DIMNP - Dynamique des interactions membranaires normales et pathologiques

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Dynamics of Membrane Interactions Normal & Pathological

DIMNP

Under the supervision of the following institutions and research bodies:

Nouvelle Université de Montpellier

Centre National de la Recherche Scientifique - CNRS

January 2014

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

Department for the evaluation of research units

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

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

On behalf of the expert committee,

– Ms Florence NIEDERGANG, chair of the committee

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

Evaluation report

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

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

Unit name:	Dynamics of Membrane Interactions Normal & Pathological
Unit acronym:	DIMNP
Label requested:	UMR
Present no.:	UMR 5235
Name of Director (2013-2014):	Ms Catherine BRAUN-BRETON
Name of Project Leader (2015-2019):	Mr Georges LUTFALLA

Expert committee members

Chair:

Ms Florence NIEDERGANG, Université Paris 5 Descartes

Experts:

Mr Alain CHARBIT, Université Paris 5 Descartes

Mr Alexandre DE BREVERN, Université Paris 7 Diderot

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Mr Kai MATUSCHEWSKI, Max Planck Institute, Berlin, Germany

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Mr Frédéric ROSA, École Normale Supérieure de Paris

Scientific delegate representing the AERES:

Mr Pierre VIERLING

Representatives of the unit's supervising institutions and bodies:

Mr Michel DESARMENIEN (representative of Doctoral School n°168)

Mr Bernard GODELLE, Université Montpellier 2

Mr Bruno LUCAS, CNRS

1 • Introduction

History and geographical location of the unit

The CNRS-Université Montpellier 2 (UM2) UMR 5235 was created in 2007 and renewed in 2011. It resulted from the fusion of 2 CNRS-UM2 research units. The proposed unit for the next 2015-2019 term is composed of 7 teams.

During the period considered (january 1st 2008-June 30th 2013), the unit was composed of 8 teams. Several changes occurred and will occur in the contours of the teams. One team leader retired in October 2012 and the remaining researcher moved to another unit. One of the successful teams will leave the unit in January 2015 but the ATIP team (obtained in 2010) that remains will keep a portion of the projects. Another ATIP was obtained in 2013 by a recently recruited young researcher and an independent team has thus been created. This reflects the positive dynamics and very good attractiveness of the unit during the last 5 years.

All teams were gathered on a single renewed floor in 2011 after a long process of renovation and moving. On June 2013, they represent 65 persons, including 42 permanent positions (i.e. 5 CNRS and 11 INSERM researchers, 9 UM2 professors and assistant-professors, 12 CNRS ITA and 5 UM2 BIATSS staff), and occupy 1700 m^2 in building 24 on the Montpellier campus Route de Mende.

Management team

The present head of the unit is Ms Catherine BRAUN-BRETON, professor at UM2. The deputy director is Mr Georges LUTFALLA, CNRS research director, and he is proposed as the director for the next 5 years period with Ms Maryse LEBRUN, INSERM research director, as deputy director.

AERES nomenclature

SVE1_LS1 Biologie moléculaire et structurale et biochimie

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	9	10
N2: Permanent researchers from Institutions and similar positions	16	15
N3: Other permanent staff (without research duties)	17	17
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	4	1
N6: Other contractual staff (without research duties)	19	
TOTAL N1 to N6	**65**	**43**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	15	
Theses defended	31	
Postdoctoral students having spent at least 12 months in the unit*	10	
Number of Research Supervisor Qualifications (HDR) taken	6	
Qualified research supervisors (with an HDR) or similar positions	17	17

2 • Assessment of the unit

Strengths and opportunities related to the context

The unit works on important issues (pathogenesis of bacteria and parasites, host-pathogen interactions, development of hematopoietic stem cells and innate immunity, cytokine responses and targeted immunocytokine drugs, and antiparasitic drugs) that are, and will continue, to be highly important. One of the strength of the unit is its outstanding translational activity, which resulted in creating start up companies. The unit made clear efforts to develop a proactive policy for creating emerging groups from young talented scientists. Persuing this endeavor is necessary to ensure the renewal of the critical mass of senior researchers and group leaders. The unit benefits also from a heavy support of staff assistant researchers, a very good throughput of PhDs and participation in international training programmes, and from their participation in European and French LabEx networks. Its publication and patent records are excellent. The reorganisation of the Montpellier universities and CNRS laboratories offers potential opportunities to pool resources and facilities and to promote new researches.

Weaknesses and threats related to the context

The overall organization of the unit still appears unbalanced with one large team that can appear to outweigh the others in the unit and several smaller groups. No clear description of the strategy to determine the future areas of investigation of the unit and to continue to ensure the renewal of the team leaders is provided. In addition, no external scientific advisory board is scheduled to promote the reflection. The development of another very large unit dedicated to host-pathogen interactions, with emphasis on systems biology, very close on the same campus could create a local competition for visibility and resources and this has to be taken into account in the future.

Recommendations

The unit should:

- foster further synergy between the teams to increase their chances to take advantage of the various expertise present on site. Small internal grants could help to support collaborative efforts between researchers within the unit. One additional advantage of such incentives is that it is helpful for non-permanent researchers to show their ability to obtain funding and start to develop their autonomy;

- continue to support the development of the biophysics and bioinformatics oriented team and to reinforce their interaction with biologists;

- encourage the non-permanent (post-doctoral) researchers to participate in career development training, or to organize career days on site;

- encourage scientists to present their work at international conferences, and to write reviews in more generalist journals, to increase their visibility and the visibility of the unit;

- encourage team leaders and PIs to brainstorm together to highlight the forces and specificities of the unit and define the ideal strategy for development, especially taking into account the micro-environment of the universities of Montpellier campus.

3 • Detailed assessments

Assessment of scientific quality and outputs

This is a well-recognized unit for its work on biological membranes with emphasis on infectious processes by various parasites, bacteria and viruses. Their studies aim also at developing original concepts for therapeutic/diagnostic approaches of these diseases and of cancers or autoimmune diseases. Among the major achievements, the unit has described the architecture of the moving junctions that are critical for host cell invasion by Apicomplexan and has described the different steps of malaria merozoite egress from the host erythrocyte. It has analysed the phosphatidylinositol-3-phosphate and the autophagy pathway in parasites. It has deciphered the degradation of the Translationnally Controlled Tumor Protein (TCTP) by chaperone-mediated autophagy. The role of mycolic acid cyclopropanation in the intracellular survival of Mycobacterium was highlighted. Finally, the development of modified and targeted interferons opens new avenues and has clinical potential.

Overall the unit has improved the quality of its output during the last term. Together, the teams have published 267 international peer-reviewed articles (ACL), 8 book chapters and 8 patents. Its productivity is relatively good quantitatively (a mean of 2,4 ACL/FTE/year) and qualitatively (nearly 12, 45 and 35 % of ACL display an impact factor (IF) > 10, 4<IF<10, and 2<IF<4, respectively). Among the most important publications having an IF > 7 and signed as first or corresponding author by a member of the unit, one can mention 1 Science (IF=31), 1 Nat Rev Microbiol (IF=21), 1 Nat Methods (IF=19,3), 1 Adv Drug Deliv Res (IF=12,9), 4 Blood (IF=9,9), 1 Nat Protol (IF=9,9), 1 Current Biol (IF=9,6), 6 Plos Pathogen (IF=9,1), 2 PNAS (IF=9,7), 1 Nucl Acids Res (IF=8,3), 4 Phys Rev Lett (IF=7,9), 1 Clin Cancer Res (IF=7,7), 2 J Control Rel (IF=7,6), 2 Autophagy (IF=7,4) and 1 J Neurosciences (IF=7,1).

Assessment of the unit's academic reputation and appeal

Since January 2008, the unit has attracted two new team leaders supported by the competitive ATIP-Avenir program, who also received a Region Languedoc Roussillon “Chercheur d’excellence” support. One subgroup of team 1 obtained the prestigious label “Team FRM (Fondation pour la Recherche Médicale)”. The unit has also recruited 7 young researchers (2 INSERM, 3 CNRS, 2 MCF UM2). This reflects a positive dynamics of recruitment of young researchers to permanent positions from the three institutions. In addition, 3 INSERM, as well as 2 CNRS researchers and one emeritus university professor joined the unit, coming from other units in Montpellier or other French cities.

The unit teams belong to several networks of excellence such as 5 national LabEx (MabImprov, LERMIT, NUMEV, Parafrap, EpiGenMed), Infectiopôle Sud RTRS, Pôle de Compétitivité, Pôle Rabelais). It also belongs to 2 European Marie Curie ITN (InterMalTraining and FishForPharma).

The unit organized or co-organized 2 international summer schools, 1 WHO Workshop, as well as 1 international symposium on “Quantitative Biology in cytokine signaling” (in Switzerland), as part of a FP7 programme.

The number of researchers invited to present their work at international meetings was not well detailed, but a few invitations to major international conferences like Gordon conferences (Red Cell), American Society of Tropical Medicine and Hygiene, International Congress on Toxoplasmosis were mentioned. Many researchers were invited to give seminars in renowned research institutes in France and abroad.

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

The experts committee has been impressed by the strong interest and efficiency of the teams in translational activities. During the period considered, 8 patents were filed. So far, this has been handled efficiently with the CNRS and the teams have not yet used the new SATT organism. One company (CILOA) emerged from the activity of team 3 a few years ago. It is still hosted in the same building on the campus and employs 8 to 9 persons, with the possibility to support PhD students on CIFRE fellowships. Another company (AZELEAD) is proposed to be created to screen compounds in zebrafish, based on a model already established in the Netherlands, and yet another to develop the activities on the promising immunocytokines generated by team 7. Concerning the translation towards clinics, a phase 2 trial of a new compound found by team 1 some years ago against malaria is ongoing: INNOMAD (Pôle de compétitivité EurobioMed coordinateur Sanofi). A former leader of team 1 will continue to handle this project. In addition, translation to clinics of the immunocytokines generated in team 7 will be pursued in collaboration with the Montpellier hospital and a clinical tumor biology group outside the unit.

Team leaders are also part of the scientific boards of the UM2 and the CEVU, which fosters strong connexions with the university.

During the last term, there were not many activities directed to popularization, no open door days past or planned, no described activities to diffuse science towards scholars or promote science among the young generation in schools.

Assessment of the unit's organisation and life

The unit governance is mediated by a steering committee that includes the director, the deputy director and the team leaders. It meets every other week. The unit discussed the opportunity to hire a Scientific Advisory Board, but this has so far been rejected. The laboratory board (conseil de laboratoire) meets every 3 months. A report is sent to all members of the unit. In addition, it was often mentioned that the director and deputy director had an open door policy, which was widely appreciated.

There is a "règlement intérieur" that defines the rules of the unit. Some researchers or engineers are in charge of common tasks such as Security and Hygiene, Radioactivity, as well as the Imaging and Zebrafish facilities that are open to teams outside the unit. The core funding by CNRS, UM1 and UM2 and 25 % of the grants are shared and redistributed to the teams based on their staff. The unit benefits from very efficient administrative and technical staff. In general, the overall organisation of the unit appears well balanced, although dominated by the largest team (team 1). The decisions to apply for technical support from CNRS or university are collectively discussed but not applications of researchers to CNRS or INSERM national positions. The general feeling was that all categories of personnel, of french or foreign origins, were happy to work in the unit, with a good "unit spirit".

The unit teams have started to work together and this is exemplified by the publication of a few collaborative articles implicating team 1, former team 2 and former team 6, as well as team 1 and former team 2. Unfortunately, it seems that it was too early for publications resulting from collaborations with the biophysics team to come out. Internal collaborations should be further encouraged among biologists and in particular with the biophysics team.

The unit made clear efforts to support the promotions of the researchers, to include them as invited speakers in meetings and as principal inverstigators in grant writing and to push them to defend their "HDR". This will undoubtedly help them to raise their international profiles, to increase their autonomy and to allow them to act as thesis supervisors. Another level of implication could be proposed to discuss the future main directions of the unit.

In addition to the weekly internal seminars, one annual scientific meeting is organized with internal presentations as well as invited speakers and round tables. The unit website has been updated and efforts should be continued in order to keep it updated with news, publications and job offers.

Assessment of the unit's involvement in training through research

The unit is extremely active in teaching. It is composed of 5 Professors and 4 MCF from Montpellier universities who have full time teaching duties. Some of the other members are also very active. Together, they are co-supervising a specialization of the "Health and Biology" Master's program called "Host-Infectious agents interactions". One former team leader was one of the founders and supervisors of the "Biotin" specialization. The biophysics team is very active and organizes seminars at the interface between physics and biology with invited speakers.

During the 2008-2013 period, 31 PhD thesis were defended and all these PhD students have publications. 10 PhD thesis are on-going. The meeting with the representative of the Doctoral School "Sciences Chimiques et Biologiques pour la Santé" ED N°168 confirmed the excellent quality of the PhD training performed by the unit.

The teams are part of a European EST Marie Curie Actions as principal investigators and lecturers. Team 4 participates in the prestigious International Physics of Living Systems network. One team leader is member of the advisory board of the PhD program of the Heidelberg and Mannheim universities. She organized a summer school for PhD students from Montpellier and Heidelberg. Two Marie Curie Action courses were organized (InterMalTraining and FishForPharma). The teams are also part of 5 LabEx networks, and PhD students are therefore supported by LabEx fellowships. All students were encouraged to participate in international meetings and trainings, with this being mandatory for students of Marie Curie Actions.

Assessment of the strategy and the five-year plan

The unit will benefit from the presence in team 7 of the leader of the hematology division of the Montpellier CHRU, which opens the possibility to lead clinical trials in the future. The phase II clinical trial lead by team 1 has to be developed with the support of large companies. The presence of two spin-off or start-up companies will continue to foster the involvement of the teams in translational research.

The unit will continue to focus on trafficking within parasites and infected host cells, in cells during the immune response, with special emphasis on translational approaches to target infected or tumor cells. The teams will no longer have dedicated projects on viral infections. The zebrafish system will continue to be developed as a model for hematopoiesis and immune responses. A description of the complementary expertise that should ideally be attracted via the next job search was not clearly defined by the team leaders nor the unit directors.

The plans to build a "Biology and Health Institute" by gathering other teams in the same building was presented but the scientific basis for such an association was not clear to the experts committee. Other teams in the building work on marine biology, plant infections and neurodegeneration. No on-going collaborations were identified with these teams and the future institute appears more like a way to share common facilities in the building than an evident scientific advantage. No clear links or discussions were developed with other teams working on infectious diseases on the campus, although some are in less than 10 min walking distance. Time should be taken to build an integrated view of the unit and its scientific environment on the university campus.

4 • Team-by-team analysis

Team 1: Plasmodium and Toxoplasma: membrane biogenesis and host cell – parasite interactions

Name of team leader: Ms Catherine BRAUN-BRETON and Ms Maryse LEBRUN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	3
N2: Permanent EPST or EPIC researchers and similar positions	6	6
N3: Other permanent staff (without research duties)	3	3
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**13**	**13**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	16	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	5	5

• Detailed assessments

Assessment of scientific quality and outputs

Team 1 is a large, outstanding team with high international visibility. 11 (+1) faculty members established and continuously adjust a very competitive, original and innovative research agenda to address fundamental problems in molecular parasitology. The team focuses on two related, obligatory intracellular, parasites belonging to the Apicomplexa phylum, *Plasmodium* and *Toxoplasma*. These pathogens share conserved strategies of host cell invasion and intracellular transformation and replication. They also display unique features, such as universal and very

restricted host cell ranges, life-long persistence and continuous re-infections, and very modest and high pathogenicity, for *Toxoplasma* and *Plasmodium*, respectively. The expertise and in-depth analysis of these two biological models is a scientific strength of this team of researchers. Both pathogens are represented equally, and studied by outstanding senior scientists and excellent faculty members. During the past 5 years, the team has mainly focused on:

I) interactions between the parasite and host cell membranes during parasite entry and release;

II) the biosynthesis of phospholipids and the genesis of intracellular organelles (rhoptries, apicoplast, autophagosomes);

III) the roles of protein export beyond the parasitophorous vacuole.

The complex *Anopheles* cycle has been recently established by one senior researcher of the team, further expanding the expertise of the team. Hence, all these research topics fit very well into the unit agenda.

During the period 2008-2013, the team has been extremely productive and has published 101 peer reviewed publications (2.4 ACL/FTE/year with nearly 50 % of the articles' IF > 4) and 5 book chapters, including articles signed by the team members or leaders in first or last author position in top journals (IF>5): 1 Science, 1 Nat Rev Microbiol, 1 Blood, 5 Plos Pathogen, 2 Autophagy, 1 Structure, 1 J Lipid Res, 2 Cell Microbiol, 1 J Med Chem, 1 Mol Microbiol.

Assessment of the team's academic reputation and appeal

Team 1 has an excellent reputation and appeal as attested by its participation in and fundings from two LabEx (EpiGenMed, ParaFrap) and the European Network of Excellence EviMalar (FP7), Antimal (FP6) and BioMalPar (FP6). The team has been recently awarded the competitive label "Equipe FRM". Morevover, the team was very successful in obtaining grants from FRM (2), ANR (5 as PI and 1 as partner), FEDER and OSEO.

Team 1 members were invited speakers at international conferences, involved in the organization of national and international meetings and invited to contribute book chapters.

Notably, two tenured researchers (INSERM CR2 and UM2 assistant professor) have been recruited during the period. This team was also very attractive for PhD (20) and post-doctoral (4) students.

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

The team developed productive interactions with industry, resulting in impressive translational research: phase 2 trial of a new compound against the malaria (Sanofi) INNOMAD (Pôle de compétitivité EurobioMed coordinateur Sanofi). The studies carried out by the team also aim at developing innovative therapeutic treatments and vaccine approaches against these parasitic diseases. Remarkably, industrial partnerships have been established to develop the findings from basic research into prospective products for human use. Together, the achievements in gaining a better understanding of pathogen-host interactions with a focus on biomembranes and in translational research result in a unique and highly recognized research agenda both at the national and international level. In this area of research, team 1 is clearly amongst the leading research teams in Europe.

One of the team leaders was member of the UM2 scientific board 2008-2012 and elected member of the UM2 board of directors 2012-2015.

Assessment of the team's organisation and life

The team is renowned for pooling resources and played a role model for the unit. The team also benefits from core facilities available to the scientific community in Montpellier, including electron microscopy, advanced light microscopy, animal facilities, and post-genomics and proteomics platforms.

The team leaders represent the 3 historical subgroups of the team and one of the co-leaders was the head of the unit. In the future, only two team co-directors will be in charge of the team, representing the two major parasites studied, and one of them will be deputy director of the unit. Hence team 1 has been and will continue to be strongly involved in the management of the whole unit. The team seems to have managed very well the retirement of their historical leaders. The leadership in the team is clear, while researchers were encouraged to defend their HDR, and to act as PI for grant proposals. Overall, the management and life of this large team appeared very good.

Assessment of the team's involvement in training through research

The team is very engaged in undergraduate and PhD training both at the national and international level. Team members are teaching to undergraduate students, participate in the training and evaluation of master's students. The team leaders are co-supervisors of the Master BioMed program «Host and infectious agents». 16 PhD students were trained in the team and were awarded their diploma between 2008 and 2013. 4 PhD students are currently trained.

The team has further been involved in 3 Marie Curie ESTs (FP7), with a coordinating role in the MalParTraining program. A lead role was also in Marie Curie Initial Training Networks FP6 InterMal (2009-2012) and is currently held in the FP7 ParaMet (2013-2016) program. One of the team leaders organized the "Malaria" core course for the InterMalTraining Marie Curie Action PhD students, Jan 2009; and the summer school "Infectious Diseases" for PhD students from the universities of Heidelberg and Montpellier, Oct 2010.

Assessment of the strategy and the five-year plan

The five-year plan wishes to pursue and expand the research axes already developed, aimed at characterizing membrane events of the apicomplexan parasites' life cycle (invasion of host cells, intracellular development and egress from host). The strategy is a logical continuation of the present highly successful research program and is highly likely to be very successful, as it was in the past.

Conclusion

- ***Strengths and opportunities:***

The team is an outstanding team with a high degree of synergism, both in pathogen models and experimental approaches. It addresses fundamental questions in infection biology and focuses on the molecular mechanisms of parasitic infections, develops their findings further and engages in translational research, aiming at innovative therapeutic and prophylactic strategies to combat these important human diseases.

- ***Weaknesses and threats:***

Due to the planned retirement of the former team leader who is an internationally recognized expert in parasite phospholipid metabolism and pharmacological approaches, the continuity in the projects could be perturbed. The large size of the team could at some point interfere with the personal development of individual talented scientists.

- ***Recommendations:***

The team is conscious that they need to develop strategies to ensure that the expertise in parasite phospholipid metabolism will be maintained on site. The possibility for the former team leader to obtain an "Emeritus" status should allow him to follow up ongoing clinical trials.

The proposed recruitment of an expert in *Plasmodium* liver stages will further strengthen the excellence of the team and is highly encouraged.

Team 2: Protein Post-translational Regulation and Bacterial Pathogenicity

Name of team leader: Ms Virginie MOLLE

Workforce

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

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

• Detailed assessments

The team started in September 2010, as the team leader was awarded as ATIP-AVENIR group to join the unit.

Assessment of scientific quality and outputs

Signaling through Ser/Thr phosphorylation constitutes an important regulatory mechanism in various bacteria that has been only recently identified. The team leader is a very dynamic young investigator whose research is focusing on the relationship between protein phosphorylation and virulence of various pathogenic bacteria. The team contributed to several major scientific findings regarding the role of Ser/Thr kinase phosphorylation in regulating : I) mycolic acid biosynthesis in mycobacteria or II) quorum sensing and central metabolism in *S. aureus* as well as in cell division mechanisms (*C. glutamicum* and *S. coelicolor*).

During the period 2008-2013, the team/team leader has an excellent level of production. It has published 26 articles among which 24 have an IF between 3 and 6.4. 10 articles have been signed as first or last author (2 Mol Microbiol, 1 Biochem Biophys Res Commun (BBRC), 3 J Biol Chem, 2 J Bacteriol, 1 Proteomics and 1 Plasmid). Additional publications as collaborator came out in good generalist journals such as PNAS (1), Structure (2), J Biol Chem (7), J Antimicrobial Chemother (1), Antimicrob Agents and Chemother (1). Among the 26 articles, 14 are signed with the leader of the former team 2, who will leave the unit in 2015.

Assessment of the team's academic reputation and appeal

The team leader was awarded an ATIP-AVENIR grant to start her independent group in September 2010, received the CNRS 2010 Bronze Medal and "Chercheurs d'avenir" prize from Languedoc-Roussillon in 2011. The expertise of the team in its field of research is clearly recognized. It benefited from 2 ANR grants as coordinator.

Although invited to give seminars in various institutes, the team leader has not yet been invited to give conferences at national and international meetings. Finally, the team leader is acting as Editor for J Biol Chem.

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

Apart from the ATIP contract, which was also supported by an industrial partner, the team has no interactions with its social, economic and cultural environment.

Assessment of the team's organisation and life

Two senior researchers (1 CR et 1 MCF) from the former team 2 will join the team in 2015. Another senior researcher, an expert in cell biology, will join the team early in 2014. This shows that this recently created team managed to attract permanent researchers, which should help its stabilization and continuous production.

Assessment of the team's involvement in training through research

The team trained one post-doctoral fellow and three PhD students graduated during the period 2008-2013 and 1 PhD student is currently trained. Thus, this is a highly effective research-training environment.

Assessment of the strategy and the five-year plan

The projects developed by the team during the four preceding years were aimed at characterizing the functional and structural properties of different phosphorylation actors, and the associated cellular regulatory events, which control pathogenicity in bacteria. The next five-year plan wishes to expand this research axis by studying:

I) the regulation via STKP phosphorylation of bacterial and host factors important for virulence;

II) the regulation by membrane peptides and search for anti-virulence peptides.

The team also wishes to use an alternative host system (*Dictyostelium discoideum*) to investigate host-pathogen interactions, using a number of different pathogens. This plan is sound, ambitious and seems to be feasible with the arrival of 3 senior researchers.

Conclusion

- ***Strengths and opportunities:***

It is a dynamic young team with ambitious plans focusing on a common mechanistic aspect of bacterial pathogenicity. It has an excellent expertise in bacterial genetics and biochemistry. The team will further be consolidated by the arrival of three permanent scientists.

- ***Weaknesses and threats:***

The field is highly competitive and there is a risk to work on several very different pathogens. The proposed projects require strong collaborations with groups specialized in the pathogenesis of the selected organisms. The small peptides project might not go as far as expected. Overall, the project should be more focused in order to

stay competitive.

- ***Recommendations:***

The team should be more aggressive at publishing in higher impact journals and getting more visible through participation in major international conferences.

The project should be more focused, and a careful selection of the most promising topics in terms of impact should be made. The team has grown very rapidly and care should be taken to consolidate their organization, to establish a clear leadership and to ensure that all members of the team will contribute to the main projects identified.

Team 3: Biogenesis of viral and exosomal particles

Name of team leader: Mr Michel VIDAL

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

The research carried out by team 3 is focused on elucidating the mechanisms of exosome biogenesis in both normal and pathological conditions, as well as on mechanisms of unconventional secretion. The team has explored various aspects of exosome physiology, notably identifying a crucial function for exosomes during the final stage of erythropoiesis. It also studies other aspects of endosomal-lysosomal trafficking and the connections between this trafficking pathway and exosomes. In addition, the team studies unconventional secretion routes involving endosomal-lysosomal pathways and autophagy. The team has thus shown that TCTP (Translationally Controlled Tumor Protein) can be secreted in association with exosomes and degraded in lysosomes through chaperone-mediated autophagy. In addition, TCTP is secreted independently of exosomes, where it induces histamine release from basophils and mast cells and IL-8 release from eosinophils. The pathway by which TCTP is secreted is apparently independent of the secretory pathway because the protein does not contain a signal peptide. The former co-team leader has recently left

the unit to lead a company that he started, and maintains close ties with team 3, providing a strong and productive synergy between a fundamental research lab and industry.

The experimental approaches used are conventional cell biological and biochemical methods applied to mammalian cell culture systems. Over the past 5 year period, the team with 15 ACL (hence 1 ACL/FTE/year) has a good level of production that is compensated to some extent by its quality (mean IF of 5.8). Of the 15 ACL, the team has produced 7 ACL for which members of the team are first or last author, among which 2 ACL in Blood (IF=9,9), which are primary research articles, and 2 reviews in Curr Opin Hematol (IF=4,5). Of the remaining 8 publications in collaboration, 5 have been published in high level journals (IF above 5), i.e. 1 Blood, 1 Cell Death Differ (IF=8,85), 1 J. Neuroscience (7,1), 1 J. Cell Science (6,1), which are primary research articles, and one review in PLoS Biology (IF=11,5).

Assessment of the team's academic reputation and appeal

The team has a very good academic reputation and attractivity both at a national and international level. The team is involved in a number of fruitful collaborations, including those with international partners. It held 4 major grants, including 2 ANR (one as coordinator), 1 Ligue contre le Cancer, and 1 LabEx LERMIT (as partner). The team leader has been invited to high-level international conferences, including a Red Cell Gordon Conference, and to write review articles in high quality journals. The team has further attracted a post-doctoral fellow, a fullbright scholar and 2 PhD students in the past 5 years.

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

The socio-economic involvement of the team is excellent. A former member of the team has indeed exploited the knowledge gained in team 3 to create a spin-off company dedicated to the custom manufacturing of nanovesicles expressing high levels of folded, selected membrane proteins. The team has also taken out a patent.

Assessment of the team's involvement in training through research

The team has been involved in training of students at different academic levels (BTS, L2, L3, M2), as well as supervising and co-supervising two PhD students (one currently in the lab, the other having obtained his PhD in the previous 5-year period). Overall, given the small size of the team, this is an excellent training activity.

Assessment of the strategy and the five-year plan

Over the next five years, the team will continue pursuing the role of exosomes in erythropoiesis, and studies of unconventional secretion. The team will focus studies on the TCTP protein, which is involved in tumor reversion and whose levels are correlated with cancer aggressiveness. The team will elucidate the unconventional secretion pathway of this protein, testing the hypothesis that an autophagy protein-mediated pathway of transferring the protein to the lumen of endocytic/lysosomal compartments results in secretion upon fusion of the compartment with the plasma membrane. The team has established internal collaborations with teams 1 and 2 to develop projects on the role of pathogen exploitation of unconventional secretion pathways.

The exosome-mediated trafficking of the ABCB6 protein during red blood cell differentiation will also be explored, by examining the expression, localization and traffic of ABCB6 in erythroid cells during the early stages of in vitro reconstituted erythropoiesis. This work will be carried out in collaboration with a group external to the unit.

The third aim will be to study unconventional secretion pathways used by pathogens for infectivity. The team has evidence that the bacterium Coxiella may subvert autophagy protein-mediated pathways that they are studying, and will explore thiese connections in collaboration with team 2. In addition, they will investigate the mechanism of Plasmodium falciparum TCTP (PfTCTP) release from infected red blood cells into the extracellular medium. This release of PfTCTP influences the inflammatory response of the host in malarial infection. The mechanism of PfTCTP release from infected erythrocytes will be studied in collaboration with team 1.

Conclusion

- ***Strengths and opportunities:***

The team works on a research topic of general interest in cell biology, with applications to human pathologies and infectious diseases. Its expertise in mammalian cell biology is a strong asset to development of projects within the unit that will focus on host cell responses to pathogen infection. The internal collaboration with team 2 addresses this question and is a very promising direction. The team has furthermore a good network of national and international collaborators, and has attracted a foreign scientist on a prestigious Fullbright fellowship. Moreover, the team is supported by the LabEx LERMIT and has also a strong collaboration with industry.

- ***Weaknesses and threats:***

Permanent researchers within the team have a level of productivity that needs to be improved and is not due to lack of interesting results (for instance, the RhoB project). The team is small, having lost one senior researcher to head a successful spin-off company thus leaving the team now at a critical point where it must rebuild.

- ***Recommendations:***

The team should reinforce internal collaborations. A collaboration with team 2 has already been initiated, as well as the collaboration with team 1 which is in the planning phase. Both of these collaborations are promising and are highly encouraged.

The project aimed at understanding exosome-autophagy connections should be developed. The project on the role of autophagy in ciliogenesis is original and promising, and synergies between this project and the exosome-autophagy project should be pursued. The collaboration with team 2 will explore the role of host cell autophagy pathways in Coxiella infection, and hence will further increases the synergies among projects with an autophagy component.

The team should reinforce efforts to increase the level of its productivity. A priority for the near future should be publication of the important results that the team has generated. The team should then concentrate their manpower on the autophagy/inflammasome/secretion links and projects on exosomes in reticulocytes. All these efforts will help achieve the goal of rebuilding the team and attracting good applicants for PhD, postdocs and permanent positions.

Team 4: Theoritical Biophysics and Systems Biology

Name of team leader: Mr Ovidiu RADULESCU and Mr Andréa PARMEGGIANI

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

Team 4 is a small interdisciplinary team working in biological physics and systems biology. It carries out multi-scale modelling of biological processes, using methodologies from statistical physics, dynamical systems and stochastic processes. These approaches are used to gain a better global understanding of complex biological systems.

Hence, team 4 works in a very dynamic research area on biochemical networks using computational biology. It models mechanistic details of a wide range of systems, including cell signaling, metabolism, and regulation of gene expression. Analyzing the dynamics of complex models are quite challenging. The team has proposed to revisit multiscaleness, an important property of these networks, to model reduction of reaction networks, such as quasi-steady state and quasi-equilibrium approximations, and, applying to practical questions, has provided practical solutions for model reduction of linear and non-linear networks. For instance, team 1 has provided a fully

parametrized kinetic model for the phospholipid biosynthesis network in the apicomplexan parasite *Plasmodium knowlesi*. This model predicts the relative importance of the various reactions in these metabolic pathways. In collaboration with the CBS (Centre de Biochimie Structurale) Montpellier, the team helped experimentalists with complex data obtained from a method based on 2-photon fluorescence fluctuation microscopy, which was applied to two *Bacillus subtilis* promoters that control the switch between glycolysis and gluconeogenesis. Their stochastic model for the transcription events reproduced the observed noise patterns and identified the critical parameters responsible for the differences in expression profiles of the promoters. The model also resolved apparent contradictions between *in vitro* operator affinity and *in vivo* repressor activity at these promoters.

Team 4 also studies different physical principles of intracellular processes. For instance, it has established a framework to model an overall network of interconnected filaments, mimicking the cytoskeleton. Team 4 has shown that although cargo motors achieve procession along microtubules constituting the cytoskeleton in a very complex manner, their behaviours can be described in terms of well-established models. In this field, they have also systematically studied an asymmetric simple exclusion process on complex networks, as a paradigm for transport processes without apparent volume interactions. They have also studied experimental problems; they developed a theory of a resonant effect in protein-membrane coupling taking place in the vicinity of instabilities in tubular lipid membranes under longitudinal force and pressure difference constraints. A second collaboration with former lab collaborator was also fruitfull. They have coupled fluorescence recovery after photobleaching and with mathematical modeling to demonstrate that Syk is actively transported to the centrosomes via the microtubules and that this transport depends on the dynein/dynactin molecular motor.

Team 4 with 33 ACL (3 ACL/FTE/year) and 7 in proceedings and book chapters is higly productive. Moreover, nearly half of these ACL were signed by a team member as last author. Another interesting point of their research agenda is its broad range, from complex theoretical approaches to modelling of biological data and metabolic networks. Their papers reflect this large range, and include high impact factor publications (e.g. 1 PLoS Biology (IF=11,5), 1 PNAS (IF=9,9), 4 Phys Rev Lett (IF=7,9), 1 FASEB J (IF=6,4), 1 Plos Comput Biology (IF=5,5)) carried out mainly in collaboration, to highly specialized journals with lower impact factors, but which are highly recognized in the bioinformatics communities.

Assessment of the team's academic reputation and appeal

The team, although small, is highly attractive with invited professors from Russia (1), Brazil (3), USA (1) and United Kingdom (1). It hosted also 5 PhD students. The team is also critically involved in numerous networks, including two LabEx (Epigenmed and NUMEV), the Health and Biology Cluster Rabelais, and international networks, IPOLs and Evimalar. It has been funded by the two LabEx, the GDR 2588, UM2, and the CNRS Interdisciplinary program. It participated also in two ANR and one AFM proposals. The team benefited further from an EMBO young investigator fellowship. Team members are also deeply involved in scientific life, e.g. as member of CNRS commission CID 51.

Assessment of the team's involvement in training through research

Overall, given the small size of the team, its training activity is excellent. The two permanent members are full time professors with very active teaching duties and commitment to the organization of the university (CEVU). One member is co-director of the “Molecular and Cellular Biophysics Program” of the Master “BioMed” in Biology and Health Sciences and co-director of the “Physics and Engineering of Living Systems”, Master in Physics. 5 PhD students have been trained during this period, with three currently in the group. Two have published 6 and 5 papers respectively.

Assessment of the strategy and the five-year plan

The next five-year project is a continuation of ongoing work. Activities will be strengthened by the new permanent researcher (who arrived in January 2014). Joint projects with team 1 continue, and new ones, e.g. with new team 6, have been initiated. Moreover, funding requests to support these internal collaborations are in progress. The team should continue to reinforce collaborations within the unit and increase the proportion of their work with other teams of the unit. The team has been successful in obtaining fundings from a variety of sources, and must continue this pro-active research.

Conclusion

- ***Strengths and opportunities:***

The expertise of the team is well recognized. The team is scientifically surrounded by many first-class experimental teams. The projects on Plasmodium metabolism and metabolomics integrate data from various high-throughput disciplines to understand structural and regulatory networks of the cell and are quite ambitious, but feasable by the different partners. Similarly, most of the other teams want to work with this team, it is a great opportunity on each side.

- ***Weaknesses and threats:***

The team is composed of a limited number of permanent staff, which are deeply implicated in teaching duties. During the last assessment, it was noted that more interactions with the other teams from the unit should be fostered, and after 4 years, this is still the case (only two common publications during the last five years). Otherwise, its belonging to this particular unit is not clearly justified.

- ***Recommendations:***

A theoretical multidisciplinary team must conserve its specificities, continue to pursue fundamental developments and research, and apply their knowledge to practical biological questions. Its current work is of high quality, and should be continued. Nonetheless, its local interactions should be reinforced greatly with visible valorisation. The team should also have direct formal partnership for grant proposals.

Team 5 : Cytokines, Evolution and Immunity Onset

Name of team leader: Mr Georges LUTFALLA

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	4	3
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)	4	
TOTAL N1 to N6	**10**	**6**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Team 5 results from the scission of a former team into teams 5 and 6, the latter being now supported by an ATIPE-AVENIR (obtained in 2013). In this section, only the output of the participants of “new” team 5 will be considered.

Assessment of scientific quality and outputs

Team 5 has developed tools to study natural immunity in normal and pathological conditions. There is also a model of metastasis, based on the migration of the lateral line primordium and the role of signaling components. A large part of these results have been achieved in collaboration, intra- or extra-unit, due to the development of new models and the progressive development of the zebrafish facility during the period. Its work led, among others, to a better understanding of the structure and function of the interferon system in fish, and of the physiopathology of notochordal infection.

The team has a solid record of publications including 14 ACL (nearly 1 ACL/FTE/year and mean IF of 6) and one book chapter. These ACL were published in general (3 PNAS (IF=9,9)) and specialty (1 Mol Microbiol (IF=5), 1 J Virol (IF=5,4), 1 J Neurosc (IF=7,3), 2 J Immunol (IF=5,7)) journals. Among these publications, 6 have been signed by the team leader as the second last author and only 4 publications are signed as first or last author by a team member. The number of publications signed by the team as first/last author may seem low but the context (development of fish facility, transition to an entirely new and exploratory program, efficient collaborative activity) can explain this situation.

Assessment of the team's academic reputation and appeal

The team has actively recruited through the period, including three permanent positions: three of them (CR1 Inserm, DR1 Inserm and Emeritus professor) from outside labs, 5 PhD and 2 post-doctoral students, testifying to their attractivity. The team has attracted a young researcher who obtained a CR1 position in 2012, who was awarded two major grants, including “chercheur d’avenir” Montpellier and ATIP-AVENIR programs and is now leading team 6.

Researchers participate in international meetings. However, the number of invited conferences are quite low (2). The team is part of the "FishForPharma" Marie Curie ITN "Training network on zebrafish infection model for pharmaceutical screens", and benefited from two ANR, one PEPS CNRS, one FRM, one ARC and one OSEO fundings.

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

Team's involvement into its socio-economic environment with 1 spin-off company being incubated and one project being upported by BIORAD is very promising.

Assessment of the team's involvement in training through research

The team is very engaged in training through research both at the national and international level. The team has been training two post-docs, 4 PhD students, and is coordinating a Marie Curie training program. In addition, the team participates in two international PhD programs and master’s courses.

Assessment of the strategy and the five-year plan

During the last 5 years, team 5 has developed tools to analyze in vivo the process of natural immunity at different levels, taking advantage of the optically clear zebrafish embryo. This has led to four approaches:

1) functional analysis of the cytokine network;

2) visualization of host pathogen interactions;

3) analysis of inflammatory consequences of inflammatory episodes;

4) onset of adaptive (B cells) immunity.

These are clearly exciting areas, in which many questions are unanswered. There is also a fifth theme, which does not appear directly related and concerns the stability of the introns in the mammalian genome.

Regarding themes 1-3, the expertise, inside the team as well as in the unit, is excellent and through interactions (existing networks and collaboration, with the Pasteur Institute for instance), the strength of these approaches is clearly reinforced. Theme 4 was developed during the presentation based on the recent arrival of a DR1 researcher coming from another laboratory in Montpellier and working on B cell responses. Tools are multifold, in terms of strains, host, pathogens, technical tools such as imaging, which is reinforced by existence of team 6, and definitely relevant to the questions raised. There are some minor weaknesses like the unclear role of IL10 in the embryo, some difficulties in promoter cloning and recruitment uncertainties. Threats include fierce competition but the size of the team (4 permanent, plus one emeritus professor), and its quality, should allow them to lead the projects. One minor caveat is the reliance on morpholinos for theme 2. Technologies to develop targeted mutations are advancing at light speed and the future of the morpholino approach is not clear, particularly because they generate partial loss of functions and because of their frequent secondary effects.

Theme 5 is based on the analysis of the degree of conservation of introns in cytokines and aims at studying the dynamics of introns and its control by the Trex1 exonuclease. This approach is based on speculations, and although tools (Trex KO) are at hand in the animal facility and collaborations are set up with experts in the genomics field

(DYOGEN, ENS), it seems to lead to too much diversification considering the tasks team 5 leader will face (unit chairmanship) and the overall limited funding. Therefore, the experts committee did not feel it was a good idea to pursue this area.

Conclusion

- ***Strengths and opportunities:***

The team is competent in cytokine and cellular analysis and tools are already established. The team has further very good local and distant interactions, including participation in networks. Moreover, its workforce has been recently increased with permanent full researchers who joined the team.

- ***Weaknesses and threats:***

The morpholino approach is a highly competitive field and the role of IL10 is not clear. Theme 5 is too risky and leads to too much diversification given the limited number of persons working on each theme and limited funding. In addition, the excellent emeritus professor might not be able to apply for funding because of her status.

- ***Recommendations:***

The team should avoid the juxtaposition of different themes supervised by different researchers. It would be better to identify the research projects of the team that appear as interesting and potentially fruitful, then to increase the manpower dedicated to them. The team should use mutants that are available from the community rather than the morpholino approach. Theme 5 should be given up.

Team 6: ATIP

Name of team leader: Ms Karima KISSA

Workforce

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

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

• Detailed assessments

Assessment of the strategy and the five-year plan

This team emanates from the former team 5 that was split into the new teams 5 and 6, the latter being now supported by an ATIPE-AVENIR obtained in 2013. Team 6 leader joined the former team 5 in november 2011 when recruited as a permanent (CR1 INSERM) researcher, coming from a group of the Institut Pasteur in Paris, which is specialized in the analysis of the development of the immune system in vivo in zebrafish. The main project is centered on the emergence of haematopoietic stem cells (analysis at different level and cancer). Four themes are envisioned:

1) origin and behaviour of HSCs, a very typical SINGLE CELL developmental biology project, which takes good advantage of the zebrafish model (genetics, optical clarity, manipulability);

2) characterization of the endothelial-haematopoietic transition (EHT). This is another excellent developmental biology project, which provides a model for EMT, in which mechanical cues (shear stress) appear critical. All the tools are available, and the project is exciting;

3) role of macrophages in EHT Process. This is a complementary approach, which explores the cellular actors of EHT. Although macrophages do not appear to be involved in the initial steps of EHT, but a later stage, this approach allows to study the macrophage podosome structures in vivo. Furthermore, the later action of macrophages can be addressed;

4) harnessing the EHT for clinical applications. This is based on a screen to identify chemicals able to alter the properties of EHT. This is clearly of high potential and highly ambitious. One point that was unclear was the capacity of the team to screen a large number of chemicals (50000) as well as the relevance of the chemical library chosen. However, this aspect has already been initiated in collaboration with the Institut Pasteur and is no longer in the project, since it was transferred to the start-up AZELEAD that has been created by the team.

Conclusion

- ***Strengths and opportunities:***

The project of team 6 is clearly an ambitious program, well integrated into the unit in terms of possibilities of interactions, and with multiple local, and distant potential interactions. The funding has been secured as Atip-Avenir, and "Chercheurs d'avenir" awards from Languedoc-Roussillon, which should help recruit post-doctoral fellows and PhD students given the high record of publication of the team leader (Nature, Nature methods). The team is also collaborating with high profile international and national laboratories. The recently developed animal facility and the local equipment available are consistent with a good expansion of this team.

- ***Weaknesses and threats:***

The team is faced with its relative small size, the fierce competition and the short duration of the initial funding sources (3 years).

- ***Recommendations:***

The team should develop in size rapidly, as exemplified by the recent recruitment of a CR1 INSERM researcher and a CNRS technician, to ensure continuity in the unique expertise developed by the team. There is a necessity to ensure quickly a transition from starting programs to general competitive grants.

Team 7: Cytokine Receptor and Signaling

Name of team leader: Mr Gilles UZE

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

The research interest of the team for many years has been the complex interplay between interferons and their signaling responses. These cytokines have potent antiviral effects and control the differentiation of dendritic cells. A first axis of research concerns the negative feedback control of signaling via interferon receptors. The team showed that USP18, an isopeptidase that cleaves ISG15, is implicated in IFNAR2 desensitization towards IFN alpha but not IFN beta. A second axis of research concerns the differential activity of IFN subtypes on the differentiation of dendritic cells (DCs). A transcriptomic analysis of the DCs treated with various IFNa or IFNb has been performed. This, coupled with functional studies, led to the characterization of the phenotypes of DCs treated with different IFN subtypes, which show different presentation and efferocytosis abilities. A third axis of research is to develop methods to target interferons, mainly using nanobodies generated in VIB (Vlaams Instituut voor Biotechnologie, Belgium). A very original and efficient idea was to decrease the affinity of the interferons for their

receptors, but fuse them with nanobodies to target cell-specific markers and increase the local avidity. This proved to be very efficient to maximise the effect of the cytokine and minimize the toxic effects and should lead to high-level publications and to promising translational developments.

The productivity (quantitatively and qualitatively) is excellent relative to the small size of the team. The results led indeed to the publication of 19 articles (2,3 ACL/FTE/year) of a mean IF of 7, 6 and one patent was filed. Articles with the team members as first or last authors were published in very good journals: 1 Mol Cell Biol, 2 Plos One, 1 Blood, 1 Biochem J, 1 J Clin Oncol.

Assessment of the team's academic reputation and appeal

The team is recipient of an ARC doctoral contract from an ARC collaborative grant (2007-2009), is part of the LabEx MabImprov (since 2011), of the Carnot Institute CALYM (since 2011) and was part of a FP7 collaborative program (IFNaction, 2009-2012), which reflects its excellent international connections and very good ability to build on national and international collaborations. This however does not translate into very strong attractivity for foreign post-doctoral researchers.

With the arrival of a clinician (PU-PH), the team has developed projects oriented towards the study of interferons in the context of lymphomas and is part of LYSA (Lymphoma Study Association since 2011) and GOELAMS (Groupe Ouest Est des Leucémies et Autres Maladies du Sang since 2009).

The team leader co-organized the international symposium “Quantitative Biology and Cytokine signalling” (Engelberg, Switzerland, 2012) as part of the FP7 dissemination activities of the IFNaction program. However, no invited conferences in national and international meetings have been given.

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

The team filed a patent on targeted mutant alpha-helical bundle cytokines, resulting from a collaborative work. Four additional patents will be taken out in order to adapt the technology to IL1beta, TNFalpha, CXCR1 and an antagonistic interferon. The team intends to found a start-up company to valorize the IP, with the support of the CNRS and Institut Carnot.

Assessment of the team's involvement in training through research

The team's involvement in training through research is very limited with only one PhD student being currently trained. No other student is mentioned for the period of evaluation. Furthermore, the team members have no teaching activities.

Assessment of the strategy and the five-year plan

The perspectives are focused only on the translational activities, which indeed appeared as the most promising direction. Non Hodgkin lymphoma will be targeted with the anti-CD20-IFN developed by the team being proposed as a new class of anti-lymphoma drugs (collaboration with clinicians in the hospital in Montpellier). Targeting the dendritic cells is also proposed as a way to increase their efficiency in their anti-tumoral activity. A collaborative work with a team renowned for its expertise in clinical tumor studies at Institut Gustave Roussy is proposed and shall be fruitful. Preclinical translation will be conducted by the PU-PH member of the team.

Conclusion

- ***Strengths and opportunities:***

The team is very successfull at rising funds and at establishing international collaborations. The translational activities seem to be extremely promising and are well oriented.

- ***Weaknesses and threats:***

The translational activity needs close consultation and guidance by professionals in order to concentrate the efforts and to prevent the team from being absorbed in this task at the expense of its research activities. The PhD training record is not strong. The team does not have very strong interactions with the other teams of the unit. Its national and international visibility is limited.

- ***Recommendations:***

The team should aim at publishing in the very best journals based on the quality of its research. The team is also encouraged to present its excellent results in international meetings to raise its international visibility. Efforts to translate the recent findings into clinical applications are encouraged.

5 • Conduct of the visit

Visit dates:

Start: Thursday, January 30th 2014 at 08.30 am

End: Friday, January 31th 2014 at 05.30 pm

Visit site: DIMNP UMR 5235

Institution: Université Montpellier 2

Address: Place E. Bataillon - Bâtiment 24 cc 107, 34095 Montpellier

Conduct or programme of visit:

Programme of January 30th, 2014

08.15-08.40 am	Presentation of the AERES by the AERES Scientific Delegate (DS) to the experts committee (closed doors)
08.40-09.00 am	Presentation of the experts committee and AERES by the DS to the unit
09.00-10.00 am	General presentation of the unit by the former and future director + discussion
10.20-11.00 am	Presentation of team 1 " Plasmodium and Toxoplasma: membrane biogenesis and host cell–parasite interactions "
11.00-11.30 am	Presentation of team 2 " Protein Post-translational Regulation and Bacterial Pathogenicity"
11.30-12.00 pm	Presentation of team 3 " Biogenesis of viral and exosomal particles "
12.00-12.30 pm	Meeting of the experts committee with the supervising institutions and body (CNRS + UM 1&2) *Audience : experts committee members and DS*
12.30-02.00 pm	Lunch (around posters of teams 1, 2 and 3)
02.00-02.30 pm	Presentation of team 4 " Theoritical Biophysics and Systems Biology "
02.30-03.00 pm	Presentation of team 5 "Cytokines, Evolution and Immunity Onset "
03.00-03.20 pm	Presentation of team 6 "ATIP" (project)
03.20-03.40 pm	Presentation of team 7 " Cytokine Receptor and Signaling "
03.40-05.00 pm	Break (around posters of teams 4, 5, 6 and 7)
05.00-06.00 pm	Closed-door meeting of expert committe members and DS

Programme of January 31th, 2014

08.30-09.00 am	Meeting with the team leaders (without the direction) *Audience : experts committee members and DS*
09.00-09.45 am	Meeting with the technical and administrative staff *Audience : experts committee members and DS*
09.45-10.30 am	Meeting with PhD students and post-doctoral fellows *Audience : experts committee members and DS*
10.30-10.45 am	Meeting with the representative of Doctoral School *Audience : experts committee members and DS*
11.00-12.00 pm	Meeting with the permanent professors/researchers and similar positions *Audience : experts committee members and DS (without the team leaders and direction)*
12.00-02.00 pm	Lunch (debriefing) *Audience : experts committee members and DS*
02.00-02.30 pm	Meeting with direction (past and future) *Audience : experts committee members and DS*
02.30-05.00 pm	Final closed-door meeting *Audience : experts committee members and DS*

6 • Supervising bodies'general comments

UMR 5235 - D.I.M.N.P.
Dynamique des Interactions Membranaires Normales et Pathologiques

Professeur Catherine BRAUN-BRETON
Head of DIMNP

March 26th 2014

Response to the AERES evaluation of UMR 5235 « Dynamique des Interactions Membranaires Normales et Pathologiques »

On behalf of the DIMNP team leaders and staff, I wish to warmly thank the AERES committee for the time and efforts spent in the evaluation of our laboratory and for their very sensitive report that highlights the originality and quality of our research achievements, without skipping a few points deserving our attention and giving some advices that we find useful for our future plans. The report itself does not call for any particular comments from us. As a minor correction: a post-doc and a PhD student (actual and for January 2015) have been forgotten in the team headed by Karima Kissa.

Best regards

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