, macrophages, T lymphocytes). They aim at understanding the molecular and cellular bases underlying the toxicity of organic compounds like aryl hydrocarbons, arsenic, and phthalates plasticisers.

Three research programs will be developed on that basis. One deals with the effect of environmental contaminants on dendritic cells physiology and the role of Nrf-2 pathway, in a context of mixture of environmental contaminants. The second will focus on the effect environmental contaminants on polarization of macrophages M1 and M2. The third part of this future work will be the characterization of the transcriptomic response of activated T lymphocytes to various aryl hydrocarbon receptors (AhR).

One Professor and one postdoc fellow should join the team in 2011.

- Conclusion :

  - Summary

A very dynamic team in terms of publications, teaching duties and ability to raise funds. It is involved in national collaborations thanks to its high visibility in its specific research field of immunotoxicology. Its projects are original, ambitious, but very amenable for this team.

  - Strengths and opportunities

- Study of the mixture of environmental chemicals on inflammatory and immunological effects (PHAs, TCDD, phthalate)

- Study of lung inflammatory effects of formaldehyde

- Development of valorization activities (Technologies Servier, EDFs)

- Good knowledge of mechanism of the environmental chemicals compounds will allow the transfer to toxicological applications and emergence of new biomarkers

- New models of knock-out mice

- Access to clinical research

- Very good interaction with other teams, especially with teams 2 and 3 as a continuation of former links in SeRaic, with teams 4 and 8 to work with phthalates, and with team 9 in synergism with the ANTIOPE Network for predictive toxicology.

  - Weaknesses and threats

- All the seven researchers are highly involved in teaching duties ; no permanent staff from national bodies Inserm or CNRS ;

- Very few international collaborations.

- Recommendations

- Identify international homologs and establish partnership in immunotoxicology

- Increase the collaboration with IRSET platforms.

TEAM 2 : Exposure to hepatotropic infectious agents

Team leader: M. Michel SAMSON

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	4
N7: Number of staff members with a HDR or a similar grade	3

- Appreciation on the results

This team formerly belonged to EA 4427 SeRAIC created in January 2008. The work of team 2 has focused on host-pathogen interactions, particularly during liver infection with hepatotropic viruses (HBV, HCV) or parasites (Leishmania). Original approaches have been developed to study the mechanisms of viral entry into hepatocytes, and immune responses such as adaptive immunity, immune mediators and cytokine production. It has given rise to novel and interesting findings such as the mapping of HBV envelope determinants, identification of PI4Ks as major host factors for HCV entry and replication, and activation of the IL-33 cytokine as a new alarming cytokine in acute hepatitis. The interplay between basic and clinical research is a strong point.

Three researchers (CR1) and 3 teacher-researchers (PU-PH or MCU-PH) in this team display very good publication tracks with a total of 70 original publications during the last four years, including 29 papers with team members as main contributors. Most papers dealing with basic research were published in good or very good journals in the field (J Virol and FEBS J in 2007, Vaccine and Eur Cytokine Netw in 2008, J Virol and FASEB J in 2009, J Clin Microbiol and Plos Neglected Diseases in 2010). Papers issued from collaborative work (41) are equally distributed between experimental and clinical aspects. Fair number of invited talks for a PU-PH, mainly in France or in Europe, and numerous communications in French or European meetings.

Stable partnerships have been established with local teams of IRSET, especially with teams 1, 3, 8 and 9. Team 2 is connected to excellent French and German laboratories. Clinical research is conducted in the context of large national campaigns and thus benefit from a good support.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team exhibits a good national impact with participation to clinical networks and collaborations with excellent groups, a fair number of invited talks and participation to national and European meetings as well as collaboration with foreign European labs. Fund raising is excellent but restricted to the local and national level (Région Bretagne, Cancéropole, ANRS, Ligue contre le Cancer, ANR). In terms of attractiveness, the team recruited one post-doc and 5 PhD students, including a foreign PhD student but no foreign scientist. New collaborative projects have been implemented with other teams of IRSET. It is noticed that, despite an obvious potential, no result has yet given rise to any patent or industrial partnership.

- Appreciation on the scientific strategy and the project

Two long term scientific projects based on recent, solid data are presented, dealing with (i) host-pathogen interaction (HBV and HCV), and (ii) immune responses to infectious agents, including new cytokines as biomarkers and mechanisms of cell polarization. A new, cutting-edge project stems from a collaborative program with team 9 on co-exposure to viral and toxic agents, such as HBV and Chlordecone. The feasibility is excellent as adequate funding levels are achieved and the BSL2 and BSL3 equipments for work on human pathogens and for development of new animal models are now available.

- Conclusion :

  – Summary

This team provides IRSET with an important competence in hepatotoxicology, and related questions of synergistic effects between infectious agent and chemicals. It has a solid background and gathers a number of scientists with strong interplay and complementary approaches in basic and clinical research. Team 2 is well inserted into the IRSET organization and programs.

  – Strengths and opportunities

The team owns a deep knowledge in its field of hepatic diseases and has developed pertinent experimental systems with which to study the impact of infectious and toxic insults in human liver pathogenesis. It would clearly gain in collaborating tightly with team 5, and the access to IRSET's platforms offer an exciting opportunity to extend the competence and productivity.

  – Weaknesses and threats

The absence of a clear policy for increasing the international visibility is detrimental for the team.

No strategy for more applied research and valorization.

  – Recommendations

The team should increase national and international funding and intensify its collaboration with foreign laboratories.

Develop a valorization policy, e.g. through interaction with the TERRA platform.

Team 3 : Stress, Membrane and Signaling

Team leader: Ms. Marie-Thérèse DIMANCHE-BOITREL

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	3
N7: Number of staff members with a HDR or a similar grade	4

- Appreciation on the results

This team results from the division of the large team EA 4427 SeRAIC which was co-directed by its leader.

Their main activity of team 3 is to study the effects of environmental contaminants (ethanol, benzo(a)pyrène, cisplatin) or TRAIL-effectors on cell membrane properties. Their work is original since few research teams in the world indeed study the effects of xenobiotics/environmental pollutants on cell membranes. For example, cisplatin is mainly described as a chemotherapy drug via the triggering of apoptosis, but its effects also result from its action on the cell membrane, through activation of specific targets (Na+ exchanger, syphingomyelinase). Researchers of team 3 showed that early alterations of the plasma membranes might play a very important role in the response to chemical agents. One of the subprojects is dedicated to the study of TRAIL-based anticancer therapy, with an interesting differential effect of extracellular pH on tumour and normal cells in regard to apoptotic and necrotic processes. This observation is also pertinent and might allow new therapeutic approaches. One consequence of this very original work is a very good production of publications: 39 publications in toxicology, pharmacology, and cancer journals (Cancer Research, Oncogene, Mol Pharm, TAP, Hepatology); with a total number of citations of 139 in the period 2006-2010. A patent was filed to protect the combination of TRAIL and propionibacteria to improve colon cancer therapy.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Team 3 is composed of 2 research directors (INSERM & CNRS), 1 Professor, 2 assistant professors, 2 research technicians, and 3 PhD students. This more compact format for the team, compared with the previous situation in SeRAIC, is due to the willingness to clarify the research strategy and the new projects. It should then provide a better visibility for team 3, which still aims to actively collaborate. The team leader is very visible scientifically and highly experienced in term of management. She will keep a high position in the new institute.

Several members of the team display a high number of communications and invitations in national and international meetings (15 invitations, 10 international communications, 6 national communications). The team also has a significant activity in term of:

• training of students :10 Master 2, 8 PhD students from 2006-2010, thanks to a good number of collaborators holding HDR ;

• teaching duties at the undergraduate level ;

• funds raising : contracts with industrial partners including Neuropharma or Astra Zeneca; and numerous public grants; “Equipe Labélisée La Ligue Contre le Cancer” 2007-2009). This capacity should encourage the team to search for post-doctoral fundings ;

• valorization: one patent in 2010 ;

• collaborations : e.g. one joint patent with a team of Agrocampus Rennes

• technology sharing : development of a technical platform dedicated to cell membranes characterization

The contribution and its integration inside IRSET is obvious. It will certainly increase the visibility and attractiveness of this team.

- Appreciation on the scientific strategy and the project

The new projects are in line with the past activity on effects of xenobiotics on the cell membrane. Team 3 now appears to be more oriented towards clinical applications than in the period 2006-2010. For example, the identification of new therapeutical targets is one of the main topics of the new project. One interesting and very original concept presented by this team is the potential to characterize the responses of cell membranes to environmental injuries as biomarkers of exposure or toxicities. Other original aspects of their research will be:

• the study of interactions between diet components (omega 3) and food contaminants (more specifically the benefits of lipid-enriched diets).

• alternative strategies to target colorectal cancer using probiotic dairy propionibacteria (development of a new therapeutic strategy).

- Conclusion :

  – Summary

Team 3 is a highly dynamic team which develops strong and original projects in line with their former studies. The formation of a more compact team focused on the interactions between environmental contaminants and cell membrane properties will clarify its research strategy.

  – Strengths and opportunities

Original results and projects, very good activity of publications, strong scientific animation, leaders with a high visibility, specific collaborations with other teams at IRSET. Research topics are well suited to the objectives of ANR-CESA or PNSE2 fundings.

Close connection with University hospital and clinical research.

  – Weaknesses and threats

The team has raised a satisfactory level of fundings but, despite this ability, lacks post-doctorants. The collaborations are strong inside IRSET but remain focused on few teams.

The technical orientation is not supported by a dedicated research assistant

  – Recommendations

The team should recruit foreign post-docs ;

Identify potential partners for collaboration on the biophysical characterization of membranes structure and function

- Support the technical platform, eventually in the frame of TERRA.

Team 4 : Death Receptors and Tumor Escape

Team leader: Patrick LEGEMBRE

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2
N7: Number of staff members with a HDR or a similar grade	1

- Appreciation on the results

Team 4 is a recent independent team which arises from the previous SeRAIC. The research of this team is dedicated to the study of the initial events leading to the ignition of the apoptotic signal upon engagement of the death receptor CD95. It showed that partition of CD95 into lipid rafts accounts for transmission of a potent apoptotic signal. Preliminary data indicate that the PI3K signaling pathway prevents the redistribution of CD95 into lipids rafts and CD95 engagement triggers an increase of cytosolic calcium concentration. Built on this solid ground, the proposed research for the next four years aims at an in-depth analysis of PI3K and calcium in the initial events of the CD95-mediated apoptotic signal. Another part of the project will be to identify the non canonical calcium / PI3K signal induced by metalloprotease-cleaved CD95L.

This team also studies cell death, more specifically FAS signaling and already obtained promising preliminary results coupled with the excellent post-doctoral publications of one recently recruited researcher (CR2-CNRS). The team leader has built a powerful model to decipher the early events responsible of subtle plastic FAS signaling.

The members of this team have reported their results in high-ranking specialty journals (Oncology, Cell Biol., Immunol., etc.), and their papers are pretty well cited.

This starting team might suffer of the absence of technicians but this is partly counteracted by a good activity in term of training (4 Master2, 2 PhD fellows). Team 4 benefited from the recent recruitment of a CR2 CNRS and of two post-doc fellows. They have developed a good connection with the University of Rennes I (1 MCU involved in the PhD program).

The capacity to raise funds is very high (8 grants between 2006-10 including ANR JC till 2012, LNRC, FRM, FdF, ARC) and is an important aspect contributing to the independence of this team. Moreover, the valorization activity is very high considering the size of the team: 2 patents, FR & US-2008, on the synergistic effect of an anti-tumor drug and an hypocalcemiant drug)

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

This recently created team studies very fundamental processes that might be instrumental in mechanistic toxicology. At the technological level, the integration in IRSET is fully legitimate and will foster its collaboration with local teams. However, this group needs to expand the projects on environmental contaminants to increase its interface with other teams. Similarly, this team should be encouraged to develop clinical projects.

This team appears to be attractive to young scientists, as exemplified by the recent recruitment of a CR2; and post-docs on grants. Good links have been established with major players in its scientific field, both in France and in the USA. The team leader has proven skills in fund raising (INCa, ANR-JC, ligue contre le cancer, etc.).

- Appreciation on the scientific strategy and the project

The team is composed of 1 CR1 INSERM (team leader), 1 CR2 CNRS (recently recruited), 1 MCF, 1 Post-doc, 2 PhD.

The projects are in the line with its past activities. Two projects will be developed: one concerning the role of PI3K and calcium in the initial events of CD95-mediated apoptopic signal (DISC) to some toxics such as dioxin, and another concerning the role of metalloproteases in cleavage of the CD95L(MISC) in some chronic inflammatory disorders or benzo(a)pyrene. The description of the project is convincing, they have already identified an activation of a src kinase (c-yes). The project is very fundamental but necessary to understand the mechanisms of this dichotomy. They should develop animal models in order to mimic the real exposition of xenobiotics to humans.

- Conclusion :

– Summary

Team 4 develops an original approach on mechanisms of apoptotic signaling. It displays a very good track record of publications. The team is composed of young and dynamic members but no technician. The team leader has the willingness to study environmental pollutants, and a very good scientific culture.

– Strengths and opportunities

Team composed of highly dynamic members, with good will to interact with IRSET teams.

Very interesting and important results in the field of apoptosis, based on specific results showing the link betweeen CD95 and Calcium signaling pathways.

Good scientific network, both nationally and internationally.

High capacity to raise fundings and develop collaborations

– Weaknesses and threats

Most of the weakness is related to the recent creation of this team ; it lacks technician.

The integration to IRSET topic is still to be strengthened.

Lack of interaction with clinicians.

– Recommendations

The team needs to recruit one technician, expand their projects on environmental pollutants and eventually develop clinical projects.

Team 5: Signaling and Modeling

Team leaders: Ms. Nathalie THERET and M. Georges BAFFET

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	4
N7: Number of staff members with a HDR or a similar grade	4

- Appreciation on the results

This team arises from the former research unit Seraic. Its work is dedicated to the study of hepatocellular carcinoma, and more specifically of tumor progression. Three subprojects have been conducted in the past period : i) involvement of ADAM12/ ADAM9, two proteases on tumor aggressiveness via the TGF-b pathway ; ii) MEK signaling and liver cell proliferation; iii) DNA repair and regulation of ERCC1. The composition of the team will remained unchanged in 2010 for the new project, excepted that two distinct leaders will now be in charge to manage the team.

The activity of publication is satisfactory, with more than 40 papers in well-ranking journals such as Hepatology, Cancer research, Oncogene, or J. Hepatology. Impact factors are varying from 3 to 11.3, with an average citation index of 4.95, and a total number of citations of 188. Members of team 5 produced numerous co-publications with other teams from IRSET.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team is highly attractive for the students (10 Master 2, 11 PhD students); however, the lack of long-term institutional funding is a barrier to recruit post-docs. The integration inside IRSET is obvious: the team develops fundamental and applied projects (cell signaling, xenobiotics, modeling), which are in direct line with the general objectives of IRSET.

The team received numerous small or medium grants in the past 5 years suggesting a high visibility on the local, regional and national levels. Team 5 also appears to be well renowned on the international arena, and several students have indeed benefited from those collaborations via visit to the corresponding laboratories. An "ANR Blanc" grant has been obtained in 2010, in cooperation with INRIA/IRISA. This is a very positive signal for enhancing the evolution towards system biology. One should not forget the active and productive international collaborations with American teams on heterocyclic amines DNA adducts.

This team is organized around two scientific leaders who share administrative, animation and training duties in a well-balanced manner. Both display a very good activity of publications and dedicate a significant part of their working time to scientific animation. One co-leader (NT) has had several responsibilities in the former SeRaic, at the scientific instance of Inserm, and in the joint doctoral school ED Vie-Agro-Santé between University Rennes 1 and AgroCampus-Ouest. The second co-leader (GB) is the current Director of the Institut Federatif de Recherche. There is a high demand for developing the training in system biology in Rennes and inside IRSET.

- Appreciation on the scientific strategy and the project

The project is clearly a continuation of past activities, feasibility being proven for the most ambitious among them. Some subprojects are very original and promising, such as the program at the interface between biology and computational science together with INRIA/IRISA. Team 5 aims at developing a computational method for TGFbeta signaling pathway, an essential step towards predictive toxicology. This implementation of integrative biology at IRSET is very welcome and might represent one of its future assets. The project dealing with the impact of environmental contaminants on “hepatocyte tensegrity” is also very original and a valuable application model for atomic force microscopy, among the multiple approaches proposed. Although less innovative technically but scientifically sound, other parts of the whole project (ERK1/2, DNA adducts and reparation) contribute to an overall project of very high quality.

- Conclusion :

– Summary

Team 5 has in hands a very complete set of skills and research topics. The hyphenation of molecular and cellular biology, with computation and biophysics represents an exceptional potential for drawing a novel vision on liver diseases. The project dealing with HAA and genotoxicity mechanisms does not directly from that approach, but benefits from solid references and undoubtedly has its place in the team roadmap.

– Strengths and opportunities

- Stability of the team

- Strong collaborative network, in particular with computational specialists at INRIA and biophysicists at University of Rennes 1

- Collaborations with clinicians

- Emergence of system biology in toxicology

– Weaknesses and threats

A risky project but definitely worth to try considering the competence and motivation of the team. The risk is balanced by a secure research project on genotoxicity.

– Recommendations

IRSET should undoubtedly help team 5 in building its original project. System biology for toxicological approaches is also promoted by the project of team 7 and by the presence of two "omics" platforms. The incorporation of more physical sciences in the project (AFM and related force spectroscopies, mechanisms and modeling of tensegrity) would be a bonus to the project, and certainly increase its visibility.

Team 6 : Transcriptional regulation and dysregulation

Team leaders: M. Denis MICHEL and M. Farzad PAKDEL

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4.5	
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	
N7: Number of staff members with a HDR or a similar grade	5	

- Appreciation on the results

The team 6 results from the recent fusion of two teams which found large complementarities in their approaches. The first one was studying the role of estrogen receptor and cofactors in the development of breast cancer, while the other one was characterizing the cell response to proteoteotoxic stress.

The mammary tumour cell line MCF7 was used to study the role of the transcription factor COUP-TF1 on mammary metastasis and the role of the MLK1 coactivator on the epithelial mesenchymal transition (process corresponding to a mammary cell dediffrentiation and to the generation of tumors). The action of MLK1 induces a broad acetylation of histones.

Estrogens or COUP-TF1 induce the MCF7-dependent secretion of the CXCL12 chemokine. CXCL12 can then be considered as a novel marker in the identification of estrogenic molecules.

The other interesting result of team 6 is the correlation between cellular stresses and the activation of HSF factors. This was shown to modulate estrogen effect on mammary tumour development.

Noteworthy, team 6 also developed a biological model to study the effects of electromagnetic fields. Induction of local heating in cells correlate well with the activation of genes involved in inflammation

During the period 2006-2010, 42 articles were published by team 6, but impact factors were often below 5. Furthermore, several publications were in common with team 10 and many of them actually correspond to previous projects of researchers before they have joined team 6. There has not yet been any joint paper between the researchers coming from the two previous teams. Some publications also resulted from occasional collaborations.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Members of team 6 were invited to four meetings, including 2 international meetings. They delivered 12 oral communications and presented 29 posters. They also contributed to one book chapter.

The team currently hosts 4 PhD students and 3 post-docs, all of them being French. Team 6 is the recipient of a number of national grants (2 ANR, 2 Ligue contre le cancer, 1 INERIS and others), but no european or international grants yet.

The team has developed local collaborations (including 4 with IRSET teams), and displays six national collaborations.

Team 6 collaborates with a local company for the study of a new anti-estrogen from soybean, and is supported by CRITT Santé Bretagne. It also works with Ineris on the effects of electromagnetic fields on cultured cells. The co-leader of team 6 is in charge of developing the TERRA platform at IRSET, which aims at providing customers with a large set of toxicological assays.

- Appreciation on the scientific strategy and the project

Some projects of team 6 are clearly defined and the tools are available to perform relevant experiments (study of estrogen modulators and xeno-estrogens on mammary tumor development at the transcription level, effect of cellular stresses and electromagnetic field on cells), but other projects are less convincing and even questionable (study of the mechanism responsible for a long term memory of estrogen stimulation leading to more intense secondary stimultations, involvement of the Warburg effect in the process of mammary cell tumorisation). Nevertheless, team 6 has to become an important component of IRSET when considering its specific competences and high level of existing interactions with local teams.

- Conclusion :
  - Summary

The goal of team 6 is to understand the interplay between estrogen response and generic downstream processes, such as cell response to proteotoxic stresses.

The scientific approaches are interesting and complementary to the skills of many teams at IRSET. The director of the Institute expressed to the Committee his willingness that the team joins this venture.

However, if the projects of team 6 are relevant, they might suffer from being too numerous considering the size of the team.

  - Strengths and opportunities

Team 6 is the only team of IRSET having the capacity to evaluate xenobiotic effects at the transcriptional level. Essentially appropriate tools available in the team for studies at the transcription level.

Good involvement in risk assessment projects and good related funding.

Good collaboration with several IRSET teams.

  - Weaknesses and threats

No full time researchers. Most of them are involved in teaching duties. Fortunately, 5 of them hold HDR, enabling the recruitment of several PhD students.

The projects are still too diverse. The fusion between the two previous teams at the level of the projects is not yet achieved. The committee indeed had the feeling that team members are still working independently from each others.

The MCF7 cell model has been validated a long time ago to study some aspects of breast cancer. This model does not allow the study of the various mechanisms of estrogen action in breast cancer development. The team lacks in vivo model or clinical collaboration. Additionnal models, mammary primary cells and transgenic mice would bring additionnal information.

Significant risk for opportunistic projects, especially after the setup of the TERRA platform.

  - Recommendations

The strategy of the team should be more clearly defined and a priority list of projects should be envisioned. The proportion of case by case collaborations should be reduced in favour of the prioritized projects ot the team.

The analysis of transcriptional effects would gain in collaborating more with the genomic center of team 7.

Increase in vivo approach

Many researchers of team 6 have the experience for defending an HDR grade. This should be made to favor the recruitment of PhD students.

Team 7 : Transcriptional networks in gametogenesis and cancer

Team leader : M. Michael PRIMIG

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1.5
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2
N7: Number of staff members with a HDR or a similar grade	2

- Appreciation on the results

The team moved from Basel (Switzerland) to Rennes in 2007 and was hosted in U625/GEHRM in the period 2007-2010. It will start as an independent team in the frame of IRSET.

During its past activities, the team carried out a complete transcriptome analysis of yeast meiosis and of spore development. It also nicely demonstrated the key role of ribonuclease Rrp6, which is degraded prior to meiotic M-phase, for the process.

The team also participated in the analysis of mammalian regulation mechanisms. It compared the testicular expression program of control individuals to that of infertile patients or individuals with variable risks of infertility. It allowed to understand the transcriptional regulatory processes that control progression through meiosis and gametogenesis and to identify mutations in genes that may be at the origin of human male infertility.

These projects appear highly innovative and already gave rise to excellent publications, including two papers in PNAS. They clearly demonstrated the relevance of comparing distinct biological systems and the conservation of several transcriptional mechanisms controling meiosis between yeast and mammals.

The scientific production is excellent for a small team. The team leader published 9 articles during the last four years as last/corresponding author. Some of them were published in high-ranking journals : 1 PNAS in press in 2010 ; 1 PNAS and 1 NAR in 2007; 1 Mol.Biol.Cell in 2008. In addition, the team published innovative bioinformatics methods of which corresponding papers are highly accessed and cited.

The team has designed two important bioinformatic platforms : MIMAS, an innovative tool for network-based high density oligonucleotide microarray data management and annotation, and Ashbya Genome Database, a cross-species genome and transcriptome browser for yeast biologists.

The team has already established strong interactions with other teams at IRSET. It also plays a pivotal role in structuring genomic approaches within the institute, in particular through its involvement in the Center for Genomics and Bioinformatics (CGB).

No PhD thesis was yet defended since the team arrived in Rennes, but two PhD students were recently recruited.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Numerous selected oral communications from several members of the team in national and international meetings and workshops. Importantly, the team leader participated as guest speaker in 4 meetings, including an EMBO conference.

The team arrived in Rennes by 2007 but grows rather slowly, having only one french post-doc and no foreign post-doc at the moment. The projects will request new recruitment of researchers.

The team has benefited from an INSERM AVENIR grant for the period 2008-2012. It displays strong ability to raise well-funded grants at the national level (Inserm Avenir, Région Bretagne, ARC) but no international grant has yet been obtained.

The team leader has very strong connections with the best experts in the field of genomics world-wide (Stanford University, UCSD and UMDNJ in the USA, EMBL in Germany).

As a starting group, it may be too early to evaluate socioeconomic output, and no transfer to companies is mentioned in the report.

- Appreciation on the scientific strategy and the project

The team will continue to explore the role of mRNAs and non coding RNAs (ncRNAs) in the transition from mitotic growth to meiotic development (production of haploid gametes) in simple model organisms (diploid yeast) and mammalian germline (human, rat). A second axis, which is less advanced and described, will consist in identifying Testicular genes de-repressed in somatic cancers, i.e. Cancer/Testis (C/T) genes and to study the underlying mechanisms of their deregulation.

These team projects are highly conditioned by the development of the CGB platform.

Proposed long-term projects will consist in establishing mouse models, but they are not mature enough to be evaluated.

The team proved efficient in raising funds for their research projects. The development of the CGB platform has been announced as a priority for the Director of IRSET.

The presentation of the team leader positively impressed the visiting committee and clarified several aspects of the team projects, as compared to the written document. As mentioned above, the projects are very innovative and should highlight the pertinence of comparing various biological systems. The combination of transcriptomic and genomic approaches, combined with strong bioinformatics is clear asset of this team and will be instrumental in this perspective. A complementary proteomic approach is also considered, in collaboration with the PPB platform.

- Conclusion :

  - Summary

A leading team in his field, with an excellent output and an invaluable expertise in integrative biology. The team owns essential methodologies for the future development of IRSET. In this favourable context, it might certainly contribute to innovative concepts in predictive toxicology.

  - Strengths and opportunities

The team has benefited from an INSERM AVENIR starting grant and already displays and excellent production. Many opportunities in "multi-omic" approaches, with the existence of appropriate local and international networks.

  - Weaknesses and threats

The team is still in development and has not yet reached the required manpower for all the projects. The feasibility of the C/T genes project still remains to be established, and the proof-of-concept should be put in the priorities.

Existence of a potential risk for the young group leader to manage both a growing team and the future CGB platform. Lack of any international grants despite a strong network in Europe and in the USA.

– Recommendations

The team is a key component of the future IRSET project. Careful support should be provided by the future Directory board to ensure availability of human ressources and technical support to this team. System biology is shared with team 5, some bioinformatic tools might be jointly developed. It would be wise to define priority among the different projects, especially to avoid conflicts of interest during the development of the CGB platform.

Team 8 : Virus, Environment and Reproduction

Team leader : Ms. Nathalie DEJUCQ-RAINSFORD

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3
N6: Number of Ph.D. students (Form 2.7 of the application file)	5
N7: Number of staff members with a HDR or a similar grade	3

- Appreciation on the results

The team 8 carries out two major projects: i) HIV infection of the male genital tract (MGT), and ii) the in vitro evaluation of endocrine disruptors (ED). After being headed by the current director of IRSET, the team will be under the direction of a new leader from 2011. She was already responsible for the HIV project in U 625.

Three results are more particularly relevant and internationally recognized : i) persistance of HIV in the MGT, making testis a new reservoir for the virus (a monkey model recently confirmed this hypothesis).; ii) some soluble factors in the semen might modulate HIV replication and transmissibility; iii) characterization of the effects of phtalates, of bisphenol A and of NSAIDS on testicular functions In fact, the study of HIV infection in testis is being achieved in a very small number of labs in the world.

The team 8 collaborates with several teams of IRSET, in addition with clinicians in Rennes university hospital. It has also established fruitful collaborations nationwide, particularly with two teams at CEA working either on gonad development or on infected animal models, and with teams in Guadeloupe, Germany and USA for the study of pesticide on reproductive functions;

Several publications among the 22 published in the period 2006-2010 by team 8 gained a high visibility ; an article in Am. J Pathol. was rated as “exceptional” in Faculty of 1000 Medicine, while another article published in PloS One was rated "Top pick of the editor".

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

This team has developed a strong network of collaborations in France, and in the world. Team 8 has a original position in its field since the technique for organotypic culture of human testis is recognized as an excellent but seldom tool.

The present director of IRSET (still member of this team) and head of the former Inserm unit U625 attracted the leader of team 7 from Basel and hosted him for the last 3 years before he launched his own team.

The research domain of this team largely corresponds to a societal concern, including Guadeloupe with the recent issue of chlordecone. That has formed a favourable ground for the development of the team. The work of team 8 is thus largely supported by various grants (ANR, ANRS, Sidaction, Région Bretagne, ECPI, CRITT, ANSES, ANTIOPES and others). These grants, including support from Univiersity Rennes has allowed to hire 5 PhD students, 3 postdoc fellows, and 2 research assistants with temporary contracts.

- Appreciation on the scientific strategy and the project

The global objective of team 8 deals with the effects of viruses and/or chemicals on MGT. In that sense, the project is a continuation of the ongoing projects by taking advantage of the sound set of techniques held by the group. Among them, one should notice the quasi-unique organotypic culture of the human MGT, its use for direct in vitro infection by HIV, the access to the in vivo model of macaque/SIV. The cooperation with team 7 is important since it will allow a powerful, in vitro evaluation of endocrine disruptor effects on MGT. This joint initiative to achieve the first extensive charactization of the transcriptomes of MGT in various models (mouse, rat and human) will be an essential step towards further characterization of a large variety of chemicals or biological agents. This approach will nicely complement the previous proteomic map established with the current leader of the PPB platform.

Another part of the project of team 8 is new for it since it deals with effects of various chemicals on organ morphogenesis and fetal development in mammals. This will involve new partnerships, in particular with clinicians and epidemiologists. It made no doubt to the Committee that the team will be able to meet the challenges of this novel orientation.

- Conclusion :

  - Summary

Team 8 has developed an original field of expertise. Its models and skills have proven very powerful for the study of HIV reservoir and sexual transmissibility, and for the characterization of mechanisms in endocrine disruption. The data of this team are recognized internationally.

  - Strengths and opportunities

The new team leader was previously involve in the research of U625 and is thus aware of current projects. Her presentation during the visit of this committee confirmed she has the capacity to manage team 8.

The team actively participates to the valorization of its research. It might be among the main benefitors from the TERRA platform.

The collaboration with team 7 (also director of the CGB platform) and with PPB, offers the possibility to perform transcriptome and proteome-wide studies of spermatogenesis. It both has exciting perspective in terms of diagnostic for human infertility and of monitoring of the effects of environemental contaminants.

The technique to evaluate the effects of ED in vitro is robust and original. This constitutes a strong asset to participate to the EU REACH project.

  - Weaknesses and threats

The number of researchers with a HDR in team 8 is insufficient.

The number of researchers with permanent position is low compared to the number of projects.

Risk of spreading the resources over too many topics (HIV, chemicals, EDs,. MGT function, morphogenesis, etc.).

– Recommendations

Some publications of team 8 could have been published in journals with higher impact factors. The quality of the results might have justified targeting more ambitious journals and the Committee recommends this for the future, in order to enhance the reputation and attractiveness of the team.

The low size of the team makes it somehow fragile when addressing such a large number of projects. The committee suggests focusing on their most differentiating techniques and on the exciting issue of synergy between chemicals and HIV infectivity.

Team 9: Epidemiological research on environment, reproduction and development

Team leader: Ms. Sylvaine CORDIER

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	6
N7: Number of staff members with a HDR or a similar grade	5

- Appreciation on the results

This team was previously part of the Inserm Unit GERHM / U625 and has been involved for a long time in the epidemiology of environmental diseases. Its researches are more specifically related to the environmental impact of contaminants on development disorders and reproductive alterations as well as on cancers related to some xenœstrogenic compounds. In the IRSET project, the team will maintain its structure and orientations, with the same DR1-Inserm as team leader.

Its results are based on the implementation and follow up of large cohorts both in Brittany and Guadeloupe, with very precise questionnaire and biomarkers information on exposure, outcomes and cofactors, and on large case-control studies. In the considered period, the team produced a very good research, and has obtained important results. This project was conducted with rigor and had participated in answering important scientific and social questions:

The team observed a strong relation between exposure to solvents during pregnancy and incidence of oral cleft or genital malformations. This is a particularly convincing result as a previous analogous result was observed by the

team in the frame of a large scale questionnaire based on a case-control approach. This result was now confirmed by the team in the frame of a prospective cohort approach using questionnaire and biomarkers.

Relevant information was obtained to characterize the pathways of exposure to pesticides in Guadeloupe. The possible role of pesticides employed in Guadeloupe's banana plantations and its impact on prostate cancer was observed for the first time.

These results gave rise to 43 papers published in very good journals, most of them with impact factors greater than 3. Some of these papers are in the most excellent journals in the field of epidemiological research (Int J Epidemiol, EHP, Environ Res), another noteworthy paper was recently published in a high impact factor journal (J Clin Oncol, IF 17). It's important to notice that some of the information obtained was published in international pooled works, confirming the maturity of the networking.

During the period, two students obtained the PhD degree, and six PhD students are currently implicated with the team.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The researchers were frequently invited in conferences by the French scientific community as well as by sanitary authorities. The team leader was invited in international conferences (USA, Denmark). The members of the team are also frequently solicited by the media to explain the results and importance of environmental epidemiology.

Considerable funds were raised by the team from different agencies: ANR, ANSES, Ministry of Health, Ministry of Environment, INERIS and European Commission.

As mentioned above, the information obtained in cohorts' follow-up and case-control studies are sometimes analysed together within international network (HiWate, ENRIECO).

In France, this project is highly visible and attractive due to the sanitary implication of the results obtained in Bretagne and Guadeloupe. This is confirmed by the recent arrival in the team of new significant scientist resources from EHESP.

- Appreciation on the scientific strategy and the project

The project will preserve a continuity of the cohorts' follow-up in Bretagne and Guadeloupe. The children involved in PELAGIE program are six years old and the project will take an interest on neurodevelopment. Indoor exposure to emerging contaminants will be taken into account. This is a new and promising orientation for this research.

The research on prostate cancer and chlordecone exposure in Antilles will be pursued especially to obtain a better understanding on genetic co-factors.

The arrival of new researchers from EHESP will permit to open new fields related to occupational and environmental epidemiology. Assessment of environmental inequities related to industrial pollution will be investigated using Bayesian approach based on geographic information.

The IRSET project will give many great opportunities to the team to test new biomarkers and to participate in mechanistic research on contaminants impact on human health. In addition, the participation of analytical platforms allows new developments in exposure assessment.

- Conclusion :

  - Summary

Team 9 addressed pertinent problems in environmental epidemiology, using large scale data bases that were implemented by the team and included both questionnaire and objective (biomarkers) information on exposures, outcomes and cofactors. Team 9 obtained important result concerning the association between solvent exposure and congenital malformations as well as between pesticide exposure and prostatic cancers. These results lead to a scientific production of high lever with publication in top lever journals in this field such as International Journal of Epidemiology, Environmental Health Perspectives, Journal of Clinical Oncology.

– Strengths and opportunities

The development of large scale prospective studies with precise and objective information on exposures, outcomes and cofactors,

Its capacity to attract new scientists,

The remarkable ability of his team leader to investigate new domains of environmental epidemiology, using truly new and demanding methodology, taking therefore scientific risks and finally obtaining authentically original results of public health importance.

– Weaknesses and threats

The main apparent weakness of the team is related to the preceding point. Taking the "risk" of developing original databases of high quality and high epidemiologic information potential, requires a lot of time, thinking, search of financial support and rigorous practical work. Meanwhile the publication record of the team, can be qualified as « Very Good » from a quantitative point of view although it is clearly of an « Excellent » level from a qualitative point of view. This relative weakness is most likely to be corrected by the arrival of new scientists in the team as well as by the availability of more and more complete data bases as time goes on.

– Recommendations

As the team has shown its ability to attract new scientists and developed very high quality databases it could try to also attract post-doc fellows.

The leader of this team created her research group and played a central role into the development of environmental epidemiology in France over the last 30 years. At the very end of the next five year mandate, a new team leader will have to be found for the still next mandate. This will have to be done ensuring the continuity of such a high level of leadership, particularly in the context of the emergent IRSET that will most likely play a major role in environmental and occupational health research in the forthcoming years.

Team 10 : Neuroendocrine Effects of Endocrine Disruptors (NEED)

Team leader: M. Olivier KAH

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2.5
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	2
N7: Number of staff members with a HDR or a similar grade	1

- Appreciation on the results

The team is studying the role of peripheral steroids and/or neurosteroids (especially oestrogens) in neurogenesis and regeneration in the fish as a model. During the period 2006-2010, the team reported very interesting observations as to the potential effect of estradiol on the neural progenitor cells. Specifically, it was shown that radial glial cells expressing the cyp19a1b gene encoding Aromatase B, act as progenitor cells in the brain of adult fish. In vitro studies showed that the promoter of this gene is controlled by estradiol in a cell context-dependent manner (ie in glial cells), as a feedback positive loop and identified the estradiol-responsive element in the promoter.

The data obtained are strengthened by the diversity of studied models (zebrafish and mouse). Team 10 has developeda comprehensive evolutionary perspective that highlights fundamental mechanisms, and highly pertinent targets for xenobiotics. The team is also very impressive in its ability to perform various techniques (for anatomy to electrophysiology), as well as the multi-dimension aspects from molecular to population levels.

The team leader published 10 articles and 6 reviews as a corresponding author in good journals (IF < 4.7; Endocrinology, J. Comp. Neurol.). The team also produced a number of publications in collaboration with internal and external laboratories, including abroad. Although the track record is not impressive in terms of impact factors, it should be acknowledged that some recent papers, especially reviews, are highly cited (about 10 citations per year). Moreover, as reflected in the increasing number of peer-reviewed publications during the past 5 years and the increasing number of invited presentations, this team has gained in productivity.

Numerous communications were presented by all the members of the team at scientific meetings. One PhD thesis was defended in October 2008. Promising international partnerships were set up, such as with Taiwan and Argentina.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Different members of the team have presented numerous communications in national and international (UK, Germany, Canada, Hong-Kong) meetings. The team leader was Guest Editor for a special issue on Fish Reproduction in General and Comparative Endocrinology (2010). He is member of various scientific boards (INRA PHASE, University of Rennes I), General Secretary of the French Society of Neuroendocrinology and European representative of the International Federation of Comparative Endocrinology Societies.

One staff scientist received a French award in 2008 (Prix Servier de la Société de Neuroendocrinologie)

Most of the students and post-docs are from France, but 1 PhD student is from Argentina. Noteworthy, the lab frequently welcomes foreign visiting scientists and PhD students from its netwwork for short training periods.

Funding by both national and European competitive grants has been secured.

Several collaborations were initiated in France and abroad in Europe, Asia and America. Concrete results of the research activity and socio-economic partnerships represent the most positive aspect of the team leader activities, with strong implications in scientific and socio-economic partnerships.

The team leader coordinates several national and european granted networks (EU projects: REPROFISH; LIFECYCLE (14 partners): building a biological knowledge-base on fish lifecycles for competitive, sustainable European aquaculture). The team belongs to the EUFishBioMed network and to the ANTIOPES research network through implication in the “Post-Grenelle Environnement” programme NEMO.

The team leader is a founding member of the zebrafish behaviour platform in Gif-sur-Yvette (grant FRM). A zebrafish model providing a sensitive bioassay of xenoestrogens useful in the context of REACH has been developed in the lab.

- Appreciation on the scientific strategy and the project

The project lies in the continuation of ongoing activities, with more emphasis put on the study of effect on endocrine disruptors on the neuro-development. This evolution is ambitious but undoubtedly based on sound preliminary data, and mature skills in this team. From the committee's point of view, the development of neuroscience would be important for IRSET and deserves a specific attention. The contribution of team 10 is original by providing a robust zebrafish transgenic model suitable with large transcriptomic and functional analyses. The work on the AromataseB-positive brain neural progenitors is also very worth to be supported since it might provide with a

very sensitive bioassay for xenoestrogens. It might be useful in the context of REACH, and would thus deserve being implemented in the TERRA platform.

- Conclusion :

  - Summary

The team owns specific knowhow and highly pertinent models that can clearly contribute to the development of IRSET. The zebrafish model is a must in predictive toxicology. Joining the Institute will also reprensent a unique opportunity for this team to have an access to clinically-oriented projects.

  - Strengths and opportunities

Very efficient participation to national and international scientific networks, establishment of long-lasting collaborations with French and foreign partners. Good ability to raise funds and to apply to competitive grant applications. Strong implication in scientific and socio-economic partnerships.

Most interesting data relevant to the wider area of neurosciences. Potential implications with respect to data on cognitive consequences of exposure to endocrine disrupters (collaboration with team 9).

  - Weaknesses and threats

As acknowledged by the team leader himself, the publication output of the team is modest in terms of journal impact factor.

Only the team leader holds an HDR, precluding the opportunity to supervise several PhD students. No staff scientist could be identified to ensure continuity with the team leader.

  - Recommendations

To improve its international visibility, the team should consider submitting their work to higher impact factor journals, even though this may result in a lower number of publications.

The effort of IRSET in neuroscience is still relatively small in comparison with the other topics. The Committee wished to support this important facet of environmental toxicolgy and recommends to rely on team 10 for this purpose. It might develop promising alternative models in neurotoxicology. We fortunately felt that this vision is shared by the Director of IRSET.

The manpower capacity requires some improvement, in particular through the rapid involvement of 1 or 2 senior researchers holding their HDR, and able to ensure the continuity with present leadership.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
INSTITUT DE RECHERCHE EN SANTÉ, ENVIRONNEMENT, TRAVAIL	**A**	**A**	**A+**	**A**	**A**
EPIDEMIOLOGICAL RESEARCH ON ENVIRONMENT, REPRODUCTION AND DEVELOPMENT [JEGOU-CORDIER]	A	A	Non noté	A+	A
VIRUS, ENVIRONMENT & REPRODUCTION [JEGOU-DEJUCQ-RAINSFORD]	A	A	Non noté	A	A
STRESS, MEMBRANE AND SIGNALING [JEGOU-DIMANCHE-BOITREL]	A	A	Non noté	A	A
ENVIRONMENTAL CHEMICALS, IMMUNITY AND INFLAMMATION [JEGOU-FARDEL]	A	A	Non noté	A	A
NEUROENDOCRINE EFFECTS OF ENDOCRINE DISRUPTORS [JEGOU-KAH]	B	B	Non noté	A	B
DEATH RECEPTORS AND TUMOR ESCAPE [JEGOU-LEGEMBRE]	A	A	Non noté	A	A
TRANSCRIPTIONAL REGULATION AND DYSREGULATION [JEGOU-MICHEL-PAKDEL]	B	B	Non noté	B	B
TRANSCRIPTIONAL NETWORKS IN GAMETOGENESIS AND CANCER [JEGOU-PRIMIG]	A+	A	Non noté	A	A
EXPOSURE TO HEPATOTROPIC INFECTIOUS AGENTS [JEGOU-SAMSON]	A	B	Non noté	A	A
SIGNALING AND MODELING [JEGOU-THERET-BAFFET]	A	A	Non noté	A+	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

• SVE1 Biologie, santé
- **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
- **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
- **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
- **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
- **SVE1_LS5 Neurosciences**
- **SVE1_LS6 Immunologie, Infectiologie**
- **SVE1_LS7 Recherche clinique, Santé publique**

• SVE2 Ecologie, environnement
- **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
- **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
- **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

PRÉSIDENCE

Guy Cathelineau
Président

Rennes, le 8 avril 2011

Monsieur Pierre GLORIEUX
Directeur de la section des unités de recherche
Agence d'Evaluation de la recherche et de
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Vos réf. : S2UR120001341
IRSET– 0350936C

Monsieur le Directeur,

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité mixte de recherche **«Institut de Recherche en Santé, Environnement et Travail (IRSET)** ».

L'université de Rennes 1 sera particulièrement attentive à ce que les recommandations formulées par le comité de visite soient prises en compte.

A la lecture de ce rapport, vous trouverez ci-joint, les réponses du directeur d'unité auxquelles nous souscrivons en totalité, en y ajoutant quelques précisions sur les trois éléments suivants de stratégie d'établissement :

La création de l'IRSET constitue pour l'université de Rennes 1 un challenge et un chantier d'envergure qui constituera une des priorités principales de la stratégie de recherche à conduire et à soutenir avec ambition lors du prochain contrat quinquennal.

Cette structure de recherche est emblématique quant à la volonté de réaliser une recherche interdisciplinaire intégrant des compétences disciplinaires au meilleur niveau d'excellence et de visibilité internationale.

L'IRSET s'intègre parfaitement dans l'axe stratégique de développement des alliances de site entre Université - Ecoles et grands organismes que l'Université de Rennes 1 souhaite renforcer lors du prochain quinquennal.

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

Le Président de l'Université de Rennes 1

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UNIVERSITÉ DE RENNES 1 EHESP Université des Antilles et de la Guyane

1th of April, 2011

RESPONSE TO THE AERES REPORT ON THE IRSET RESEARCH UNIT

On behalf of all the staff members of IRSET, we wish to thank the members of the visiting committee for their evaluation of our project.

The in-depth and thorough report produced by AERES was immediately communicated on Marsh 18t, to the *Team leaders* of IRSET to be analysed at the level of each *Team*. On March 28th a meeting of the *IRSET council* was held to develop and complete the collective and individual (*Team*) responses to the report. This meeting was followed on March 30th by a *General Assembly* of IRSET, during which all staff members received complete information about the AERES report and the responses by IRSET management and the different *Teams*. The comments and responses below represent a consensus of IRSET members and management.

General comments:

We appreciate that the AERES committee: **1.** Shares our analysis of the importance of structuring the field of Health and Environment and, in this context, the "added value" and attractivity that IRSET represents; **2.** Has perceived the strongly collegial and determined nature of this project; **3.** Recognises: (*i*) the very strong support of the institutions which supervise IRSET (UR1, EHESP, UAG); (*ii*) the close interaction and complementarities between the 10 *Teams*, and between the *Teams* and the technological *Platforms* whose high quality is acknowledged; (*iii*) the very good productivity of the *Teams*; (*iv*) the strong activities and prospects IRSET presents both in terms of education and consultancies; and *(v)* the effectiveness of IRSET's internal organization, at all levels.

The creation of a multidisciplinary research institute is indeed a challenge, but it is a challenge we have accepted collectively and that by itself justifies the creation of IRSET, which brings together in an unprecedented manner scientists from a large array of disciplines. Special attention will be paid by the management team to promoting the cohesion of the group. We will follow the recommendation to develop internal scientific leadership and scientific exchanges, notably through the thematic working groups we are setting up, as stated in our document.

We also acknowledge that special attention must be paid to building IRSET's international dimensions. Although some *Teams* already have strong international activities, this aspect can and should be significantly improved at the level of IRSET as a whole. It is nonetheless noteworthy that an IRSET delegation met in London with a delegation from the Environmental Health MRC (Imperial College London) in April 2009, with the aim of launching collaborations. Interactions already exist with the College of Life and Environmental Sciences (University of Exeter, UK) and with EAWAG in Switzerland, a leading aquatic research institute. A bilateral agreement will be signed in April with the

Centre for Advanced Research in Environmental Genomics of the University of Ottawa, and a collaborative program is ongoing with the Leipzig Helmholtz Center for the Environment (GmbH – UFZ).

In addition, since the reception of the AERES report, several decisions have been taken to accelerate the construction of IRSET's international policy: **1.** The designation of a chargé de mission, Dr Olivier Kah, who has long-standing experience in international collaborations on all continents, and who will be responsible for assisting the management team in structuring IRSET's activities and public relations in this domain; **2.** Starting during the second half of 2011, IRSET delegations will visit some of the main European research centres in the domain of health and environment to present the institute's activities, to study their internal organization, and, when possible, to suggest bilateral agreements; **3.** The IRSET web site, somewhat delayed due to frantic activity going on in the weeks preceding the AERES visit (including the "Grand emprunt"...), has been on line since February 2011 (http://www.irset.org) and will pay special attention to the international aspects.

We agree with the AERES recommendation that the number of HDR should be increased to improve the recruitment of PhD students in all *Teams*. Therefore *Team leaders* will be strongly encouraged to focus on this, even though one limitation is the particularly strict standards that the doctoral school/VAS (Vie-Agro-Santé) of the University of Rennes 1 applies for this diploma (HDR).

We are confident for several reasons that "internal competition for funding" is not a danger. Among these reasons are that: (*i*) the *IRSET council* (to which all *Team leaders* belong) which meets every two months and can schedule extraordinary meetings to coordinate activities and monitor objectives; and (*ii*) instead of competing for the same funds we have already developed an inhouse culture of co-applying to calls for proposals, as exemplified by several recent applications to ANR, ANSES and Antiopes.

We also agree that some PhD students and post-docs are rather reluctant to envisage working abroad. This reluctance does not, we feel, stem directly from weaknesses in IRSET's international policy, since the PhDs and post-docs interviewed by the committee had for the most part been recruited before IRSET's creation. We would like to emphasize that a very high proportion of our former Ph.D. students are currently post-doctoral fellows in foreign countries (see the *Team's* answers below), and that several of our present students have already done stays in the foreign laboratories of our partners, thanks to the funding from Rennes Metropole and UEB PRES.

Another point of agreement with the visiting committee is that SAB is a rich resource to help us to develop IRSET's strategic vision and policies. We had planned before receiving the AERES report to share with SAB the evaluations by AERES and Inserm, and we expect to do so once Inserm makes the final decision about IRSET, that is, by the end of 2011 or at the latest at the beginning of 2012. For financial reason as well as to save time to everybody (and first that of the SAB members), the next meeting will be held as an international videoconference.

Major progress has also been made regarding the future IRSET building. We now have a detailed design prepared by professional building planners, which is the basis for final discussions with the local funding institutions, scheduled for April 11, 2011. An official announcement of the construction of a 16 M€ building is expected to be made on June 21, 2011, by officials of UR1, EHESP, Region Bretagne and Rennes Metropole.

We appreciate the different comments about the high quality of our *Platforms* and about their articulation with the *Teams*. **1.** The access fees for LERES are as follows: (*i*) for analysis already available in the catalogue, to be conducted completely by the LERES *Team*, a discount is available depending on the number to be determined; (*ii*) if the researcher participates in the analysis or development, after training if needed, agreement for joint commercialization is possible, depending on the LERES involvement; (*iii*) for special requests or other cases, estimates or agreements as desired; **2.** There are several modes of access to the Proteomics Platform Biogenouest (PPB) but as members of the Biogenouest network, all IRSET *Teams* benefit from discount prices on basic services and collaborative projects. Prices are advertised on the platform website and accessible to registered users; **3.** To respond to the comment on the TERRA *Platform* we want to stress that: (*i*) we are on the process of creating this new *Platform*; (*ii*) during this process, we will be guided for all aspects of TERRA's functioning, including its business model, by assistance from Biogenouest and our previous experience with LERES and PBB, both IRSET *Platforms* that have proved very successful. Please note that TERRA may be developed in association with other partners at a national level; **4.** Finally, we also wish to emphasize that some IRSET members are presently heavely involved in a project aiming at setting up a new company specialized in genomics (see *Team* 7 below). If successful, IRSET members will have privileged access to a fourth *Platform*. Furthermore, 3 biotech companies (BioProtein Technology, Innova proteomics, and natureGenomics) will have been (co) created. In addition to the 5 patents mentioned in the AERES report, this history demonstrates the strong commitment of IRSET's members to the economic and commercial development of their work.

Comments concerning the different *Teams*:

***Team 1*: "Chemical Contaminants, Immunity and Inflammation"**

First, we thank the visiting committee for its work and the constructive comments and positive appreciation to our *Team*.

We would like to provide the following additional informations, especially with respect to the recommendations given by the visiting committee: **1.** Our funds also include the Ligue Nationale contre le Cancer since our *team* was "*Equipe Labellisée La Ligue contre le Cancer*" (2007-2009); **2.** We have planned to recruit a permanent researcher from national bodies Inserm or CNRS in the next years, either through the presentation of a young researcher to entrance examination to these national bodies or through transfer of a senior researcher belonging to these bodies to our group. We think that the context of IRSET will help us in a major way to be attractive for such researchers. In addition, two former PhD students of our *Team* are presently in a post-doctoral situation in North America laboratories and may constitute valuable candidates for becoming permanent researcher in our *Team*. Moreover, we are currently recruiting a post-doctoral fellow which may also be candidate for a permanent position in our *Team*; **3.** We will reinforce our present international collaborations, especially in the lung domain (with Dr J Holmes and Dr M. Läg, University of Oslo) and in the drug transporter domain (with B. Stieger, University of Zurich). Moreover, international collaborations will be extended in a major way to immunotoxicology and, in this context, we have already promising contacts with American and German teams working in this field; **4.** Collaboration with the IRSET *Platforms* is an important goal for us. We have already planned to work with LERES (analytical chemistry) for measuring contaminants for our occupational medicine project (COBP in farmers) and with TERRA (toxicological models and methods) for our valorisation studies. Studies with PPB (Proteomique Platforme Biogenouest) and with the *Team 7* (nativeGenomics *Platform*) will be also developped in order to support our research projects.

4 PhD out of 6 hold post-doctoral positions abroad

***Team 2*: "Hepatotropic infectious agents and environmental cofactors"**

We thank the members of the visiting committee for the evaluation, their comments and their constructive criticisms.

Regarding comments and/or recommendations, we would like to provide additional information and/or comments: **1.** In terms of international funding and collaboration, we decided to involve ourselves in a proactive policy, and collaborations are already taking place with Canada, Germany, US. Our collaboration with a Canadian group on murine hepatitis initiated two years ago will lead soon to a joint publication and we commit ourselves into a more formal programme of exchange between our two universities to get fund for PhD thesis co-supervised with the Canadian team and a post-doc fellowship has already been applied last October (reply April). Other funding and collaboration projects with foreign countries in the field of hepatitis virus and Leishmania are also considered. In particular, a project of trilateral *consortium* has recently emerged between several African countries, Germany and France, with the aim to study the interplay between anemia, inflammation and parasitic infections; **2.** Besides, we want to develop a valorization policy that could begin with the Kepone/hepatitis project which should lead to a valorization of the process of measurement of kepone in the liver by mass spectrometry MALDI on the *Platform* Proteome Biogenouest (PPB) and with the compagny "Innova proteomics". This project will be funded by "CRITT Santé Bretagne" (a not-for-profit organisation from Brittany) serving the health-care industry.

Moreover, with the development of the TERRA *Platform*, we will transfer the cell-based HCV and HBV infection assays, that we have already developed in our own *Team*, to a greater scale.

3 PhD out of 5 hold post-doctoral positions abroad

***Team 3*: "Stress, Membrane and Signaling"**

First of all, we would like to thank the committee for their work and constructive criticisms, and their positive appreciations on our original concept concerning the potential role of membrane remodelling in cell response to toxicants.

Here, we respond to the weaknesses identified by the committee: **1**. The first point relates to the lack of post-docs. We want to inform the committee that our *Team* has already hosted two French post-docs for short periods (from 6 months to 1 year), and presently hosts one for 1 year, renewable and funded by "*Vaincre La Mucoviscidose*". We will intensify our efforts to recruit young foreigners to strengthen our *Team*. Several strategies are available to us: (*i*) rely on our existing partnerships abroad (Norway, Germany, Belgium, Great-Britain) that have already led or will soon lead to exchanges of staff (1-3 months); these contacts will be helpful in spreading our offers for post-doc positions; (*ii*) disseminate these offers through the website of IRSET (http://www.irset.org), Association Bernard Gregory, Nature ...; (*iii*) advertise these offers when participating in international conferences; **2**. The second point relates to our internal collaborations which involve only a few *Teams* of IRSET. We fully agree that the present efforts should be amplified to develop our projects by further relying on the broad know-how of IRSET *Teams/Platforms* in order to apply for common grants and help better structuring the overall research strategy of IRSET; **3**. The third point is the "lack of a dedicated technical staff on the technology platform" "Membrane and Stress". Indeed, for the proper development of this *Platform*, which is already used by several IRSET *Teams* (but not only), recruitment of a dedicated technical staff would be essential. With regard to this, a position of engineer has been applied for at the University of Rennes 1. This recruitment could also be done *via* the transfer request to Brittany of INSERM staff next year. Moreover, as suggested in the recommendations, this recruitment could also be done through the development of the TERRA *Platform* that includes the expertise of our technology *Platform*; **4**. The fourth point concerns the recommendation on the need to "identify potential partners for collaboration on the biophysical characterization of the membranes in terms of structure and function". However, we wish to remind the committee that collaborations regarding such aspects are already ongoing (Bioquanta; University of Nottingham). Nevertheless, contacts could be made with our specialist colleagues of the plasma membrane, Didier Marquet and Hai-Tao He who lead the *team* "Membrane Dynamics and lymphocyte Signaling" (Centre d'Immunologie, Marseille-Luminy).

3 PhD out of 5 hold post-doctoral positions abroad

***Team 4*: "Death Receptors and Tumor Escape"**

We would like to highlight that our *Team* has been created in January, 2010 around a young researcher who came from the University of Bordeaux in the perspective of joining IRSET.

Notably, in 2011, a young talented researcher (CR2, CNRS) has just been recruited in this *Team* (Dr Aubin Penna).

Regarding the concerns raised by the committee we wish to provide the following informations and / or comments: **1**. The AERES committee has raised some concerns about the fact that our *Team* did not possess ongoing collaborations with clinicians. We would like to draw the attention of the committee on the fact that long lasting collaborations already exist

between the *Team leader* and clinicians, namely Pr J-F Moreau and P Blanco (CNRS UMR 5164, CHU Bordeaux, Bordeaux) and Pr Paul Hofman (CHU Nice). These close collaborations address the role of FasL in patients suffering from autoimmune disorders such as systemic lupus erythematosus and ulcerative colitis, respectively (manuscript in revision in Plos Biol); **2.** The AERES committee emphasized that our *Team* should strengthen its integration to the IRSET topics (*i.e.*, to study the impact of environmental stresses) and develop animal models in order to mimic the exposition of xenobiotics to humans. Our national and international expertise is well-recognized in the field of the death receptor (Fas) signaling pathway and its modulation by the biophysical properties of plasma membrane (lipid rafts) that can be affected by environmental pollutants. According to the notions that zebrafish exhibits the complete Fas signaling pathway and represents a powerful animal model to study the impact of xenobiotic, we plan to recruit a post-doc on the ANR blanche that we recently obtained (SphingoDr) with know-how in inflammation/immunology using zebrafish as a model-system. Using this model, our goal is to decipher the role of Fas on T-cell extravasation and the impact of pollutants (*e.g.*, BaP) on this process. In parallel, we will take advantage of the zebrafish expertise of *Team 10* of IRSET (*Team leader*: O Kah) and initiate a collaboration to develop this animal model in the context of Fas signaling; **3.** Last but not the least, to get a technical support remains one of our priority to stabilize this young *Team*. The *Team* will benefit from the full support of the IRSET Director which will priorized this demand.

1 PhD out of 2 holds a post-doctoral position abroad

***Team 5*: "Signaling and Modeling "**

We wish to thank the committee members for their thorough evaluation.

We are strongly encouraged by their overall positive judgment about our scientific program as well as the motivation and enthusiasm of our group. As noted by the committee, we develop risky projects; however, we trust that the risks inherent to the approaches we have chosen are fully mitigated by our own expertise and the strong collaborations we have established with interdisciplinary groups. We also agree with the committee that long-term financial support would greatly strengthen our project and allow it to be more solidly grounded. As a case in point, we wish the committee to note that we have two ANR grant applications currently under review.

6 PhD out of 7 hold post-doctoral positions abroad

Team 6: "Transcriptional regulation and dysregulation"

We thank the AERES committee for analysing our proposal and are pleased that our *Team* is considered to be appropriate for joining IRSET. Indeed the fusion of the two constituted groups originating from a CNRS unit (UMR 6026) now forming our *Team* has recently occurred. Our collective participation to a common project is intensifying, while maintaining and increasing external collaborations since the AERES visit. We agree that a mean impact factor over 5 would be preferable, but certain articles on risk assessment are published in journals with modest IFs and nevertheless considered as very good in these particular specialized fields. Besides, some studies mainly conducted in our group were published in general journals of cellular biology of reputation (J. Biol. Chem., Traffic, Oncogene). Since one of the pre-existing groups of our *Team* was studying breast cancer metastasis, which is a particular case of epithelial-mesenchymal transition (EMT), we have proposed as a fundamental and unifying project, to elucidate the environmental deregulation of the transcriptional mechanisms underlying the EMT program. Our principle is to select the experimental tools on the basis of their appropriateness to the precise scientific questions

addressed. In this respect, we presented refined cellular tools allowing conditional and reversible EMT. In addition, genome-engineered mice will be used in collaborative projects. We are only marginally studying (for its impact on gene expression) the Warburg effect, whose sensitivity to environmental conditions and pivotal roles in EMT are now well established. We wish to emphazise here that the silent memory of past exposures has profound ecotoxicological consequences. This is the reason why, in the context of IRSET and with the full support of its Director, we proposed to examine its possible transcriptional bases, dynamic (networks) and structural (chromatin marks), which seem to raise some concerns for the expert. Although we admit that such a subject is still emerging and daring, the first comments received from journal's reviewers encourage us to persevere in this original direction. Finally, certain points in the report should be corrected: *(i)* there are two full time researchers in the *Team* (Gilles Flouriot, CR_1 CNRS and Farzad Pakdel, DR_2 CNRS); *(ii)* the collaboration with INERIS concerns xeno-hormones but not the millimeter wave project the latter being developed in collaborations with IETR and CEA. We wish to precise that if we coordinate two ANR programs, we participate in fact to a total of four ANR projects, and want to indicate that our ANSES fundings have been forgotten in the list of our grants.

4 PhD out 7 hold post-doctoral positions abroad

***Team 7*: "Reproductive and cancer Genomics"**

First off we would like to thank the committee members on behalf for the very encouraging assessment of our accomplished work and the suggestions concerning our future integration into IRSET's work environment.

We are humbled by the committee's positive evaluation of our work and do indeed expect that ongoing work will lead to far reaching insight into regulatory networks driving meiotic development and to the discovery of mutations in genes essential for spermatogenesis with emphasis on its meiotic phase. **1.** We should like to mention that Ash by a Genome Database is in fact a side-project we are no longer involved in while GermOnline (array database) and AMEN (high-throughput data analysis tool) are being maintained and further developed; **2.** Our efforts to recruit new group members were seriously hampered in 2009 because of the precipitous and, as far as its scale was concerned, unprecedented evacuation of building 13 where our Inserm Unit is located. We have now received a grant (Bretagne CREATE) and more proposals are submitted (F. Chalmel: ANR Jeunes Chercheurs; M. Primig: ANR blanc, ERC advanced grant) or in preparation (ARC, FRM) which should enable us to recruit new postdoctoral researchers. F. Chalmel has received his first grant (action incitative UR1) which facilitates his efforts to obtain the right to train PhD students (HDR). Furthermore, we are currently exploring possibilities within the 7th EU framework program, the Human Frontiers program and a call from the Michelson foundation based in the US (http://michelson.foundanimals.org/) which has recently solicited M Primig because of his publication record. Finally, A. Lardenois (senior post-doctoral researcher) is postulating for Inserm and CNRS positions at the Chargé de Recherche level in 2011 which, in case she is successful, would add another permanent staff member to the group. **3.** We do not share the view of the committee that our projects critically depend upon the Centre for Genomics and Bioinformatics platform. The experiments meant to be carried out by our *Team* are highly feasible within the framework of our established collaborations with M. Snyder, R. Davis and L. Steinmetz. Moreover, we have already worked with I. Davidson at the IGBMC in Strasburg who is in charge of their sequencing platform. Since the CGB platform did not receive Equipex funding, our current work together with SHI Consulting is focusing on a market analysis and the development of a business model for a genomics company of which the University of Rennes 1 will be a direct partner. The role of the leader of this *Team* (M. Primig) in this company (nativeGenomics) will be limited to consulting work. **4.** Our CT gene

project has indeed suffered from lack of access to experimental samples and man-power for validation experiments up until recently (which in part was due to our evacuation which disrupted most of our experimental work for many months). We have now obtained tissue microarrays (TMAs) from normal and cancer samples via a new collaboration with R. Simon and G. Sauter (University Hospital Hamburg) and we are in close contact with F. Guillé (Centre Eugene Marquis, Rennes) as well as N. Rioux, S. Vincendeau and K. Bensalah (CHU Rennes) to obtain kidney, liver and prostate cancer samples (some in the form of TMAs). Importantly, R. Mathieu, a young surgeon, is currently doing a Master II project in the *Team* which is yielding important information on CT protein presence in cancer samples notably in castration-resistant prostate cancer.

The 2 PhD students of the Team are from India and China

***Team 8*: "Viral and chemical environment & Reproduction"**

We would like to thank the committee for their assertive and constructive criticism and appreciate that our original expertise and international recognition has been acknowledged.

The committee rose two issues in particular for which we would like to offer the following responses: **1.** A relatively low number of HDR (3) and researchers with permanent positions (5) within the *Team*. We are conscious of this relative limitation and taking steps to rectify. Specifically, we have recently received the support of the University of Rennes I for the recruitment of two new lecturers: (*i*) one will be hired in September 2011 to work on the HIV topic; (*ii*) a second position will be awarded for the chemical topic. In addition, Dr S Mazaud-Guittot (who has just been promoted CR1 and awarded with two grants as PI) currently co-supervises one PhD student and will pass her HDR in 2012. The delay in her doing so is a result of the strict rules enforced by the doctoral school of Rennes (VAS) for HDR; **2.** Concerning the risk of spreading our resources over too many topics, in terms of human resources, each project is served by specifically appointed staff members including PhD students (5), post-doctorates (3) and technical assistants (7). Importantly several projects are carried out as collaborative works with other groups equally involved and thus they do not solely depends on our internal resources (*e.g.* the project on BPA-ANSES grant-carried out with R Habert group (CEA), the project on semen soluble factor & HIV infectivity carried out with C. Pineau *Team* (*Platform* PPB), the project on SIV persistence in the male genital tract following treatment carried out with R. Le Grand's group (CEA); **3.** As regards the obtaining of biological material, we are in the process of increasing the supply of human testis tissues through a unique agreement with Rennes University Hospital to give us access to multi-organ donors and to post-mortem tissue, in accordance with the National Agency of Biomedicine, which will significantly add to our current source (orchidectomy). In addition, we carefully select distinct biological materials for the different projects to avoid shortage of material (*e.g.* rat testis *versus* human testis, foetal *versus* adult testis, human semen, ovaries...). **4.** We appreciate that the committee has recognized the quality of our production and will continue to focus on the objective of publishing in the highest possible impact factor journal. However, unfortunately it is too often the case that findings in the field of biology of reproduction are "ghetto-ised" to specific journals of the discipline. In addition, studies on HIV transmission have been largely neglected by generalized journals which tend to focus on such issues as vaccines or the eradication of latent reservoirs. By way of example our PLOS One paper on SIV infection of the semen producing organs (which ended up as "Top pick of the editor" in 2008) was rejected by PLOS Medicine on the ground that "although this work contributes significant data to the literature on this topic, it does not represent a specific clinically oriented advance". Considering the rising interest of the scientific community in prevention strategies, we are optimistic that this situation will change.

The 2 last PhD students of the Team hold post-doctorate positions in England and Australia

***Team 9*: "Epidemiological Research on Environment, Reproduction and Development"**

We want to stress that since its creation *de novo* in 2000, with two researchers and one technician, our *Team* has devoted a lot of time building new cohorts and other study populations including overseas, getting funds, training and attracting collaborators. In doing so it became visible in the European networks and participated in a number of EU funded projects (HIWATE, ENRIECO). We agree that now more time should be assigned to publishing results, task that shall be conducted in parallel with cohort follow-up. Of note is that since the committee's visit, we had 2 publications accepted (Environmental Health Perspectives IF=6.19; Occupational Environmental Medicine IF=3.64), 4 new manuscripts are currently under review, and that 6 abstracts have been submitted to the next meeting of the ISEE (International Society for Environmental Epidemiology) in Barcelona in September. We now wish to attract post-doctorates and this will be best organized in the framework of formal links established with institutions such as MRC Environmental Health Center in London (Imperial College), Centre for Environmental Epidemiology (CREAL) in Barcelona, in addition to GSF or IRAS already mentioned. Further thoughts will have to be given concerning the next *Team leader* both at the level of the *Team* itself and of IRSET. Furthermore, there will be simultaneously an incentive for an internal candidate to emerge, and openings for national or international candidates.

The 2 last two PhD students of the Team spent months in UK and Denmark.

***Team 10*: "Neuroendocrine Effects of Endocrine Disruptors"**

We agree with the overall content of the report regarding our *Team*. In particular, we generally appreciate the fact that the committee recognizes the strategic importance of our *Team* with respect to both the value of the zebrafish model and the perspective in neurosciences. There are however a number of precisions to be given: **1**. Regarding engineers, technicians and administrative staffs the correct figure for the past 4 years period is 1.15. One of the staff of the future IRSET *Team* is indeed affected to general tasks and does not work specifically for our *Team*. This is the reason why we hire a technician on our own resources; **2**. The relative slowing down of productivity during years 2008 and 2009 is explained by the temporary moving of the whole building (bâtiment 13) for sanitary reason (this is true for almost all *Teams)*; **3**. We wish to correct the assertion that most of the students and post-doctorates are from France when one post-doctorate is Italian and one student is Argentinean (40% are not French); **4**. For several reasons, we do not fully agree with the statement "As acknowledged by the team leader himself, the publication output of the team is modest in terms of journal impact factor". We recognize that improving the impact factor would be preferable and we will do our best. However, we are also convinced that our work on the roles of steroids on neurodevelopment in *fish* is more and more recognized as indicated by the number of quotations of our recent articles. We try to publish in the most appropriate journals. The mean impact factor should not be mixed up with the real impact factor that measures the actual strength of a given paper. A clear example is that in year 2002, we published one paper in EMBO J (mean IF=10) that today has received only 19 quotations (real IF = 1.9) and another in Biol Reprod (mean IF=3.5). This paper has been now quoted 124 times (real IF = 12.4) and we could present multiple examples of this type. Additionally, we have been invited to write 13 review papers or book chapters over the last 3 years (2009-2011); **5**. "Only the *Team leader* holds an HDR, precluding the opportunity to supervise several PhD students. No staff scientist could be identified to ensure continuity with the *Team leader*". While this seems a weakness, we believe that 2 students at a time is more than enough for a *Team* like ours. We

place stronger emphasis on the quality of the training than on the quantity. Our students are trained in English to become true international scientists and they all spend some time abroad during their PhD. Nevertheless, we agree that, on the long run, this could become a drawback and we will do our best to change this situation.

Our last PhD holds a post-doctoral position in Belgium

Bernard JÉGOU

Directeur du GERHM-Inserm U.625
Directeur de l'IRSET