Immunité, infection, vaccination

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Immunity, Infection, Vaccination (I2V) - U851

From the

INSERM

University Claude Bernard Lyon 1

Mai 2010

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

Section des Unités de recherche

AERES report on the research unit

Immunogenomics and inflammation

From the

Université de Lyon 1

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

Mai 2010

Research Unit

Name of the research unit: Immunity, Infection, Vaccination

Requested label: UMR_S INSERM

N° in the case of renewal: 851

Name of the director: Ms. Jacqueline MARVEL

Members of the review committee

Chairperson

Mr. Marc BONNEVILLE, INSERM U892, Nantes

Other committee members

Ms. Fiona POWRIE, Sir William Dunn School of Pathology, Oxford, UK

Mr. René VAN DER LIER, Academic Medical Center, Amsterdam, The Netherlands

Mr. Mathias HERRMANN, Institute of Medical Microbiology and Hygiene, Homburg and Saarland, Germany

Mr. Rudolf MANZ, Institute for Systemic Inflammation Research, Lübeck, Germany

Mr. Oliver PABST, Institute for Immunology, Hannover, Germany

Mr. Philippe ROINGEARD, Tours Medical School, Tours, France

Committee members nomminated by staff evaluation committees (CNU, CoNRS, INSERM and INRA CSS....)

Mr. Jean-Marc REICHHART, CNU member

Ms. Naomi TAYLOR, CSS INSERM member

Observers

AERES scientific advisor

Ms. Claude-Agnès REYNAUD

University or School representatives

Mr. Jean-Pierre MORNEX, Université Lyon 1

Research Organization representatives

Ms. Christine TUFFEREAU and Ms. Armelle REGNAULT, INSERM

Report

1 • Introduction

- Date and execution of the visit

The site visit started on February 2 at 9:00 AM and ended on February 3 at 7:00 PM. The scientific program included an overall presentation of the unit by its director, and 30-75 min presentations of the achievements and projects of the 7 teams from the Unit, each followed by a 15 - 30 min discussion. The visiting committee also met with staff members (students, technical staff, PIs and post-docs), the Lyon 1 University representative and the Unit director.

- Management team

This research unit (UMR851 INSERM/Lyon University) is located in four distinct buildings in the Gerland/Lyon Sud area : Cervi/INSERM (900 m2), UCBL/Laënnec (450 m2), CI/Lyon Biopôle (420 m2) and the University hospital Lyon Sud CHLS/UCBL (250 m2). This unit brings together most of the immunology research teams of the Lyon area, with complementary expertise in human and murine DC, T and B cell immunobiology. These teams address both basic questions dealing with T and B cell memory, skin and mucosal immunity and more applied issues, with strong clinical and industrial applications in the field of bacteriology, virology, allergy, vaccinology and immunotherapy.

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	18	19
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	13	15
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	27	24
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	26	23
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	30	28
N6: Number of Ph.D. students (Form 2.7 of the application file)	23	21
N7: Number of staff members with a HDR or a similar grade	24	24

2 • Overall appreciation on the research unit

• Overall opinion

This research unit brings together 7 teams (or "topics") involving about 150 people, who primarily work on host/pathogen interactions. Five of these teams correspond to the merger of projects previously run independently by different PIs, in order to increase the critical mass of researchers working on a particular topic and foster new interactions between these researchers. All the PIs have proven and complementary expertise in human and murine cellular and molecular immunology, basic and applied bacteriology and virology, mucosal immunology, vaccine design and immunotherapy. The overall scientific output of the unit since 2005 is excellent, with several important results published in high profile journals such as Science, Nat Immunol, Immunity, J Exp Med, PNAS, Cell Host Microbes, ... Most research teams have established fruitful collaborations with clinical departments within the University Hospital and many industrials partners, as indicated by the high number of well funded joint R&D and clinical projects. These teams also benefit from privileged access to several excellent platforms and core facilities (A2, A3 and A4 animal facilities, L3 and L4 laboratories, imaging facilities at the ENS, flow cytometry facility within the IFR...). While the overall scientific output of the unit and the translational component of its research are very good to excellent, the coherence of the unit is affected by the location of its teams at 4 distinct sites and by yet limited interactions between several teams. Regrouping of the teams on at most two sites should be a top priority. Moreover the percentage of the overall budget allocated to common services, internal organization and transversal strategic programs should be significantly increased in order to enhance synergistic interactions between the Unit components and the international visibility of the Unit as a whole.

• Strengths and opportunities

- Several PIs from the Unit have an excellent track record, have made several seminal observations and have an excellent international visibility in their respective fields.
- Accordingly the overall scientific output is very good to excellent.
- Teams have privileged access to presumably high quality platforms (e.g. with IBiSA label), although they were not described into sufficient detail during the AERES meeting to allow their in depth assessment
- The research achieved by many teams has an excellent translational component, both with the industry and the clinic. Along this line, the integration of clinicians is excellent, and the research training of young MDs substantial
- All the teams from the Unit have raised considerable amount of funds, from both public agencies and private partners
- There is a real interest of the unit in promoting young scientists, with external promising young scientists recently recruited and many young "chargé de recherche" having signed papers as last author
- The technical and engineer staff has a real sense of being part of the unit
- The Unit is a key element within the Rhône-Alpes research network in the field of infectiology, and has established tight links with the Lyon Biopôle competitivity cluster, the FINOVI RTRA and the Infectiology research cluster
- The good attractiveness of the Unit is supported by the recent arrival of several young PIs with a very good to excellent track record
- The teams foster use of funds to send students/postdocs to international meetings

- Creation in the next future of a new international center developing basic and applied projects in the field of infectiology represents a great opportunity to enhance the international visibility of the Unit.

Weaknesses and threats

- The teams from the Unit are located in 4 different buildings, some of them being at quite remote places.
- Although the international visibility of several teams is excellent, the visibility of the Unit as an Infectiology research center is still limited
- There is no specific funding by the Unit of transversal, strategic or emerging programs that could strengthen its overall coherence.
- It does not appear that each team pays for common services
- The added value of the organization of the Unit into 3 main research axes is not obvious since there is no specific budget allocated to each axes and no specific actions done within each axis to promote internal collaborations
- The AERES committee was not fully convinced of all in-house actions in terms of mergers
- Some teams develop too ambitious programs or address too many questions, and would greatly benefit from stronger interactions with other teams from the Unit
- Internal seminars by students or researchers are in French, which may affect the attractiveness of the Unit for foreign researchers

Recommendations to the head of the research unit

- There is an urgent need to regroup the teams on at most 2 sites (eg working primarily on basic vs clinical research, respectively)
- Some young group leaders could benefit from mentorship by experienced PIs from other teams
- The Unit should try to create monies for new strategic objectives
- The Unit should improve interactions between teams working in related and complementary fields (eg TLR and inflammation)
- Organization of retreats once a year or every other year with an overnight away could strengthen the links between teams and their feeling of being part of a research center
- The Unit should add fee to contracts to pay for common services (to improve administration, accounting, laverie)

- Data on the work produced :

(cf. http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf)

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	31/31
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	27/27
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	100%
A4: Number of HDR granted during the past 4 years	5
A5: Number of PhD granted during the past 4 years A6: Any other relevant item in the field	34

3 • Appreciation team by team

Title of the team : Bacterial Pathogenesis and innate immunity (topic #1)

Team leaders: Mr. François VANDENESCH, Mr Gérard LINA (former team 6), Mr Thomas HENRY (former team 11)

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	8	8
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	4
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	3
N7: Number of staff members with a HDR or a similar grade	8	6

- Appreciation on the results

Team 1 is a merger of two teams (T6 and T11) from the current research unit, with team 6 having a long standing expertise in the biology and pathogenicity of staphylococci, and the young investigator team 11 providing of a more recent yet substantial expertise on innate immune signalling cascades upon infection with obligate intracellular bacteria. T6 has made several contributions of landmark quality regarding several courses of S. aureus disease and RNAIII-mediated regulation of bacterial gene expression, which have been published in high profile journals (eg Science 2007, EMBO J 2005) and /or described in highly cited papers. Such studies are of utmost importance for major S. aureus disease and provides promising avenues for novel diagnostic and treatment strategies. T6 has also made significant contributions regarding T cell recognition of new staphylococcal superantigens and designed a barrier model to study the mechanisms for TSS-related neurological syndromes. The work is highly relevant although the in vitro CNS barrier experiments await confirmation in experimental (e.g., in vivo) settings. The young PI from T11 has made several major observations dealing with modalities of inflammasome activation along F. tularensis infection. His publication record is excellent (J Exp Med, PNAS, J Immunol, Mol Microbiol as first author, Science, PNAS, Nat Immunol as co-author) and his work can clearly be considered as cutting-edge science. The significance of his results for other, not obligate intracellular pathogens (i.e., staphylococci) needs to be determined, yet, they provide an excellent basis for the planned, hypothesis-driven research. Considering the amount of work concluded, the number of theses (9) and HDR (1) degrees compares not extensive, underlining the high quality of the respective thesis work.

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

The previous work of team 6 is of huge impact and international visibility, documented by above summarized publications, multiple invited lectures of PI's at major international meetings, organization of major meetings in Lyon. The group has strong relations with industry (including participation on industrial grants (EDF, Leo Pharma, Prolysis Ltd, Pfizer...) and three patents) and provides of robust extramural funding (FP6 Concord Grant, FINOVI, INSERM-DHOS, 4 ANR grants, AFFSET, INVS...). In the "staphylococcal community", the contribution of the previous T6 group to the current status of knowledge can be viewed as among the upper 10% of groups in the field. The young PI that joined the team has presented his work in several international meetings, and recently got strong financial support from the Finovi RTRS.

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

The joint project #1 by team 6 and team 11 is a promising merger which allows team 6 to extend its proficiency into areas of innate immunity hitherto not addressed, and to integrate pathogenic organisms other than staphylococci (e.g., Legionella) in their research. On the other hand, team 11 will undoubtly benefit from the experience, infrastructure, translational research opportunities, and clinical impact provided by team 6. The presentation of the joint research topic #1 appears to be homogeneous, and is expected to result in sizeable add-on value of overall results.

- Appreciation on the project

The groups have outlined projects clearly based on and emerging from their previous work. The scientific questions including investigation on host genetics and signatures for susceptibility, adaptability of PVL expression and PVL-PBP1 interaction as a result of environmental challenge, further investigation into the role of ncRNAs, and translation of innate immunity work in the staphylococcal pathogenesis are highly promising. The delineation of novel effects of SAg's on tumor treatment appear to be challenging, yet, this project provides for promising interaction with other INSERM teams.

- Conclusion :

  – Summary

Promising collaboration of an established senior, highly productive and translational research group with solid local, national and international collaborations, and a young scientist's group with a documented achievements record and promising, hypothesis-driven, cutting-edge research in intracellular pathogen survival and innate immunology.

Clear prospects with strong, competitive, creative research projects. Excellent prognosis on fulfilling the research goals through the upcoming 4 years of funding.

  – Strengths and opportunities

Strong infrastructure, both of scientific experience and innovative research topics in a research environment characterized by multiple translations and cooperations between academic and non-academic partners.

There are opportunities to unravel novel, unknown roles of staphylococcal virulence and regulation mechanisms in conjunction with novel aspects on the intracellular fate of staphylococci and other intracellular pathogens

  – Weaknesses and threats

Some projects (e.g. SAg projects on tumoricidal activity) will be of more "risky" nature, yet, they are promising and will be backed by lower-risk, straightforward attempts of other aspects of the overall proposal.

Heavy clinical work duties for staff and non-permanent MD researchers may suggest additional forms of funding for MD's, e.g. by creation of "rotational" positions to be allocated for MD's (while being replaced by clinicians).

Title of the team : Cell biology of viral infection (topic #2)

Team leaders: Mr Vincent LOTTEAU, Mr Patrice ANDRÉ (former team 4), Mr Mathias FAURE, Ms Chantal RABOURDIN-COMBE (former team 5)

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	9	8
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	5
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results

Team 2 will be constituted by the merger of two pre-existing teams within the unit, focusing on virus/cell interactions. Both teams had excellent results in the past. A great achievement of the « HCV team » was the establishment of the proteome-wide HCV-human interactome, although it is at this time too early to evaluate the future impact of these results. The team has also generated major results to understand the role of the lipids in the HCV infectious cycle. The « measles team » has provided major results on the CD46/measles virus/autophagy pathway interplay. Several of these observations have been published in excellent journals (eg Nat Med, Cell Host Microbe, Mol Cell Proteomics, J Immunol, J. Virol as leading authors…). This team has supervised 11 theses and 1 HDR.

- 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 an excellent international presence, recognized notably as a pioneer in the discovery of lipo-viro-particles (LVP) associated with HCV infection. The team has strong collaborations with foreign academic research teams, extremely strong ties with industrial partners (currently 5), and impressive capacities to raise funds among the academic and industrial network (ANR, ANRS, FP6-EU, Biocluster Lyon Biopôle, FINOVI, INCa…) totaling 3,600 k€ since 2005. This team has also issued 4 patents.

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

The team is well organized with excellent complementarities between the different members. The committee is very supportive of the real benefits that will be potentialized by merging the two teams. A strong support is given to young leaders within the group and the professor involved in providing this environment should be commended. The team leader is highly involved in structuring the research in Infectiology in the Lyon area.

- Appreciation on the project

The project on measles virus and autophagy is very interesting and supported by strong results recently published in Cell Host and Microbes. The different projects on hepatitis viruses are very original and innovative, although it is still a bit early to judge their pharmacological and clinical impacts. Other projects such as those on influenza virus or protein transfer through micro vesicles deserve also interest, although there is a risk of dispersion of the team in too many projects.

- Conclusion :

  – Summary

Team 2 constitutes an excellent research group with exciting basic and applied projects. There is a real added value of merging the two previous teams in terms of management and scientific complementarities.

  – Strengths and opportunities

The team has excellent connections with industrial partners and an outstanding ability to raise funds for its research. Its overall project has many complementary aspects, from basic science projects to clinical/translational projects. The management is excellent with the recent reinforcement of promising young scientists with the potential to establish their own groups.

  – Weaknesses and threats

The team should be aware of the risk of dispersion through their involvement in too many projects.

  – Recommendations

The overall impact of the data obtained with the interactome project will be strengthened if relevant data are now obtained from more in vivo experiments and more mechanistic studies.

Title of the team : Mucosal immunity, vaccination and biotherapy (topic #3)

Team leader : Ms Dominique KAISERLIAN (former team 7)

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	5	4
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	3	4

- Appreciation on the results

The project is carried out by a single team. The team has a long-standing interest and expertise in mucosal immunology and reported seminal contributions in highest ranking international journals including Immunity and Gastroenterology. The team exploits sophisticated mouse models to investigate the mechanisms of intestinal tolerance in vivo and recently reported that plasmacytoid dendritic cells might contribute to intestinal tolerance. Beside its basic research on intestinal tolerance the team studies the development of inflammatory bowel disease. Again the team focuses on so far rather neglected aspects of this topic and concentrates on the role of CD8 T cells. This part of the project has a strong link to clinical aspects. The productivity of the team (since 2005, 26 publications including 3 Immunity as first, last or coauthor, 2 Gastroenterology as last author, J Immunol as last author) is outstanding. This team has also supervised 4 theses and 2 HDR, which is an excellent output for such a small team.

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

The team's work is well recognized by the international community, and is developed within several international collaborations and networks (eg FP6 EUROPRISE). Numerous invitations to international meetings (10 invited seminars since 2005, eg at Gordon conference, Keystone meeting, ECI...) and close collaborations with other researchers further strengthen the team's productivity. The team has access to excellent new mouse models and the opportunity to push frontline research. The team has raised several grants from public agencies (EEC, FINOVI, INSERM PNR), and has established strong connections with both industrial partners (2 bioclusters projects : "ExpandID" and "Microvax" involving Becton-Dickinson derived from several patented results dealing with DC adjuvants and mucosal induction of IgA responses, 2 industrial grants with Danone and ALK Abello) and clinical departments. In this regard the team has developed a strong translational research component supported by many grants (from several public agencies and charities including FRM, PHRC, WHO and INSERM).The good contact to the local clinical partners provides access to human material which in the future will further strengthen these translational approaches.

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

The teams PI encouraged and supported two team members that obtained the HDR and are likely to act as independent PI´s in the near future. It is impressive to see that 3 medical student obtained a training as PhD. The decision to strengthen the link to clinical partners is rated as excellent strategic decision. The team is comparably small and does profit from a focused topic and close interaction in the team.

- Appreciation on the project

A clear outline of the planned work was presented that builds up on the team's previous results and expertise. It can be expected that the team will continue to produce outstanding publications of very high interest. A subproject investigating immunity to HCV proteins seemed less well connected to the other topics. Another idea of using intra vital microscopy cannot yet be fully judged but might require a substantial effort to set up.

- Conclusion:

– Summary

The team carries out excellent research, supports young scientists and enforced its interest to translate its work to the clinic. Since the field is becoming increasingly competitive, it is recommended to further enforce regional and international collaborations to maintain the excellent standard of the team's work. The team might benefit from the recruitment of talented researchers potentially from outside of France.

– Strengths and opportunities

Excellent scientific output, recruitment of several young talented researchers, excellent translational research activity and training of MDs, excellent international visibility.

– Weaknesses and threats

Some subprojects (eg regarding immunity against HCV) seem less connected and may loosen the overall coherence of the program. The feasibility of the intravital microscopy project remains unclear and its competitive implementation will certainly require substantial support and involvement of qualified researcher with well-proven expertise in this area. There is a risk of diluting efforts with too many projects since this is a rather small team.

Title of the team : Skin inflammation physiopathology and new vaccination routes (topic #4)

Team leaders : Mr Jean-François NICOLAS, Ms Ana HENNINO (former team 8)

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	10	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	3
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	7	6
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	3
N7: Number of staff members with a HDR or a similar grade	4	3

- Appreciation on the results

The team is led by an MD and a PhD. The MD has long standing expertise in skin immunity and arising immune pathologies. The group nicely brings together basic mouse models and applied experimental approaches in the clinic. Specifically they have developed mouse models to mimic aspects of drug allergy and allergic contact dermatitis. Using these they have revealed the pathogenic role of CD8+ T cells and immune suppression by regulatory T cells. There is a good flow of information from the models to testing relevance in human skin immunity. Nevertheless while the mouse models are relevant, the physiopathological studies remain a bit descriptive and empirical. The group has published a large number of papers in specialty journals (3 J Invest Dermatol, J Immunol, 4 Allergy, Transplantation...) and has good visibility in the allergy field. However they should be encouraged to aim for publications in higher impact journals. There is a good training output, with 5 PhD theses since 2005.

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

The international visibility of the PI is excellent (about 20 invitations at plenary sessions at both national and international meetings, recent invited review in Curr Opin Allergy Clin Immunol). The impact of the team is high as the work has direct clinical application, and has led to creation of biobanks (Allergobiotec) and website (Allergolyon) that are very useful for the community of allergologists. Using an ELISPOT assay for allergen-specific T cells the team developed a more sensitive assay for drug allergy which is now applied in the clinic. The group has applied their understanding of skin immunity in collaboration with industrial partners to probe vaccination strategies. This has led to enhanced anti-flu immunity in immune compromised individuals. The group appears to be very well-connected both locally and internationally with both academic and industrial collaborations (2 Lyon Biopôle R&D projects, and has secured several regional and national grants (above 3 M€ raised since 2005, from FRM, INSERM, Region Rhone-Alpes, Pierre Fabre, Galderma, Colipa...).

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

The team appears to work efficiently at the hospital and basic sciences Gerland site. There is good communication between members of the team and good mentoring of younger scientists. The combination of a clinician and a basic scientist managing the team is clearly an added value.

- Appreciation on the project

The proposed projects build on the expertise of the group. There is a particular focus on the development of more clinically relevant models of contact sensitizers, which is an important issue. It is a novel idea to test the role of skin desensitization to promote tolerance induction in humans. However a more rational approach to distinguish peptides that may stimulate one T cell response from another may be more fruitful. The concurrent use of mouse and human models is commended but the team could benefit from the use of more sophisticated mouse models.

- Conclusion

Overall this is an impressive team that has combined basic science findings with real experimental medicine approaches in drug allergy.

– Strengths and opportunities

Excellent international visibility of the PI.

Several very relevant questions addressed with major clinical and societal impact. Very good continuum from basic to clinical research.

Strong links established with clinical and industrial partners

Excellent fund raising activity

– Weaknesses and threats

The upstream research remains a bit descriptive and empirical

Although the publication output is quantitatively important, the number and impact of publications in the main topic of the team (allergy) could be higher, considering the rather large size of the team.

Some basic aspects of the project may lack technical originality and would benefit from more mechanistic approaches

– Recommendations

To increase the impact of the work the team should adopt more sophisticated immunological methodologies to provide more rational strategies to take forward in patients. Recruitment of experienced postdoctoral fellows from outside may help to increase the overall impact of the group.

Title of the team : Innate immunity and cancer, Toll like receptors and viral induced cancers (topic#5)

Team leader : Ms Uzma HASAN (previous team 9)

- Staff members (on the basis of the application file submitted to the AERES)

	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)		
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
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		

- Appreciation on the results

The scientific program of the team can be subdivided in (i) a triple short-term goal, which consists in understanding the molecular mechanisms responsible for Epstein Barr (EBV), Human Papilloma (HPV) and hepatitis B (HBV) virus-induced "down-regulation" of TLR9 in infected cells, and (ii) two longer term goals, which aim at understanding the regulation of the inflammasome in viral induced cancers and analyzing Innate immune polymorphism in cancer. The short-term goals are straightforward and clearly mechanistic, and benefit from proven expertise of the PI in vitro mechanistic studies involving good level molecular and cellular biology. Biology of the inflammasome is cutting-edge science, but this is a challenging project in a highly competitive field. The fourth goal is based on large-scale systematic analysis linked to strong interactions with clinicians, who will provide patient-derived biological samples. The team leader publication record over the last four years is of good quality, with seven publications obtained in the laboratory where she made her post-doctoral research (including 2 J Immunol, J Biol Chem and PNAS as first author). However since the team was created about a year ago, and the PI has not obtained publications yet from the work she has been supervising, it is still too early to assess her ability to run in an autonomous and competitive fashion her own projects. Of note, the team attracted a young scientist with several recent publications of excellent quality (including PNAS as first author, and Nat Immunol, PNAS, JBC and J Immunol as co-author).

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

The PI has given 7 oral presentations in plenary sessions of international and national meetings, indicating good visibility. As mentioned above, the committee cannot judge the value of the research as a team, but part of the program (i.e. biology of the inflammasome) if successful, should clearly have a high impact on knowledge. It is also difficult for the committee to appreciate the impact and attractiveness of the team, but the fact that the team leader could attract a PhD student with an already excellent track record demonstrates some qualities in this aspect. Finally, the recent publication record of the team leader shows the quality of her links with excellent international partners. As a visiting scientist in the laboratory of R. Medzhitov, one of the leaders in innate immunology research, the PI has strong international connections. The PI has obtained grants totalizing up to 800 k€ since 2005, exclusively from public agencies. Although she got two patents, her links with industrials partners remain limited.

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

This is a small team when compared to the average size of other teams within the Unit, obviously because it is only starting. The PI joined the unit in January 2009 with an Inserm CR position and is leading a group made of two post-doctoral researchers, one technician and two PhD students. Owing to its small size and its recent creation, the committee is unable to appreciate the strategy, management, and life of the team. However the attraction of a PhD student (with an MD background) with a very good track record is a very positive point. Nevertheless the committee was concerned by the fact that the team leader does not have an HDR, which is normally required if you want to independently supervise PhD students. More importantly, this young team seems quite isolated and should be more closely associated with other PIs from the unit, who either focus on mechanistic studies dealing with inflammation for the first goal, and/or have more clinical links allowing the systematic monitoring of large patient cohorts that have been planned for the second goal.

- Appreciation on the project

While it might be too early to judge about the feasibility and competitiveness of the team, the project looks very ambitious with a clear dichotomy in the approaches, and too disconnected from the scientific environment provided by the Unit.

- Conclusion

– Strengths and opportunities

Very good visibility of the PI, whose postdoctoral publication record is very good.

This team has attracted an excellent PhD student with already a very good track record.

Several questions, most notably dealing with inflammation are highly relevant.

Very good fund raising activity

– Weaknesses and threats

The team is located in a rather remote place, which hampers establishment of collaborations with other teams from the unit.

The overall project is too ambitious for a small team in view of the important international competition, particularly in the inflammation field.

Some sub-projects are a bit phenomenological

– Recommendations

The three projects on TLR9 regulation are strongly based on mechanistic approaches and are anchored on four publications that are still in preparation and should be published in order to validate the mobilization of resources in this direction. In addition the basic biology of TLR9 in the target cells and the physio-pathological relevance of the observed TLR9 suppression should be ascertained.

The two long-term goals (inflammasome in viral-induced cancers and innate immune polymorphism in cancer) are clearly of utmost importance and definitely exciting. The committee therefore recommends the integration of this small team into another team from the Unit working on a related field. This would allow sharing of resources and would bring mentoring for the young team leader, an important key for success.

Title of the team : Protective and pathogenic B cells (topic #6)

Team leaders : Mr Thierry DEFRANCE (former team 2), Ms Nathalie BONNEFOY-BERARD (former team 1)

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
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)	4	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	6
N7: Number of staff members with a HDR or a similar grade	4	5

- Appreciation on the results

This project results from a collaboration between team 1 and team 2 from the current unit. Team 2 has great experience in the field of B cell biology. Previous results from team 1 on IL-17 showed that this cytokine has a profound effect on B cells, thus motivating the investigation of this issue in greater detail. Experimental approaches of the two teams are highly complementary: team 2 uses sophisticated mouse models and team 1 studies human samples. The former T2 made several important observations regarding the contribution long-lived bone marrow plasma cells to T-independent (TI) B cell memory, and the role played by TLR signaling in the generation of long-lived protective immunity against poorly immunogenic Ag (such as polysaccharidic pneumococcal capsular Ag). Such findings should help in the development of more effective polysaccharidic vaccines, thus also allowing their broader application. In parallel the PI from former T1 provided strong evidence for implication of the IL17 pathway in B cell mediated autoimmune diseases and the development of B cell neoplasia, and more recently obtained highly original results implying a novel role for IL-17 in the rescuing of a self-reactive B cell repertoire in patients suffering from autoimmune disease. This team also showed that disruption of survival pathways of B cell tumors involving Bfl-1 could represent a promising anti-tumor strategy and to this end, have identified through high throughput screening approaches small organic compounds interfering with the anti-apoptotic effects of Bfl-1. These studies, with both significant physiopathological and therapeutic implications, have led to 19 papers since 2004 for former T2 (including 2 Blood, J Clin Invest, and 2 J Immunol as first or last author), and 23 papers for former T1 (including Nat Immunol, Oncogene, Cell Death Diff, J Biol Chem, J Virol, J Immunol, 2 Eur JI as last author). These two teams have also supervised 5 theses and 1 HDR since 2005, which is a good output given the rather small size of these groups.

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

The work of team 1 and 2 has clearly an impact in the field, and both teams are internationally visible, as indicated by several invited conferences to both national and international meetings (eg ESF/EMBO symposium and the International Congress of Immunology). The groups have also partnerships with industry (2 patents, founder scientist of one biotech (OREGA), 2 industrial grants (Sanofi-Pasteur, OREGA Biotech)) and obtained robust extramural funding (totalizing > 1,700 k€ since 2005).

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

The joint project is a promising merger of two teams with complementary approaches investigating human samples and mouse models. The planned experiments are expected to lead to results with great impact in the field. However, the very recent merge of these two groups (who have no past record of joint publications) makes it difficult to evaluate the added value of their future cooperation. Overall, the future plans are very promising, although no definitive plan exists how the available resources will be prioritized for individual projects, which could lead to difficulties in the project management.

- Appreciation on the project

The groups developed their new projects clearly based on their previous work. The planned investigations on the formation of TI-memory, the impact of IL-17 on B cell malignancies and autoimmune disease and the research on potential compounds inducing apoptosis of B cell tumor cells are expected to yield important results and have a potential impact in the clinics.

- Conclusion :

  – Summary

Promising collaboration of two experienced and successful teams with complementary expertise. Competitive, creative and enthusiastic research projects. Very good prognosis for the research results that will be obtained during the upcoming 4 years.

  – Strengths and opportunities

Excellent and complementary expertise of the two partner groups. Innovative research topics in a strong research environment.

  – Weaknesses and threats

Very promising research plan, which however lacks clarity with regard to the allocation of available resources to individual experiments. The project exposing p53+/- mice to infections has great potential but is somehow risky.

  – Recommendations

It is recommended that the two teams use their collaboration to make optimal use of their complementary expertise in human and murine experimental setups and to favor the use of the new sophisticated mouse models planned for the next period.

Title of the team : Cytotoxic lymphocytes and memory CD8 T cells (topic #7)

Team leader : Ms Jacqueline MARVEL (former team 3), Mr Thierry WALZER (former team 10)

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
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	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	3	4
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	2
N7: Number of staff members with a HDR or a similar grade	2	3

- Appreciation on the results

Relevance and originality. Part of the research of the group (former team 10) has contributed significantly to recent important observations in the NK field. Further, the NK-deficient mice provide a very solid basis to set up strategic collaborations. Additionally the SP1P5 line has yielded novel hypotheses on the migration of NK and effector CD8+ T cells that form the basis for solid new research. The research line on CD8 memory cell formation (former team 3) has good quality and impact.

Overall output. The output of the NK line has been excellent with several publications in the top journals since 2004 (Nat Immunol, PNAS, Blood, 2 J Immunol, J Allergy Clin Immunol, EJI... as first or last author). The CD8 positive T cell line has provided decent output in terms of quality and quantity (4 J Immunol, Oncogene, PLoS ONE, EJI as last author, J Clin Invest as 2d author), yet does not reach the excellence of the research on murine NK cells. Good training output with 5 PhD theses supervised since 2004.

Contractual relations. Long-term implication in several international networks involving primarily academic partners. Important role played in the Eumodic consortium dealing with large scale generation and characterization of new mouse models.

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

Visibility and attractiveness. It has been an excellent achievement to recruit a young PI from one of the top labs in France, whose emerging international visibility is attested by at least 5 invited conferences at national and international meetings recently. However the lack of (mentioned) invited conferences and citation analysis suggests more limited international visibility for the longstanding CD8 memory research line.

Fund raising. Excellent fund raising capabilities : INCa, LNCC, ARC, EU-FP6, Bio-Cluster Lyon Biopole, ANR, FINOVI junior team award, totaling 2.7 M€ since 2004.

Collaborations. Team well represented in competitive regional, national and European clusters. In addition, the NK-deficient mice provide a strong starting point to initiate novel national and international collaborations.

Socio-economic output. 2 international patents and one database software. Recent implication in a collaborative project on the development of an immunomonitoring platform involving several private companies (Platine, Transgene, Innate Pharma, immune ID).

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

The team has a very good internal organisation and the embedding of the young PI provides enough independence for his visibility. Moreover, the weekly team meeting will provide a platform for both PI's, investigators, students and technicians to discuss and to further improve the coherency and performance of the team. Besides, the senior PI is heading very efficiently U851 and has been involved in the coordination and organization of several local networks involving both academic and private partners.

- Appreciation on the project

Relevance and feasibility. It appears that the program on NK cell migration and effector functions is very well developed. Moreover, the good agreement with the former lab of the young PI of team 10 will assure a proper division of labour and the possibility to work on the topic at a level that is highly competitive. For the work on CCL5 to become even more relevant, a better link to (human) pathophysiology is desirable. Finally, in this day and age, the novel array approach seems risky in the absence of proper leads. Given the ambition of the overall program, there is a crucial need to clearly prioritize and strengthen the synergies between the two teams.

Originality and risk-taking. The group is in the process of making innovative tools (e.g. KO mice) for the in vivo analyses of molecules and pathways of interest. Moreover, they plan to perform additional microarray analyses to identify novel molecules characteristic for certain aspect of murine memory cell formation.

- Conclusion :

  - Summary

- Topic with a number of strong and highly vital research lines but also lines that would improve by an enhanced focus.
- The group has the ability to generate innovative tools.
- Good management structure.
- An even better exchange of ideas and tools between the two research lines would increase the competitiveness of the team.
- In contrast to some other topics within INSERM 851, topic 7 lacks a clear translational research link.

  - Strengths and opportunities

- Unique mice are available and have been generated.
- Interesting new concepts developing.
- Young, ambitious team.
- The opportunity to establish real synergy between the different research lines.

– Weaknesses and threats

- Although recently a number of research projects have been terminated, still diverse arrays of (sub)projects
- Some of the lines are not as competitive as they should be.
- Resources may be too limited to carry all the different projects.
- Translational research that is so characteristic for U851 is absent within the topic. At the long term the lack of a link to human studies may give problems in raising funds.
- No evident links with other topics within the unit.

– Recommendations

- Actively exchange of ideas and tools between the two research lines.
- Explore if (more) translational research would strengthen the position of the team.
- Strengthen collaborations with the other teams within INSERM851.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Nom de l'équipe : RÉPONSES B PROTECTRICES ET PATHOGÉNIQUES

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	B	A

Nom de l'équipe : INNATE IMMUNITY AND CANCER

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	A	B	Non noté	B

Nom de l'équipe : IMMUNITÉ DES MUQUEUSES, VACCINATION ET BIOTHÉRAPIES

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A+	A

Nom de l'équipe : BIOLOGIE CELLULAIRE DE L'INFECTION VIRALE

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A+	A+	A

Nom de l'équipe : IMMUNITÉ ET LYMPHOCYTES CYTOTOXIQUES

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	A	A

Nom de l'équipe : PHYSIOPATHOLOGIE DE L'INFLAMMATION CUTANÉE ET NOUVELLES VOIES DE VACCINATION

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	B	A	A	A

Nom de l'équipe : PATHOGÉNIE BACTÉRIENNE ET IMMUNITÉ INNÉE

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A+	A+

Université Claude Bernard Lyon 1

Le Président
Lionel Collet

Villeurbanne, le 24 Mars 2010

M. Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne

75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'unité de recherche :

«Immunogénomique et inflammation» rattachée à mon établissement.

Ce rapport n'appelle pas de commentaire particulier de la part de l'université.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma meilleure considération.

Le Président de l'Université

Lionel Collet

Directeur : Jacqueline Marvel
Directeur adjoint : Vincent Lotteau

Instituts thématiques

Inserm

Institut national
de la santé et de la recherche médicale

For attention of AERES

Lyon, march 31st, 2010

We would like to thank the evaluation team for their time and excellent expertise of the unit. The aims of this letter are: to comment on some of the recommendations that were made, provide some missing information that was omitted from the activity report and give some update on decisions that have been made since the visit.

Comments on the overall appreciation on the research unit:

- There is no specific funding by the Unit of transversal, strategic or emerging programs that could strengthen its overall coherence.

- The added value of the organization of the Unit into 3 main research axes is not obvious since there is no specific budget allocated to each axes and no specific actions done within each axis to promote internal collaborations

As mentioned during the director's presentation the department PI's have thoroughly discussed the structure of the department and have decided to define the topics in order to improve the strength of the different line of investigation but also the interaction between the teams. However, we think that the transversal projects that have emerged from these discussions should be funded by joint grants. This policy is already ongoing and has been quite successful as a number of grant applications for joint projects inter- or intra-topics have been obtained or applied for in the past 6 month. (FINOVI grant obtained between topic 2 and 3, ANR applied for by topic 3, 4 and 7; INCA applied intra topic 6, ARC applied intra topic 7…).

- Internal seminars by students or researchers are in French, which may affect the attractiveness of the Unit for foreign researchers

As from the first of March 2010 the seminars are given in English.

- The Unit should add fee to contracts to pay for common services (to improve administration, accounting, laverie)

This will be done in the near future; the implementation modalities are currently being discussed.

Comments on individual topic reports.

For topic 5, after discussion with the different topic PI'S, we have decided that the creation of this topic should be delayed. The project will be developed within one of the other topics. Furthermore, collaborative links have already been created with one PI in topic 1 working on the inflammasome and a joint research grant has been submitted.

For topic 7, we would like to add some missing information and comment some of the conclusions reached by the experts.

"However the lack of (mentioned) invited conferences and citation analysis suggests more limited international visibility for the longstanding CD8 memory research line. "
The information concerning invited conferences was omitted from the activity report for former team 3. The PI was invited to 4 conferences (Joint meeting on infections and cancer CLARA-DKFZ 2009, Annual Meeting of the French Society for Immunology 2007, Club Vaccinologie de la SFI, Institut Pasteur 2006; European Congress of Immunology 2006). One invited lecture (The John Humphrey Lecture, Imperial College, London). In addition 6 submitted abstracts from team

IFR128 - BioSciences Lyon-Gerland

Lyon 1

Hôpitaux de Lyon

Unité 851 "Immunité, Infection et Vaccination"
Université de Lyon, Université Lyon 1, IFR 128, HCL
21 avenue Tony Garnier - 69365 LYON cedex 07
Tél : 04 37 28 23 50 - Fax : 04 37 28 23 41
jacqueline.marvel@inserm.fr

members were selected for oral presentation in different meetings (Plasmacytoid DC function in immunity and tolerance organized by the CLARA network on “PDC in cancer” 2009; Annual meeting, Club Francophone des cellules dendritiques 2009, Antigen cross presentation, Gordon conference 2007; Annual Meeting of the French Society for Immunology 2007, European Congress of Immunology 2006)

- Translational research that is so characteristic for U851 is absent within the topic. At the long term the lack of a link to human studies may give problems in raising funds.

We are in the process of creating translational links with industrial partners, project such as the Platine project that aims at developing new assays to monitor human immune response, is a first step in that direction. Although, most of our models are pre-clinical mouse models our aim in the next four years is to move towards more human immunology. This was maybe not stated strongly enough in our project.

- No evident links with other topics within the unit.

Former team 3 has a long-standing tradition of collaborating with other teams within the unit. This is highlighted by 4 publications in the past four years that involved other teams from the unit. Publications (398, 424 and 429) describe an original discovery showing that CD8 T cells express TLR2 and that TLR2 engagement at their surface is involved in CD8 T cells co-stimulation and memory cell maintenance, this project was developed jointly between former team 3 and former team 1. Publication 428, describing a new subset of memory CD8 T cells that is generated under sterile inflammatory conditions, was performed in collaboration with former team 7, 8 and 1. This tradition of collaboration will be maintained in the future and is illustrated by the submission of a research grants involving topic 3, 4 and 7, in the past few months.

Jacqueline Marvel

Unité 851 "Immunité, Infection et Vaccination"
Université de Lyon, Université Lyon 1, IFR 128, HCL
21 avenue Tony Garnier - 69365 LYON cedex 07
Tél : 04 37 28 23 50 - Fax : 04 37 28 23 41
jacqueline.marvel@inserm.fr