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

Section des Unités de recherche

AERES report on the research unit

Molecular Immunology and Embryology

From the

Université d'Orléans

CNRS

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

Name of the research unit : Molecular Immunology and Embryology

Requested label: UMR CNRS

N° in the case of renewal : 6218

Name of the director : Ms. Valérie QUESNIAUX

Members of the review committee

Committee chairman:

M. Vassili SOUMELIS, Institut Curie, Paris, France

Other committee members:

Ms. Vily PANOUTSAKOPOULOU, Biomedical Research Foundation, Athens, Greece

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Ms. Anne LAVIGNE, Université d'Orléans

Report

1 • Introduction

The visit took place on the site of the Unit on Monday, November 29th, 2010. The organization allowed the visit to go smoothly. The committee had enough time to listen to the presentations and discuss their scientific content, assess the activity of all research groups, and discuss with the students around their posters and also in a more informal manner.

At the end, the review panels met to exchange their views and to organize the preparation of the final report.

This unit includes 4 teams:

- Team 1: Host pathogen relationship

- Team 2: Allergy and lung inflammation

- Team 3: Autism, mental deficiency and genetics

- Team 4: Injury-induced lung inflammation

Inflammation is the common link between all teams and research projects: allergy, infection, and injury. A future perspective is to develop a collaborative project on neuro-inflammation.

The unit's annual budget is over one million euros, largely covered by research grants. The unit obtained the quality assurance label ISO 9001.

A peculiarity of the unit is that it was created in order to develop research projects in connection with the Orléans animal facility. The scientists recruited had a strong expertise in mouse models of inflammation, and they benefited from the environment and the proximity of the animal facility, including the possibility to host, breed and maintain hundreds of mouse strains for the purpose of local and/or collaborative research projects.

- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6	6
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	7	8
N6: Number of Ph.D. students (Form 2.7 of the application file)	9	9
N7: Number of staff members with a HDR or a similar grade	8	8

2 • Overall appreciation on the research unit

- **Summary**

This unit has developed an important independent research and is centrally involved in the teaching of immunology at the regional level, as well as in a number of industrial and academic collaborations. The publication output is of good level, but will have to be strengthened by a more in-depth investigation of cellular and molecular mechanisms. New recruitment will be critical in this respect, including in particular young scientists and an expert in bio-informatics, although the committee understands the difficulties in a small city.

- **Strengths**

- Expertise and visibility in mouse models;

- Good publication output and research funding;

- Connections with the pharmaceutical industry;

- Help research efforts of the hospital;

- Good partnerships and international collaborations;

- Important interactions with the central animal facility, leading to original models and scientific collaborations.

- **Weaknesses**

- Research projects mostly driven by the availability of the animal models, with a lack of conceptually challenging and original projects;

- Large number of diverse models, which makes more difficult the in depth study of a given model;

- Animal facility depends on CNRS;

- Turnover of personnel. Need more stable positions from University, CNRS or hospital;

- Difficulty to attract young scientists and post-doctoral fellows.

- **Recommendations to the head of the unit**

- Continue to build on original research questions in connection with the animal facility: this is the main expertise and originality of the unit.

- Improve the in depth characterization of cellular and molecular mechanisms instead of multiplying small studies in diverse models: this will improve the originality and impact of the research, and benefit to the scientific training of students. Hiring young scientists and post-doctoral fellows with a strong background in immunology may greatly help in this matter and should be a priority for the team.

- The two teams "Allergic asthma and systemic Inflammation" and "Injury-induced lung inflammation" should merge in a unique team. This will keep a critical mass in the team and better prepare the future developments.

- Promote and strengthen the original research of the team "Molecular and Experimental Genetics " by focusing on the areas where the team is the most competitive.

- Hiring an expert in bio-informatics, who will be of great help in the analysis of microarray data. This should benefit many projects related to inflammation and also neurological disorders.

- If the team leaders decide to develop an interface in the field of neuro-inflammation, this would require to invest more resources and/or make some selection among all the research themes, in order to be competitive in this very interesting but challenging area.

- Improve connections with clinical teams, and develop more research on human samples, in order to validate results obtained in mouse models. This should improve the impact and physio-pathological relevance of the research.

- **Production results**

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	3
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	4
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	6
A5: Number of PhD granted during the past 4 years	9
A6: first and/or last authors original publications in peer review journals	55

3 • Specific comments

- **Appreciation on the results**

The unit has a significant research output in terms of publications. The large number of national and international collaborations participates in this output. The different teams published 115 articles in the past 4 years, among which 12 with an impact factor >10. The head of the unit is the coordinator of the TBREACT European project. This recognized scientific activity also attracts international speakers and visiting scientists, in particular from South Africa and Brazil, because of the infectious diseases animal models. Other outputs include one spin off company, three patents, and some industrial partnerships.

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

The unit hosts 40 people, including 17 tenured members, which corresponds to a medium size unit, as compared to others. Staff scientists benefit from a good work environment, connections with hospital teams and international academic as well as industrial collaborations. Technical and administrative staff has a good degree of autonomy and is well integrated in the unit. It is actively involved in training young researchers. Three technicians are responsible for maintaining 150 mouse lines. Students and post-doctoral fellows also benefit from a good environment in terms of material, space, financing, international seminars and invited speakers. A general problem is to replace retired staff as well as attracting new lab members at all levels, in particular staff scientists or a junior group leader.

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

The unit is actively involved in the training of masters and PhD students, as well as in the teaching of immunology. It is the only immunology group in Orléans, and has an important responsibility in teaching this discipline. It is integrated in the life sciences department of the university. As compared to other units/departments of that university, it is small but very productive with a good visibility. The university supports its activities in immunology and neuroscience, including by a small recurrent funding.

- **Appreciation on the scientific strategy and the project**

The unit plans to continue developing new animal models, as well as national and international collaborations around these models. An important perspective is the validation of research findings in a human disease setting. The unit currently has few clinical connections based on each individual project, but these should be strengthened. Clinical collaborations should also facilitate the identification of biomarkers. The Orleans general hospital, although not a teaching university hospital, plans to invest in clinical and translational research, in particular in dermatology, neurology and rheumatology, all specialties with possible connections to immunology and inflammation. It has initiated a strategic partnership with the Tours medical school, which should further facilitate translational research. Last, recruitment of young researchers should also be an important perspective, in particular in bioinformatics.

4 • Appreciation team by team

- **Title of the team: Host-Pathogen relationships**
- **Name of the team leader: Ms. Valérie QUESNIAUX**
- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	4
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3	3
N6: Number of Ph.D. students (Form 2.8 of the application file)	4	3
N7: Number of staff members with a HDR or a similar grade	2	2

- **Appreciation on the results**

This team is interested in understanding the mechanisms of host response to mycobacterial infections, with a special focus on pathogen pattern recognition receptors, and cytokines. During the last period, they investigated the role of different members of the TNFa family in the resistance to mycobacteria. For this purpose they proposed and coordinated an FP6 NEST project called TB REACT, which aim was to investigate the role of different forms of TNFa and TNF receptors in the pathophysiology of tuberculosis. They also investigated the role of TLRs and other PRR in host-mycobacteria interaction. This work enabled the identification of mycobacterial TLR ligands, either agonist or antagonist, among extractable mycobacterial lipids, such as Lipomannane. They finally enlarged their project to lectin-like receptors and seven transmembrane fragment-bearing receptors families. This project led to the conclusion that PRR have a redundant role for the control of M. tuberculosis infection, in the difference to TNFa and IFNg receptors, which are essential.

A third project was described about the molecular mechanisms of cerebral malaria. In this last project, the team assessed whether TLR could be involved in the brain response to malaria. Using a model of cerebral malaria developed in mice, they took advantage of their large knock out mice collection to investigate the role of members of the TNFa family.

Between 2006 and 2010, this team co-signed 35 articles, among which 7 of were signed as senior author, the 28 others were collaborative works where the team mainly contributed in sharing knock out animals from their collection.

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

The team has a very good impact in the field of Mycobacterial immunity, and this is mainly due to its great knockout mice collection. This gave them the opportunity to create a very large number of national and international links

during this period of time. The scientific quality of the work produced since 2006 is in the average, but the best publications from their list are the one where they only collaborated. Surprisingly, despite their very large collaborator list, the team is not very attractive for researchers or even post-docs, it even seems to decrease for the future period.

- ## Appreciation on the project

The proposed project strictly follows the current work of the team on mycobacterial immunity. For the next period of time the team proposes to investigate: 1- innate factors:the role of TLR ligands in the formation of « foamy » cells, and the role of different cytokine/chemokine families for the control of TB ; and 2- adaptive immunity : the role of MyD88/TIRAP pathway mainly using invalidated mice for TNF, IL12/23, and dendritic cell activation markers.

They also propose to use a mouse model of bacterial latency they developped in 2002 to address the question of bacteria reactivation, which is one of the major goals in TB research. Using this model they will also use their knock out mice for TNF and IL1, in order to evaluate the respective role of these molecules in reactivation.

Another project deals with the identification of bacterial factors favouring immune evasion and limitation of inflammatory response. For this purpose they will collaborate with a local colleague from the chemistry department who will synthesize mimetics of mycobacterial anti-inflammatory antigens, namely PIM1 and 2. Microarray analysis of the pathways activated by such inhibitory compounds will help better understand immune evasion strategies mediated by these compounds.

The sixth project proposes to investigate the role of iron homeostasis on host resistance to infection. This emerging project will be developed by a recently recruited professor, who joined the team as an expert in iron metabolism. In this project, mice models defective for several genes involved in iron homeostasis will be used to better understand the pathway of iron homeostasis, and evaluate its role in the control of mycobacterial intracellular survival.

Finally, the last project will continue the characterisation of cerebral Malaria, which was started during the previous period. Again, using knock out mice, the team will investigate the respective role of: PRRs, IL1, IL12/23/17 in the development of CM and in the associated circulatory shock and lung inflammation. They also propose to identify the molecular mechanisms of host response regulation by parasite GPI anchors.

In general, this large number of projects may be too much for just this team. The questions are all of interrest, but the technology proposed is often limited to analyzing the effect of a given gene knock out on a given phenotype, which should only be a first step and not a unique question.

The strategy of the team is quite clear. Their goal is to better understand the immunity to mycobacterial infections. And the strategy is to use for this purpose a panel of knockout mice, mainly invalidated for TNF or IFN-related pathways, that they have. Unfortunately, the team does not take advantage of their main force of the knock out mice collection to really ask in depth questions about mycobacterial immunity. They rather appear to immediately switch their focus to another gene/pathway as soon as they have described whether the corresponding knock out mouse has a different phenotype than the wild type.

A better management of the team in terms of researcher recruitment and project development may increase their publication scores in terms of quality. Recruiting young scientists with good technical skills in immunology would enable more in depth work in any of the questions that are asked on the project.

- ## Conclusion

  - Summary

The main scientific project of this team is focused on the identification of the molecular mechanisms of mycobacterial immunity, a field in which the teal leader alone has a real expertise in the team. These studies mainly consist in assessing the phenotypic variation induced by gene knock out in a mouse model of mycobacterial infection. Another ongoing project deals with the molecular characterization of cerebral malaria. This question is of interest, but given the expertise of the team leader in Tuberculosis, where cerebral forms also exist and have still an unknown etiology, it is not clear why the team did not rather investigate cerebral TB.

- Strengths and opportunities

The main strength of the team is the unique knock out mice collection and “knowhow” in such mice development. They also have a good expertise in immunology and Tuberculosis, which are the main focus points of all their projects.

- Weaknesses and threats

The main weakness is the number of different projects that are proposed as compared to the number of staff members in the team. The main threat is that if one day the CNRS, which is heading the animal facility, decides to move it outside from Orleans, the team will be directly affected and may have to stop some projects. This is mainly due to the fact that they only propose to assess phenotypic changes induced by gene knock out mice and not any in depth characterization of such phenotypic changes. The lack of young researcher recruitment in the team could be problematic for the progress of such in depth research projects but also for the supervision of students.

- Recommendations

The main recommendation will be to strongly reduce the number of proposed projects (6 for tuberculosis and 4 for C. Malaria). Then on every project, it would be nice to have more in depth characterization of the mechanisms investigated. For this purpose it could be helpful for the team to hire a couple of young researchers with good skills in immunology to take such in depth work in charge, and help in the supervision of students. Several interactions with teams working with TB patients will help answer the questions that are asked in a more relevant way than mice can be, for given pathophysiological questions.

- **Title of the team: Allergic asthma and systemic Inflammation**
- **Name of the team leader: M. Bernard RYFFEL**
- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	1
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	3
N6: Number of Ph.D. students (Form 2.8 of the application file)	3	3
N7: Number of staff members with a HDR or a similar grade	3	2

- **Appreciation on the results**

This team has been a founding member of the research unit. For the next period, it is proposed that this team split in two teams called “allergic asthma and systemic inflammation” and “Injury-induced lung inflammation”.

Beside the team leader, the team “allergic asthma and systemic inflammation” will include a Professor and an Assistant Engineer as permanent members. The team proposes to focus on the exploration of innate immune effector mechanisms in the development of allergic asthma and in parallel, based on recent developments, will also assess mechanisms in systemic inflammation. Since many years the team has capitalized on the availability of a large selection of knock out mouse strains at the adjacent TAAM to explore the implication of innate immune effector pathways in models of inflammatory lung diseases such as allergic asthma, bleomycin-induced fibrosis, and ARDS. Since 2006 the team has published more that 80 research papers with about one fourth directly emanating from the team, the rest being collaboration either with the other teams of the Unit or outside research groups. Major contributions were the demonstration of a dual role of IL-17 in allergic asthma, being disease promoting in the early desensitization phase, while being protective in the effector phase (J. Exp Med, 2006). Another important contribution was to show the implication of the IL-1 and inflammasome pathway in bleomycin-induced lung inflammation (J Clin Invest, 2007, Am J. Resp. Med 2010).

- **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 a well-established, nationally and internationally recognized research group in the field of lung inflammation. This is underlined by the invitation of the team leader to International meetings (Keystone) and significant attraction of funding from both national agencies, charities (FRM) and the European community (FEDER, Asthma, European Mouse disease clinic). Over the years, the team has built a large number of fruitful national and international collaborations. The team has also obtained international contracts for collaborations with emerging countries such as Brazil and South Africa. Based on his educational background, the team leader has also developed

collaboration with pharmaceutical companies partly based on filed patents and is founding member of a new biotech spin-off company located presently in the Unit.

- **Appreciation on the strategy, governance and life of the team**

The team is highly integrative and collaborations with other team members are favored in a highly efficient manner. The committee could appreciate that other permanent staff members recognize the value of the leadership of the team leader. By restructuring the group the team leader wished to favor the emergence of a new team working on the related subjects of injury-driven lung inflammatory models. Some committee members felt that a co-leadership may have been more appropriate in order to allow a smooth transition.

- **Appreciation on the project**

For the next mandate the restructured team proposes to separate the activity of antigen-driven and injury-driven models and focus on the role of the innate effector pathways in the antigen-driven models of allergic asthma as well as on more systemic inflammatory models based on recent results. The first topic to be developed is based on preliminary findings indicating a role for the NLRP3/IL-1 inflammasome pathway in the development of allergic asthma. A precise characterization of IL-1 and IL-1-related cytokines will be undertaken. The second topic will continue to explore the role of IL-17 family members in acute and chronic asthma, in particular by focusing on the potential cross-talk between IL-17 and IL-22, based on new results. A third topic will analyze the role of the aryl hydrocarbon receptor (AhR) in the regulation of IL-17 and the asthmatic response. This is based on the discovery that this receptor has been shown to induce TH-17-type responses. The forth topic will investigate the IL-1-IL-17 axis in a more systemic inflammatory model such as the septic shock model. Finally a potential fifth topic relates to the study of the impact of the commensal flora on allergic lung inflammation.

While these projects are building on the established results and are intertwined, the committee members felt that given that the group was split into two parts, elaboration of five different research topics may somehow dilute the research focus. For example studying the impact of the aryl hydrocarbon receptor in influencing the TH17-IL17 axis in allergic asthma without asking the question of relevant “possible” internal or external (in an EOPS facility?) ligands may lead to partial results. The team may also consider transfer of specific immune cell subsets into Rag-/- or other mice in order to dissect the mechanisms in terms of cellular source and specificity. If, for example, Th17 cells are the important players, in vitro polarized OVA-specific Th17 cells could be adoptively transferred into recipients that have ongoing allergic airway inflammation. On the other hand, if Tγδ cells are the source, a more systematic and persistent immunological analysis should be followed before transcriptomics. The committee felt that the commensal flora project, although important, may lead to questionable results. For example, re-colonization of certain cytokine knockout mouse strains does not guarantee the persistence of the same flora as in wild-type mice.

- **Conclusions:**

– Strengths and opportunities

This team has developed a strong research pole in the analysis of innate immune effector mechanisms in experimental models of antigen-driven (asthma) and injury-driven lung inflammation, where it has gained both national and international visibility. The scientific questions asked by the team leader are potentially significant.

– Weaknesses and threats

Given the large number of ongoing and future projects presented, the splitting of this research pole in two different entities may weaken the team. It was also felt that research should be more focused by limiting the number of projects to allow for more extensive studies on a couple of projects analyzing the mechanisms involved down to the molecular level.

– Recommendations

The team has made major contributions in analyzing the role of innate immune effector mechanisms in lung inflammation. The team should stay focused on the mechanistic analysis of their significant findings instead of widening their research area. It should also avoid asking similar questions using different models of inflammatory diseases. It is understandable that this is possibly a way of attracting funds but limits their ability to ask fundamental

questions. In addition, collaborations with clinical teams could be very important to link their findings to human disease and to assist in attracting European funds.

It is also felt that the separation of research activities may dilute the critical mass. A co-leadership between team leaders could have been envisaged in order to keep a strong research axes; this also would allow a smooth transition to the next mandate.

Given the expertise of the team in the study of innate immunity, recruitment of a researcher with strong expertise in adaptive immunity could be a significant addition to the team. Also, this appears to be important in light of the antigen-driven models that are employed by the team.

- **Title of the team: Injury-induced lung inflammation**
- **Name of the team leader: Ms. Isabelle COUILLIN**
- **Staff members**

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0
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)	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2
N6: Number of Ph.D. students (Form 2.8 of the application file)	2
N7: Number of staff members with a HDR or a similar grade	1

- **Appreciation on the results**

The team leader is currently a member of the team "Allergy and lung inflammation". For the next mandate the existing team proposes to allow the team leader to form her own team studying immune response to tissue damage. She has already been a leader on certain projects of the team as evident by her publications as a senior author. Her expertise is mainly on the innate immune response during lung damage and fibrosis.

Since her recruitment in 2008, the team leader studies are a significant contribution to the team. Her team has demonstrated that IL1-R1/MyD88 signalling and the inflammasome are essential in bleomycin-induced lung fibrosis (J. Clin. Invest., 2007). Furtermore, she showed that cigarette smoke-induced inflammation is dependent on TLR4 and IL-1R1 (J. Immunol., 2008). Her team also demonstrated the effects of uric acid and extracellular ATP on the inflammasome during lung inflammation and fibrosis (Am. J. Resp. Crit. Care Med., 2009; Am. J. Resp. Crit. Care Med., 2010).

- **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 has a research team (mainly Ph.D. candidates) that appears to be established. She has been invited speaker to national and international meetings (World congress on inflammation), participates in important meetings (World immune regulation, ATS) and has served as an expert reviewer in FP6 and FP7 panels. The team leader has also formed her own collaborations and has received funding for her work. She is the coinventor of a European patent.

Up to now, the team leader has been a member of another team. For the next mandate, the unit proposes that Dr. Couillin will lead the team studying the non-specific inflammatory injury of the lung while Dr. Ryffel will lead the team studying the antigen-specific driven inflammation of the lung. However, both teams are involved in studying innate immune responses. Some committee members felt that a co-leadership may have been more appropriate in order to allow a smooth transition.

- **Appreciation on the project**

The team proposed to study (1) the role of IL1a, calpains, calpastatin, extracellular ATP, cathepsins and BAFF in the bleomycin model, (2) the role of extracellular ATP, IL1a, calpains, calpastatin during inflammatory/fibrotic response to microparticles, (3) the role of nanoparticles in lung fibrosis. She also proposed another study involving innate mechanisms and Alzheimer's disease.

Most of the projects are based on preliminary results generated by the team. The experimental approach mainly involves employment of mouse models (wild-type and transgenic), blocking antibodies and inhibitors. In certain cases, molecular pathways are going to be analyzed. The team has the expertise to carry out these projects.

However, the committee felt that the projects are too many to allow deep analysis of the mechanisms involved down to the molecular level. In addition, the Alzheimer's project may be a "distracting" one with questionable depth of analysis.

- **Conclusions**

— Strengths and opportunities

The committee felt that the team leader has developed a strong research team in the analysis of innate immune mechanisms in experimental models of injury-driven lung inflammation. The scientific questions asked by the team leader are potentially significant especially if mechanisms are extensively analyzed.

— Weaknesses and threats

The number of the future projects proposed is very large for the team. Research should be more focused by limiting the number of projects to allow for more extensive studies on a couple of projects analyzing the mechanisms involved down to the molecular level.

— Recommendations

The team leader has contributed to the understanding of the role of innate molecules in lung inflammation/fibrosis after injury. Some of these findings are in a way preliminary and should form the ground for extensive analysis on the mechanisms involved. Thus, the team should focus on fewer questions instead of expanding their research area. For example, they should not jump to different animal models in order to study the employment of the inflammasome but rather try to find the molecular links inducing it in one model. It would also be valuable to use human material as an attempt to evaluate the mechanisms in the human disease. This will assist their efforts for further funding.

It is also felt that the separation of research activities may dilute the critical mass. A co-leadership between team leaders could have been envisaged in order to keep a strong research axis; this also would allow a smooth transition to the next mandate.

- **Title of the team: Molecular and Experimental Genetics**
- **Name of the team leader: M. Sylvain BRIAULT**
- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	4(7?)*
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1(3?)*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	1
N7: Number of staff members with a HDR or a similar grade	3	3

* The team is planning to integrate in the near future 3 assistant professors working at the University of Orleans and has already obtained ANR funding to hire 2 additional post-docs.

- **Appreciation on the results**

This team is young since it was created in May 2009, making it difficult for us to judge on the quality of the research output. However, the publications by the team leader on the genetics of autism and mental retardation during the past 4 years indicate a good scientific production, with several papers in high-ranking journals. In particular, the identification of a child with autism and mental retardation with a disruption of a gene coding for the alpha subunit of a ion channel, provided a novel and promising target for functional studies and the development of potential therapeutic strategies, which are at the core of their scientific research project. Furthermore, their ongoing project on the analysis of copy number variants (CNVs) in patients with autism using high-resolution genome-wide arrays has already allowed them to identify several pathogenic CNVs as well as CNVs affecting novel putative autism genes. If confirmed, these findings will expand the increasing number of monogenic forms of autism and have important repercussions in our understanding of the pathophysiology of this disorder.

- **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 a member of the European consortium studying the genetic basis of X-linked mental retardation (EuroMRX), which has a long track record of gene discovery and excellent publications. He continues to collaborate closely on the genetics of autism and mental retardation with the team in Tours with which he was affiliated before moving to Orleans (INSERM U930).

Although the team was created in 2009, it has already attracted 2 assistant professors, and recruited 1 post-doc, 1 PhD student and 1 master student. They are also discussing the possibility of integrating 3 additional assistant professors from the neurobiology laboratory of the Orléans University, with whom they have already started a close collaboration. The recent ANR obtained by the team to work on the effect of pesticides on glutamatergic synapses will allow them to hire 2 post-docs in the near future. Research on genetics of autism is supported in part by the CHR of

Orléans; the hospital has also promised an engineer position for the post-doc currently in the team, whose contract will finish at the end of the year.

One of the team members is responsible for the Affymetrix genomics and transcriptomics platform located in the UMR 6218 (purchased jointly by CNRS, the CHR of Orleans and the University for clinical and basic research); this is a considerable asset for the team's work on the identification and characterization of CNVs in autism.

- **Appreciation on the strategy, management and life of the team**

One of the main strengths of the team is the clinical activity of 2 of the team members at the CHR of Orleans, as head of the Genetics department and manager of the Molecular Biology laboratory. The multidisciplinarity of the team members is also a strength, including expertise in molecular and clinical genetics, electrophysiology, neurodevelopment, neuro-anatomy, biochemistry and cellular neurobiology. However, the fact that there are no full time researchers in the team and the 4 permanent researchers all have either hospital or university positions could be problematic for the progress of the research projects and the supervision of students. Moreover, the team has no technical staff, either temporary or permanent.

Two of the team members have teaching positions in neuroscience and genetics at the Biology Department. Three members also teach courses on human genetics at the license, M1 and M2 levels. Moreover, the team leader is a member of the Scientific Orientation committee and the Research subcommittee of the CHR of Orleans.

- **Appreciation on the project**

The team's scientific project on the identification of novel genes etiologically involved in autism and/or mental retardation, their functional characterization and their study as potential therapeutic targets is a highly relevant and promising approach. Indeed, although autism is a highly heritable disorder, the underlying genetics remain largely unknown, with a genetic cause recognized in only ▫10%–20% of cases. Their approach to identify novel genes, based on the study of CNVs using genome-wide arrays, has proved to be very successful in many disorders. Their proposal to couple the genomic analysis with expression analysis in lymphoblastoid cell lines using expression arrays to help in the identification of the pathogenic CNVs is novel and promising.

The team also studies a ion channel (disrupted in a patient with autism) as a potential therapeutic target. They examine the effects of an opener of this channel (which has already been tested in human clinical trials for cerebral stroke), in the Fragile-X syndrome model mice (fmr1 knock out mice) through cognitive and social behavioral tests as well as neuronal activity studies using patch-clamp. If these studies show beneficial effects, clinical trials could be considered in a near future in subjects with mental retardation or autism linked to dysfunction of this ion channel.

Another project that will be developed by this team concerns the study of pesticide exposure on the glutamatergic synapse, with potential implications in neurodevelopmental disorders. Although this appears as an interesting project and was funded by the ANR in 2010, it is not related to the main focus of the team's other projects, which address the genetic basis of autism and mental retardation. Given the small size of this team and the fact that none of the permanent researchers are full time researchers, there is a risk that spreading too thin their resources in disparate projects might jeopardize their ability to make real progress in any given subject.

Concerning the transversal project on neuroimmunology to be developed jointly by the 3 teams of the laboratory, this is a vast and complex research field and it is difficult to imagine how the current lab members are going to develop this totally new research line in addition to their own research projects.

- **Conclusions**

  - Summary

The main scientific project of this team is focused on the identification of genes involved in autism and/or mental retardation, a field in which some members of the team have real expertise. These genetic studies are combined with functional studies in mouse models to test the therapeutic effects of a compound targeting a gene product identified by the team. Other ongoing projects based on the neurotoxicity of pesticides and the transversal project on neuro-immunology represent a significant departure from the central themes of research developed by this small and new team.

— Strengths and opportunities

The strengths of the team include the clinical and molecular genetics activities of 2 of the team members at the CHR of Orleans, their experience in the identification of disease genes, as well as the multi-disciplinarity of the team members. The availability of the Affymetrix genomics and transcriptomics platform onsite is a considerable asset for the study of copy numbers variants in patients with autism. The animal facilities available in the laboratory are also a plus.

— Weaknesses and threats

The lack of full-time researchers in the team could be problematic for the progress of the research projects and the supervision of students. The team also lacks technical staff. The attempt to develop too many research projects without the necessary human resources could be a threat.

— Recommendations

Because this is a small team, in which permanent researchers have hospital or university positions that take much of their time, it is important that they work together on a few, focused research projects, rather than starting too many new projects on different subjects on which they won't be able to be competitive. The proposal to develop a neuro-immunology axis in collaboration with the two immunology teams in the lab seems premature and risky at this point, given the limited resources in personnel.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
IMMUNOLOGIE ET NEUROGÉNÉTIQUE EXPÉRIMENTALES ET MOLÉCULAIRES (INEM)	**A**	**A**	**A**	**A**	**A**
AUTISM, MENTAL DEFICIENCY AND GENETICS [QUESNIAUX-BRIAULT]	A	A	Non noté	A	A
INJURY-INDUCED LUNG INFLAMMATION [QUESNIAUX-COUILLIN]	A	B	Non noté	A	A
HOST-PATHOGEN RELATIONSHIPS [QUESNIAUX-QUESNIAUX]	A	A	Non noté	B	A
ALLERGY AND INFLAMMATION [QUESNIAUX-RYFFEL]	A	A	Non noté	B	B

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**

UNIVERSITE D'ORLEANS

Le Président

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Orléans, le 27 avril 2011

Monsieur Pierre Glorieux
Directeur de la section des unités de recherche
AERES

Objet : commentaires sur le rapport d'évaluation du laboratoire INEM

Monsieur le Directeur,

L'université d'Orléans remercie le comité de visite pour son travail d'évaluation du laboratoire Immunologie et Neurogénétique Expérimentales et Moléculaires (INEM). Le rapport d'évaluation appelle les commentaires suivants.

At the general level, the report mentions "a lack of conceptually challenging and original projects" which might be seen as unfair and does not pay justice to the activity of the research unit. For instance, investigation of of TLRs and TNF pathways, or inflammasome and purinergic signaling, in inflammation and host response, for which the unit has developed sophisticated analyses, go well beyond looking at a simple phenotypes. In all these pathways the unit was fore-runner, and is recognized as such in the field (Keystone, INSERM workshop, ANR, European Projects). The 'difficulty to attract young scientists and postdoctoral fellows' is repeatedly stated although the unit has attracted 10 post-doc, 5 long-term international visiting scientists, 18 international students, MD and PhD, since 2006. It applies regularly for post-doc and young scientist positions, and obtained a CNRS CR1 position in 2008. This recently recruited young scientist will be given more independence in the next period, rather than a team co-direction as recommended in the report.

- Regarding the team : *Host-pathogen relationships* (head: V. Quesniaux)

On page 7 (last sentence), the report mentions that "Between 2006 and 2010, this team co-signed 35 articles, among which 7 of were signed as senior author, the 28 others were collaborative works where the team mainly contributed in sharing knock-out animals from their collection." This team is involved in several active and fruitful international collaborations, and is careful to share authorship with collaborators. The team head believes that sharing mice by itself does not qualify for co-authorship, and every single publication with her name is the result of an active collaboration.

The report (page 9) also asserts that "it is not clear why the team did not rather investigate cerebral TB". This aspect is indeed interesting and is being addressed within our International Associated Laboratory (LIA) by the team's collaborators at the University of Cap Town, South Africa. The first step is to establish a reproducible and relevant murine model of TB meningitis.

- Regarding the team : *Allergic asthma and systemic inflammation* (head: B. Ryffel)

Page 10, it is written that "Since many years the team has capitalized on the availability of a large selection of knock-out mouse strains at the adjacent TAAM". None of the KO mice used in the research projects was 'just available at the adjacent TAAM'. The collection of KO mice that has been put together in the last 10 years was the result of interactions with scientists all over the world, with the constant scientific aim of targeting most promising pathways for our research interests. Contacting, importing, rederiving and managing these lines is a constant effort and the team has been largely opened to the scientific community ...

- Regarding the team : *Injury-induced lung inflammation* (head: I. Couillin)

The report asserts (page 15) that 'the team should focus on fewer questions instead of expanding tthier research area'. The team's head shares this view: indeed, although several projects were mentioned, the team will focus on the funded projects: the role of purinergic signalling in lung fibrosis (including the relationship with Alzheimer disease); the role of cathepsins in lung fibrosis; mechanisms of lung inflammation to nanoparticules (role of inflammasome and purinergic signalling).

- Regarding the team: *Molecular and Experimental Genetics* (head: S.Briault)

The committee pointed out the limited human resources of the Molecular and Experimental Genetics team. Aware of this situation, the team led a strategy of development of the staff. Since the visit of the committee, the team has obtained two additional post-docs from FEDER funding (2011-2012), one engineer and one technician position from Hospital (2013). Additional BIATOSS technicians could be allocated to the team in a near future.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de mes meilleures salutations.

Youssoufi Touré