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

Section des Unités de recherche

AERES report on the research unit

Centre de Recherche Méditerranéen

de Médecine Moléculaire (C3M)

From the

University Nice Sophia Antipolis

INSERM

Mars 2011

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University Nice Sophia Antipolis

INSERM

Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

Mars 2011

Research Unit

Name of the research unit: Centre de Recherche Méditerranéen de Médecine Moléculaire (C3M)

Requested label: Unité Mixte de Recherche INSERM

N° in the case of renewal: U 895

Name of the director: Mr. Patrick AUBERGER

Members of the review committee

Committee chairman:

Mr. Marc BILLAUD, University Joseph Fourier, Grenoble, France

Other committee members:

Ms. Dorothy BENNETT, University of London, London, UK
Ms. Anne-Françoise BURNOL, University of Paris Descartes, Paris, France
Mr. Philippe CHAVRIER, Institut Curie, Paris, France
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Mr. Albert MAROUANI and Mr. Jean-Marc LARDEAUX, University Nice Sophia Antipolis

Report

1 • Introduction

- Date and execution of the visit

The site visit took place on February 15 and 16 at the C3M premises. Yannick Le Marchand-Brustel, the actual Director of C3M presented the C3M past activity. Then, Patrick Auberger, the forthcoming Director of C3M, gave an overview of the C3M projects. During the two days of the visit, each group leader presented his past and future activity. Committee members met local representatives (UNS, Hospital, Dean) and also PhD/post-doctoral fellows, as well as ITA and Scientists working at C3M. Overall, this visit was very well organized; the committee members had sufficient time to discuss in-depth scientific and management questions with the Directors and group leaders.

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

The C3M was created on January 1st, 2008. The laboratory was constituted by 9 pioneer groups that came from 5 distinct INSERM teams located on the Pasteur site in Nice. Five teams moved into the new Archimed building on the Nice Hospital (CHU) site of l'Archet. Then, in January 2010, the 4 other groups joined the C3M. In its new organization, the future Centre (2012-2015) will comprise 11 independent teams. The former Team 9 has left C3M. A novel team (Team 6 headed by Sophie Tartare Deckert) will emerge, resulting from the fusion of part of Team 1 with the group of the unit INSERM U 576 (Nice). A team (Team 9) directed by Paul Grimaldi, who was the former Director of INSERM U 907 on the Pasteur site, applied to integrate into C3M. Finally, a novel team (Team 11) for which the group leader (Michele Trabucchi) has been granted an ATIP/AVENIR contract will join the C3M. Of note, Team 5 will be directed by Mohamed Benhamed in the new C3M format. The Centre belongs to the IFR 50 which includes all the research Units from the Medical Faculty. The Archimed building is a large structure (163m X 35m) that comprises three main facilities : IBiSA imaging platform, cytofluorimetry, animal housing.

The C3M is a multidisciplinary Unit. Three main research lines have been defined:

1. Cell death, differentiation, inflammation and cancers (teams 1-6)

2. Metabolic diseases (teams 7-9)

3. Infection and inflammatory diseases (teams 10-11)

- Management team

The current Director is Yannick Le Marchand-Brustel (DRCE, INSERM) and the Deputy Director is Patrick Auberger (DR1, INSERM). In January 2012, Patrick Auberger will become the Director of the C3M and Jean-François Tanti (DR2 CNRS), currently head of Team 7 will be the Deputy Director. An adminstrative Director (Philippe Rostagno, IE INSERM) assists the Directional staff. The C3M activity relies on several consultative and decisional committees: the steering Committee at C3M composed of all the group leaders, the laboratory council, the general assembly and an International Scientific Board.

- 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)	12	15
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	24	26
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	15	19
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	25	26
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	12	13
N6: Number of Ph.D. students (Form 2.7 of the application file)	24	25
N7: Number of staff members with a HDR or a similar grade	31	32

2 • Overall appreciation on the research unit

- Summary

Overall, the research developed at the C3M is evaluated as being good to outstanding. The general impression of the Committee members was very positive. Yannick Le Marchand-Brustel and Patrick Auberger should be praised for having succeeded in creating this Unit that has now settled down in a brand new building with most of the facilities required to develop biomedical science at a high level. Furthermore, despite the diversity of the projects developed, a real effort has been made to foster the emergence of three main research topics that cover major health issues. The Committee has also been favorably impressed by the conspicuous determination of the group leaders to develop projects in collaboration with clinicians, especially with medical groups located at the L'Archet Hospital. These close interactions will certainly contribute to the dynamics of the Centre.

However, the Committee has also identified some frailties and raised several points of concerns. Firstly, there is a certain heterogeneity in the levels of the C3M groups with some teams reaching the international level while others have more difficulties to achieve this standard. Secondly, the third topic « Infection and inflammatory diseases » comprises only two teams and therefore, this research line appears somehow fragile compared to the two others, even though the quality of team 10 is indisputable (team 11 has just been created and it is too early to comment on its activity). Also, two biological research Centres has been created in Nice, the C3M and the Centre for Research on Cancer and Ageing, which develop related projects on cancer. The C3M is exploring the links between metabolism and tumor development and is focused on specific cancers (melanoma, haematopoietic neoplasms). However, care should be taken to clearly identify the respective domains of investigation of these Centres, since there is an inherent risk of thematic overlaps that might become the source of future tensions and may cast prejudice upon the consistency and the visibility of cancer research in Nice.

- Strengths and opportunities

1. Teams are solid in terms of structure, in most cases they are numerically balanced between staff scientists with permanent positions (CR, DR, lecturers and professor-researchers), ITA, fixed-term contracts (CDD), post-docs and students.
2. The level of publications is good and the C3M has demonstrated a steady scientific production, with the majority of the articles published in the best speciality journals (the average IF of papers at C3M is around 7).
3. The C3M has shown the capacity to attract young and promising scientists as group leaders. The coming of Michele Trabucchi who has been granted an ATIP/AVENIR constitutes a prominent sign of the attractiveness.
4. Several researchers have been recruited during the four past years (4 CR1 and 1 CR2) and 4 CR1 has been appointed as DR2 during the same period of time.
5. Excellent interaction with clinicians allowing the development of transversal programs and conditions of real synergy.
6. High quality of the platforms (imaging, cytofluorimetry). The imaging platform has been labeled IBiSA and an engineer dedicated to this structure has been hired.
7. Competitiveness in raising funds from national, and in a few cases European, agencies.
8. Professionalism of the management, with a clear governance, a defined budget policy, and the presence of an administrative Director whose input is crucial for the functioning of the Centre.

- Weaknesses and threats

1. The C3M needs to strengthen its International recognition. This is not an unusual situation for mid-size Institutes in France and the C3M is a novel structure that has many cards in hand to succeed in this endeavour (see below for recommendations).
2. Although most of the scientific projects are well thought-out, address relevant questions and are based on skillful groups, the Committee feels that too few programs are cutting-edge and venture in unexplored directions. Group leaders should consider how to tilt the balance in favour of high-risk projects without withdrawing from more classical approaches.
3. As mentioned above, the third topic is numerically too weak in terms of groups and should be reinforced to become a high priority of investigation at C3M. The recruitment of Team 11 is, however, an encouraging sign in this direction.
4. The Committee members have noticed a gender bias with regard to the group leaders at C3M. Careful attention should be paid by the steering Committee to this question when new applicants with similar track records are selected in future to join C3M.
5. The coming of Team 9 to C3M did not appear as a top priority the Committee members. Whatever the scientific quality of this group is, the recruitment of non local teams has to be preferred to convene the true conditions of a novel dynamics.
6. Considering that most of the groups at C3M use the animal facility for mouse projects, this platform is strategical for the development of research programs. Thus, it is a high priority to finalize the equipment of the animal facility (at present 1/3 is equipped) and to recruit a full time engineer on this platform.

- Recommendations

The C3M is starting to operate in the Archimed building with all the founding teams. At this stage, the priority of the directorate is certainly to secure the daily functioning of the Centre and to promote the local coordination of research activities with the Hospitals in Nice, the University (UNS), and the other Research Centres in Nice and the PACA region. However, in the medium and long run, the C3M aims at national and international recognition. For that purpose, the head of C3M should strive to recruit high-levels professional investigators, either French but preferably from outside Nice, or foreigners. The Committee members do not underestimate the difficulties of succeeding in this challenge and attracting top scientists, especially foreigners, to a novel Institute in France. However, C3M presents several assets that contribute to its attractiveness. Thus, all available means should be used to attain this goal : i) increase the level of publications with papers in higher IF journals ; ii) increase efforts (novel calls for tender) to recruit new teams since available space has been left for this kind of operation ; iii) stimulate the participation of C3M teams in European networks ; iv) encourage the group leaders to hire foreign post-doctoral fellows ; v) organize an international meeting at C3M once every two years as proposed by the future Director. The Director is also advised to coordinate the research programs at C3M with those of the Centre for Research on Cancer and Ageing, in order to create the proper conditions of synergy. Finally, the head of the research unit is recommended to take into account the weaknesses listed above and to propose concrete solutions.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	15
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	25
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	40/41
A4: Number of HDR granted during the past 4 years	9
A5: Number of PhD granted during the past 4 years	24
A6: Other relevant item in the field *(i.e. number of first and/or last authors original publications in peer review journals)*	

3 • Specific comments

- Appreciation on the results

The C3M is a multidisciplinary Centre that develops competitive research projects in domains concerning major public health priorities: diabetes, cancer, infection and inflammatory diseases. According to the anticipated organization chart of the C3M in January 2012, the Centre will include 128 people comprising 26 scientists with tenured positions (CR/DR), 19 MDs, 39 ITA, 19 other researchers including post-doctoral fellows and 25 PhD students. Since its creation, the C3M has been very productive and published more than 50 articles/ year with an average IF above 6. Most of the teams are involved in strong collaborations with clinicians and several teams have contract with industries, two factors reinforcing the ability of C3M to develop translational research. Also, several patents have been filed since the creation of C3M. Clinicians working at C3M as well several group leaders have teaching duties and the Centre has been successful in attracting PhD and Masters students. The C3M appears to be a good place for the training of students and 16 doctoral fellows have defended their thesis between 2009 and 2010. Taken together, these elements attest to the dynamism of C3M and confirm that this Centre rests on solid foundations to develop ambitious and innovative research projects.

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

The C3M has demonstrated the capacity to attract young and promising scientists as group leaders. The successful establishment of Jean-Ehrland Ricci as a Team leader at C3M and the recent coming of Michele Trabucchi who has been awarded an ATIP/AVENIR grant attest to this dynamic. However, more effort should be put into recruiting foreign post-docs and scientists.

All the Teams have been very successful in obtaining funding from National Charities and scientific agencies (ANR, INCA…). A few groups participate in European networks and ERC funds have not been granted to C3M groups. Teams 1 and 6 participate to Axis 3 (Functional genomics of cancer) of the Canceropole PACA and group leaders coordinate axes of this Canceropole. Team 10 participates in the Infectiopole PACA. Teams 1, 2 and 7 are involved in pre-clinical studies.

Several teams are engaged in active partnership with industries (contracts, programs supported by the Technological Transfer Society ValorPACA, Ciffre fellowship). However, too few patents have been filed during the past contract.

- Appreciation on the strategy, management and life of the research unit

The governance of C3M is detailed in the organizational chart of the Centre. The Director, assisted by a deputy Director are in charge of common tasks of the Unit. An administrative Director supervises the personnel working in the platforms, the glassware washing facility, the maintenance of the building and the directorial secretary. The steering Committee at C3M is composed of all the group leaders, meets monthly and takes decisions on budget and administrative issues as well as on questions related to the C3M equipment and the recruitment of new groups. The laboratory council which includes additional representatives of C3M meets twice a year and a general assembly is called once a year. Finally, an International Scientific Board which comprises 11 international scientists assists the Directors in strategic orientations.

Scientific animation includes monthly medical seminars with MDs from the Hospital, specific meetings for PhD students and post-docs as well as annual scientific meetings which reinforce exchanges between scientists working in the Centre.

Overall, the management and the scientific animation at C3M are based on explicit rules and are adequate for the functioning of this Centre. Since 3 main topics have been defined, it may be useful to identify one group leader for each of the 3 research lines. This action would help to create, in the future, real Departments for each topic and to rationalize the recruitment and other strategic choices by ensuring a balanced evolution of these 3 programs.

- Appreciation on the project

Without doubt the C3M has the potential to take up the challenge to become a recognized Centre in its fields of expertise. The next 4-5 years of this contract will be critical to confirm its ability to become a key player at the national level and to gain scientific credibility at the international level. For that purpose, the Directorial staff of C3M and the group leaders will have to demonstrate a strong will to invigorate the 3 main research lines defined in the Unit project.

The policy for the allocation of resources is defined by the C3M chart. 25% of the recurrent budget is allocated to a common budget to support expenses of C3M, and the rest is distributed to the Teams according to criteria fixed by the Steering Committee and listed in the internal rules. Furthermore, 8% of each grant obtained by the groups (limited to consumables) is deducted and used for the common budget.

As mentioned before, the Committee has found that too few programs are cutting-edge and most of the approaches developed are classical, well defined and solid but lack originality. These high-risk projects should be encouraged because if they pay off, they will certainly contribute to the renown and attractiveness of C3M.

4 • Appreciation team by team

Team 1: Biology and Pathology of Melanocytic Cells: From Cutaneous Pigmentation to Melanoma.

Team leader: Robert BALLOTTI

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	6	4
N7: Number of staff members with a HDR or a similar grade	7	6

- Appreciation on the results

The research is partly in an internationally highly competitive area of the pigment-cell field (MITF signalling and function), yet the team regularly producing original papers in high-profile international journals. Possibly their best-known previous work is on cAMP signalling in melanogenesis, which links to MITF. More recently they have identified a novel MITF polymorphism seen in 3% of melanomas and promoting cell survival. They also took up an interest in cell senescence in relation to melanoma, also a competitive area. Again they published novel work. (However apparently not being continued.) Studies of a new gene for cysteinosis, possibly normally regulating pheomelanin synthesis, have also been novel – this area is important yet relatively poorly understood.

The output seems very commendable. The group was very productive, with 45 publications from 2005-2011, including 10 reviews, and generally in high-impact international journals (IF around 4-10), though not the very highest (e.g. Nature or Cell journals). Original publications included 10 on clinical topics. Team members attended a good many international meetings and regularly gave invited talks. 8 research students obtained their PhD, and there were also 3 patents.

There were 8 collaborative publications up to 2010. The team evidently has strong clinical links and the listed clinicians also have strong research interests and likewise appear at conferences – One of the PI for example is internationally known and respected in dermatology. The team seems to work very well together, with many multi-author publications. There are continuing collaborations with several other C3M teams.

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

This large team has a very solid track record. The leaders are well known in the field, regularly participating in or invited to European and international conferences on pigmentation, dermatology and/or melanoma (e.g. 5 such invitations for the team leader in this period). They also organize some useful meetings in Nice. The team leader is reviewing grants for a number of French and overseas sponsors as well as papers for various international journals such as EMBO J.

The team seems to have some excellent researchers, of whom 3 obtained promotions in the period. The future research is planned so that 4 senior researchers will each direct one sub-project. There are plenty of research students and 2 post-docs currently. Information is not provided on whether any researchers came from abroad.

The team has been very successful in fund-raising, with external research income of 1.3M € in the period, and with 5 different team members as PIs for different grants. None of these appear to be collaborative/network grants, but various international and national collaborations are listed anyway, past and present. These collaborations appear to be binary rather than participation in larger networks. One team member is however a Council member for the European Society for Pigment Cell Research and a member of the editorial board of the field's primary journal, Pigment Cell and Melanoma Research (IF 4.3).

As mentioned, 3 patents have been obtained, with therapeutic or diagnostic relevance. The team will be working with a Biobank and the Nice Dermatology centre, including organizing sequencing of known and novel melanoma proto-oncogenes in excised melanomas, with a view to relating genotype to therapeutic outcomes, in line with recent successful trends internationally in melanoma treatment.

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

Organization and recruitment in this team seem generally excellent and productive. The team has reached maximum size and it is proposed to split off a new team (Team 6) from this one. Full-time INSERM researchers have evidently been encouraged to develop independence and apply (successfully) for grants and promotions. Postdocs have been recruited, and one promoted to CR2. There are many PhD students, who seem to have progressed well, with 8 obtaining their degrees. Atmosphere seems good. Perhaps the only scope for improvement might be in international recruitment and network participation.

These have included participation in international and European conferences and societies as mentioned, and also the organization of conferences themselves in Nice, which would stimulate the interest of the team.

All team leaders at C3M form a council that contributes to planning and organization. Three of the clinicians in Team 1 are also involved in University teaching. Two team members do some teaching in a course on skin biology, and the team trains many PhD and Masters students.

- Appreciation on the project

The future plan retains the previous successful branched structure of 4 subprojects each led by a DR or CR researcher. Future proposed extension of the MITF research using genetic approaches seems strong, and competitive even though MITF research is a highly competitive area. The proposed area of stem cells in melanoma is a topical one, again with several other strong groups already at work, but there seems to be a "niche" for this team. The investigation of mechanistic involvement of MITF seems logical and important. Regarding the theme of metformin (or related drugs) for melanoma therapy: this is interesting, but care may be needed: a recent conference report suggested that metformin can accelerate growth of xenograft melanomas with oncogenic BRAF. (About 50% of human melanomas have this). Still, at the presentation, the team leader proved to be aware of this other work and had not found it repeatable. Lastly the work on function of the newly identified CTNS (cysteinosis) gene seems novel and interesting.

Allocation of resources is defined by the internal rules of C3M accepted by all team leaders at the level of C3M.

The proposed research seems novel and worthwhile. The CTNS project is perhaps the furthest away from what is being done by other groups.

- Conclusion :

  - Summary

Overall the Team 1 project proposal seems original and interesting, and the previous track record is very satisfactory. This is a large and successful team that proposes to split into two teams in 2012 to allow further growth.

  - Strengths and opportunities

Effective and sympathetic management of this large team with very good career progression and a supervisory structure branched into interacting sub-projects. Very good track record; very productive of publications; European and international reputation. Participation in collaborations and scientific societies. Novel and interesting set of proposals.

  - Weaknesses and threats

Weaknesses are minor. There is scope for more international recruitment, and for participation in collaborative and network (e.g. EC or Human Frontiers) grant applications. The group will doubtless aim to obtain publications in top-ranking general journals, not achieved in this reporting period.

  - Recommendations

The Committee recommends to support this productive and renowned group. Participation of this team to International networks would again increase the recognition of its work and may ease the recruitment of foreigner scientists.

Team 2: Cell Death, Differentiation, Inflammation and Cancer

Team Leader: Patrick AUBERGER

- Staff members

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

- Appreciation on the results

The team has made original contributions to the understanding of the molecular basis of resistance of CML cell lines (mostly K562) towards inhibitors of BCR-ABL kinase activity (TKI). This topic is important since acquired resistance to TKI is a prime mechanism of relapse of CML patients under TKI treatment. Several upregulated genes were uncovered that include several tyrosine kinases (Fyn, Axl, Nter-cleaved Lyn), integrins and ECM proteins (SPARC) and possibly mir-451. The team also reported that Resveratrol and Acadesin induce death of TKI-resistant lines, a process associated with autophagic cell death. Transgenic mouse lines expressing Nter-cleaved Lyn were generated, that display a TNFR-dependent inflammatory syndrome similar to human psoriasis. The team also studied BCL-B, an ill-characterized BCL2 family members and shown that its targeted expression in lymphoid cells resulted in a disease resembling multiple myeloma.

Publications are regular and in solid journals (38 publications in 2006-2010) of cancer and leukemia research (Canc. Res.; Leukemia; Oncogene), cell death research (Autophagy, Cell Death & Diff). 1 EMBO J., 1 Faseb J. No manuscript in outstanding journals.

Three patents have been licensed.

Three PhD Thesis have been defended during the 2006-10 period.

The team is structured adequately with a good balance of experienced and young researchers.

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

The team leader was invited to 2 international (Cell Death Society in 2006, 2007) and several national meetings. Team leader gives 1 seminar/year.

The team obviously attracts good students and promising post-doctoral fellows trained locally. It would be important to attract and recruit non permanent researchers from abroad.

The team leader was successfull to raise funds at local and national granting institutions including governmental (INCA) and charities (LNCC, Equipe labellisée 2008; ARC; Fondation de France; Fondation Recherche Medicale). Several partnerships with pharmaceutical industry were established (e.g. Novartis, Pfizer, Galderma, CellGen, GSK).

A number of local (inside C3M) and national collaborations that translate into joint publications; several international contacts are mentioned.

Identification of several mechanisms of resistance to first line treament of CML, thus providing novel targets of potential therapeutic value.

Interesting and promising mouse models for psoriasis and multiple myeloma (for which few or none exist so far) were obtained, that however require further studies and refinements to qualify as pre-clinical.

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

Team organization (good balance of young and experienced researchers on each topic) and quality of structure is good; management is good. All team members publish. Not clear that, besides team leader, lab members participate/communicate to international meetings.

The team leader has been appointed deputy director of the unit created in 2008. He thus played an important part in the organization the Institute, structuration of research at the local level and in preparing the Institute new research program. Additional organisational and administrative tasks are looming ahead for the team leader; special care must thus be taken to reinforce the team in experienced researchers.

As deputy director and likely even more so in all likelihood in the future, the team leader had and will have a critical importance in shaping the scientific policy of the Institute. The quality of the Institute general set-up and maintaining/enhancing the performances of common technological platforms should be kept an absolute priority.

The team leader has made a very important contribution to the organization of the C3M Institute as he is acting as a deputy director since 2008 and is the proposed director for the next term.

- Appreciation on the project

The proposed research project is the continuation of past/ongoing experiments/observations. The announced major objectives can undoubtedly be attained in the next 4 years. The proposed project is thus perfectly feasible. Three directions emerged from past/ongoing research: (i) targeting CML resistance mechanisms; (ii) evaluation of the mouse models for psoriasis; (iii) evaluation of the mouse model for multiple myeloma. Of note, these 3 research lines have little in common. Attention should be given to an inherent risk of thematic dispersion. A solution would be the recruitment of experienced postdoctoral fellows to minimize the risks to loose critical research mass in one of these topics.

Allocation of resources is clearly organized and accepted (contractually) by all team leaders at the level of C3M. The committee is not aware of a team policy.

The three topics currently under investigation have the potential to lead to important findings either as novel therapeutic options (project 1), or to the development/refinement of novel mouse models of human diseases.

- Conclusion :

  - Summary

The team has produced interesting mechanistic views on resistance of CML cells to TKI treatment and generated original mouse models of important human diseases. The research proposal emanates from past/ongoing projects and, with the help of adequate collaborations, the team has clearly the expertise to carry them over.

  - Strengths and opportunities

Strength is obviously coming from the expertise and reagents/animal models developed in past studies, and the network of dynamic internal and external collaborations. The CML project was so far limited to cell lines ; the present research project appropriately propose to extend observations to mouse models of CML and xenografted CML patient material.

  - Weaknesses and threats

Publication level is good; however the overall impact factor is average. International and funding visibility are limited and should be improved.

  - Recommendations

The team should improve attractiveness and visibility by recruiting experienced researchers at a post-doctoral level from abroad (international calls) and through participation to international meetings. The size of the team should be increased especially for the CML project through the recruitment of non permanent researchers (at least 1 postdoctoral fellow and 1 PhD student) to remain competitive. This will become critical especially since the team leader is expected to be heading the C3M Unit as a director, a task which will distract him from every day bench work.

Team 3: Metabolic control of cell deaths

Team Leader: Jean-Ehrland RICCI

- Staff members

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

- Appreciation on the results

The project of this team is to investigate the metabolic control of cell death. The project is based on solid results already obtained by the team, including a paper published in Cell in 2007 reporting that GAPDH protects cell from caspase-independent cell death.

The project is intended to explain how metabolism could impact on cell death mechanisms in cancer cells, a highly relevant question for understanding cell death and chemoresistance in cancer cells. In the past, this team has investigated the cross-talk between apoptosis and metabolism and identified the cleavage enzyme in glycolysis by caspases. Moreover, in collaboration, it has shown that GAPDH regulates caspase-independent cell death by increasing the expression of Atg12, which stimulates autophagy. Moreover, the overexpression of GAPDH is a form of resistance to treatment in chronic myeloid leukemia.

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

The PI is a young investigator (38 years old) who created an AVENIR team in 2006.

The team has good international visibility, highlighted by collaborations leading to major publications (Cell, Immunity, EMBO J, PNAS).

The PI has been successful in raising fundings.

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

The PI has an excellent leadership. He has established a solid team and a very good network of collaborations.

- Appreciation on the project

The project fits in with previous results. The research will be extended to in-vivo models, and part of the project will be dedicated to identifying the molecular signature of caspase-independent cell death.

The project will develop along 4 lines:

1. To investigate the beneficial effects of combining glucose metabolism inhibitors with chemotherapy in pre-clinical models of lymphoma and clinical model of HIPEC (Hyperthermic intra-peritoneal chemotherapy) in patients
2. To uncover the molecular signature of caspase-independent cell death by a proteomic approach
3. To analyze the role of caspase-independent cell death in the occurrence and treatment of B cell lymphoma
4. To identify the role of caspase-independent cell death in vivo during T-cell maturation.

- Conclusion

  - Summary

The proposed project is original and at the cutting edge of the field of cell death.

  - Strengths and opportunities

The quality and originality of the project.

The recognized expertise of the PI in the field of cell death.

Previous publications have been in good journals (Oncogene, Cancer Res, cell Death Differ).

  - Weaknesses and threats

This young and promising team needs to recruit a tenured researcher and tenured technical assistance without delay.

  - Recommendations

The recommendation of the committee is to continue this excellent direction.

Team 4: Inflammation, cancer and cancer stem cells.

Team Leader: Jean-François PEYRON

- Staff members

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

- Appreciation on the results

The team has along standing interest in NFkB and has particularly focused on its role in proliferation and survival of CML and AML cell lines, engraftment of these cells following xenotransplantation in NOD-SCID mice and resistance to BCR-ABL-targeted therapies in vitro. Potentiation of the anti-tumor activity of conventional therapies and inhibitors of the NfkB pathway is also reported in AML patient material and a colon cancer cell line xenografted into immunosuppressed mice. In the colon cancer system, in vivo clones resistant to the chemotherapeutic compound CPT-11 were studied and shown too display higher NfkB activation and evidence found that calpain upregulation can be linked to enhanced NfkB activation and resistance to CPT-11. These studies made use of pharmacological inhibitors of IKK2 (provided by Serono). Dissection of the pro-oncogenic function of NfkB through genetic approaches is proposed in PTEN-/- mice, which have been shown by others to rapidly develop T-ALL/lymphoma (see below). A Pfizer-supported clinical study is ongoing to correlate NfkB activation and calpain 2 expression in colon cancer biopsies, in collaboration with group in CHU Angers.

This work, although not outstanding in its creativity, is important, solid and has clear relevance to cancer therapy.

The observation that pharmacological NfkB inhibition interferes with tumor xenotransplantation lead the team to become interested in the leukemia stem cell field. They thus developed a CML cellular model (K562) in which expression of the Polycomb protein Bmi1, a well known chromatin remodeling and pro-oncogenic factor, can be experimentally repressed by RNA interference. Preliminary data show that down-regulation of Bmi1 impairs engraftment of these cells in mice.

A « private » researcher joined the team to study the influence of S. boulardii on the response of intestinal cells, in particular NFkB activation, to infection by pathogens such as Salmonella, using both in vitro and animal studies. A protection of this probiotic in inflammatory bowel disease has been shown.

10 original publications that directly emanate from the activity of the laboratory in the NFkB field in scientific journals of good/medium impact factors; no publication in high profile journals which is not unexpected given the choice to study the impact of inhibition of a known pro-oncogenic pathway (NFkB) through conventional (pharmacological) approaches; 2 PhD Thesis in 2007, 2009.

Except for one, permanent researchers are drivers or associated with published work; PhD students publish. A number of national and international collaborations are reported, but only few are associated in published work. Several, fruitful collaborations with industry are listed.

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

The team lacks international visibility as judged by the lack of oral presentations in international meeting. In addition, there are few collaborative papers with international partners. The participation as member to INCA and ANR-funded grant indicate a certain level of national visibility.

The team has a high proportion of permanent researchers. Turnover comes from low/medium profile postdoctoral fellows, and PhD students educated in the Nice area.

Clear ability of the team to establish funded collaborations with pharmaceutical industry. The team participated(s) to 1 ANR and 1 INCA grant; 1 "standard" ARC grant during the time period.

Through ANR and INCa, the team participates to national network, although networking added value is not apparent from the scientific report. Contacts with international partners, but few joint publications with them.

The research activity has clear relevance to the potential therapeutic value of NFkB targeting in various cancers and has raised interest by several major pharma companies. Efforts are made to translate laboratory findings in vitro and pre-clinical observations up to clinical investigations, a very positive point.

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

Team organization favors staff researchers (CR) which compose half of the lab personnel in the period. Management is good. Most lab members publish. However, neither team leader nor lab members participate/communicate at a significant level to international meetings (only 1 participation to an international meeting in Nice by team leader is reported).

Team leader intervenes in occasional teaching at Master 2 level at Nice University and Ecole Polytechnique Universitaire de Nice, and belongs to the Advisory Committee of the Ecole Doctorale 85 (University of Nice).

- Appreciation on the project

The research project covers a number of items, most of them unfocused.

NFkB activation has been proposed to be involved in the resistance of CML cell lines to BCR-ABL-targeted therapies (see above). For reasons that are not explained, focus will be put on the role of SOCS1 and it is proposed (on weak grounds) that SOCS1 downregulation in resistant cells might be under miRNA control. Irrespective of the fact that other mechanisms are involved besides SOCS1 deregulation, many other mechanisms can be evoked to explain SOCS1 downregulation; it is not clear why they are not studied.

The functional screen to identify rescue pathways to acute NfkB activation-induced cell death (in the context of a collaborative ANR grant) is interesting but essentially alluded to without details of the role of the team and on how the identified pathways will be followed-up.

The proposed genetic investigation of the function of the NFkB pathway in PTEN-/- ALL is more solid, but also presents caveats. The cross to IKK2 floxed mice will be informative to investigate the requirement for IKK2 activation in this model. It should be noted that the design of the experiment will assay the consequences of IKK2 on tumor initiation, progression and maintenance. The link to IKK2 pharmacological inhibition in established leukemias may not been straightforward. The proposed cross to RelA conditional mice could very well lead to no phenotype due to redundancy with other NFkB members that are known to be activated through IKK2 (NKkB1, Rel) ; this point is not taken into consideration.

It is proposed to use the PTEN-/- mouse model of ALL to look for genes deregulated transcriptionally (what was compared to identify them is unclear), that sustain the leukemogenic process. Two genes are selected for further studies (the CD98 amino-acid transporter; carbonic anhydrase 2) seemingly on the grounds that inhibitors (of poor specificity anyway) are available and show therapeutic effects in preliminary experiments.

It is also proposed to identify markers of leukemia stem cells in this model and to purify them; how precisely and why this will be done is not described. Given the published work of the involvement of Bmi1 in hematopoietic cell self-renewal, the conditional knock-down cellular model described in K562 (see above) has been used to identify a Bmi-dependent signature. It is proposed to study its functional relevance. This is interesting but represents in itself a major task. The involvement of Bmi1 in PTEN-/- ALL will be also be studied genetically in double knockout mice and is hoped to generate models useful pre-clinically (not clear what human disease is actually modeled here).

An unclear purification/crystallographic analyses of the Bmi1 complex is also proposed in collaboration with other Nice labs to screen for new inhibitors.

The mode of action of S. boulardii on bacterial infection and NfkB activation will also be pursued.

Taken individually, several of the projects items are of clear potential interest. It is however unrealistic and illusive to believe they can be carried out in parallel given the size of the team. Strong choices will thus have to be made by the team to develop an in-depth research project on a subset of the proposed items.

Allocation of resources is clearly organized and accepted (contractually) by all team leaders at the level of C3M.

As described, the research project will scratch the surface of many questions, but will very unlikely lead to cutting edge observations. Choices will have to be made (i) that build upon previous observations to insure credibility ; (ii) that investigate in-depth pathways/phenotypes etc. that could lead to original findings.

- Conclusion:

  - Summary

Past activity, mostly based upon pharmacological approaches and collaborations with industry, have led to interesting observations that call for further, in-depth investigations in a subset of the systems investigated so far. The present project is way too wide, unfocused in most parts and the logic behind some of the proposals sometimes hard to understand.

  - Strengths and opportunities

They come from past models, observations and expertise, on which the new projects should be built.

  - Weaknesses and threats

Past activity: lack of international visibility and of publications of excellence.

Present: besides dispersion, several aspects of the project (e.g. search for leukemia stem cells; Bmi1 cellular and molecular biology) are highly competitive fields internationally. Unless a clear niche of opportunity/originality is defined, which is not apparent in the present proposal, their continuation is unlikely to lead to significant conclusions.

  - Recommendations

There is an absolute need to redefine priorities in the numerous objectives of the research project, drop certain items while amplifying the focus on others, while taking into account the existing strength and actual size of the team.

Team 5: Environment, reproduction and hormone dependent cancer: epigenomic mechanisms

Team Leader: Mohamed BENAHMED

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	1
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)	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	1
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results

The project of this team is to investigate the impact of environment on hormone dependent cancers, mainly testis cancer and prostate cancer. This group also studies the impact of environmental endocrine disruptors (EEDs) on non tumoral syndromes such as testis dysgenesis syndrome, including cryptorchidism and hypospadias. Their aim is to clarify molecular and cellular mechanisms of action of EEDs. The major findings of the team are:

1. the identification of vulnerable developmental periods for the testis
2. the identification of epigenetic mechanisms
3. the transgenerational consequences for some ED

More specifically, the group identified alteration of connexin 43 in most tumor cells, alteration of methyltransferases (DNMT3a, b and DNMT1) and a role of Nrb02, an orphan nuclear receptor in the modification induced by DES perinatal exposure. They showed that low doses of bisphenol A promote human seminoma cell proliferation by activating a G protein coupled receptor.

The team has been quite successful with an excellent record in terms of publications (a total of 58, among which 39 with a member of the team as first or last author). Some of these papers are in very high quality journals: 1 Mol Endo, 1 Cancer Research, 1 Envir Health Persp, 1 Mol Endo, 1 JCI in 2009, 1 Hum Pathol

This team is involved in studying the impact of environment on hormone dependent cancers, mainly testis cancer and prostate cancer. They have long standing funding from National research funds.

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

The team is well recognized for its expertise on EEDs and their potential impacts on male tract and dysgenesis syndrome. M Benahmed has been regularly invited in international conferences, consistent with the high quality of the work performed.

During the presentation of the team, a lack of visibility of the other members of the team, other than M Benahmed and the former team leader, raised questions about the future of this team.

Mohamed Benahmed is the main contributor with respect to finding extra-institutional fundings, for which he has been very successful with a total amounting around 800 Keuros, since 2009 (ANR, INCA, PHRC).

The team is involved in several National research programs such as ANR, INCa and PHRC.

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

The head of the team has changed last year going from a professor of medicine to the present team leader who is a full time researcher. An active researcher left the unit because he retired.

The former team leader is the president of the scientific committee of the clinical research department of CHU Nice, since 2002.

Three team members are involved in teaching Reproduction, Histology and Biology in Medical Faculty in Nice, one of them teaches in Master 2, Molecular Endocrinology and Reproductive Biology.

- Appreciation on the project

The project presented is in continuation with present activities. It is interesting and seems totally feasible.

Resources are being collected on a regular basis.

- Conclusion:

  - Strengths and opportunities

1) The clinical relevance of this project in order to identify the role of EED on potential male infertility and cancer.
2) The project is quite ambitious, with important and timely questions. It is mainly based on data obtained by the team in the period presently being evaluated. Therefore, even though, some hypotheses seem risky, preliminary data are supporting the proposed view.
3) The animal models and cell lines to be used are interesting models, and the future approaches combine whole genome and targeted approaches
4) This team and the clinical Unit linked to this team have a recognized expertise in the field of EED and testis development.
5) Many funding in the past years

  - Weaknesses and threats

1) Generation of biomarkers to identify a disrupting activity of chemicals or no chemicals is very interesting but is the least realistic, and particularly far from application to clinical practice
2) There are few full time researchers in this team, with a strong team leader but no clear young investigator; pursuing of this research line might be compromised in the near future.

  - Recommendations

The committee suggests that a young researcher should be attracted into this team.

Team 6: Microenvironment, Signaling and Cancer

Team leader: Sophie TARTARE-DECKERT

- Staff members

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

- Appreciation on the results

Team 6 is a proposed new team and therefore there are no previous results from this team as such. It will comprise former members of C3M Team 1 including the proposed team leader Dr S Tartare-Deckert, and former members of the INSERM Unit 576 Team 2 associated with another DR2 scientist. These two DR2 scientists have collaborated fruitfully in the past, a strong point in favor of the proposed team. They produced some interesting and original findings in this period, separately or together: for example on SYK roles in both melanoma and CLL, and on SPARC in melanoma biology and "mesenchymal transition"; also a range of interesting and original research on roles for various protein tyrosine kinases and other signaling components in leukaemia or related cellular processes like survival.

Both DR2 scientists have strong publication records, often publishing in high-impact international journals such as Blood, EMBO J., Cancer Research and Oncogene. They have 36 first- or last-author papers from 2005-2011, with average IF >7. As stated in the proposal, a future goal should be to get some very high-impact papers (e.g. Nature or Cell journals). In this period 5 research students obtained their PhD degree and many master students were supervised. Both PI regularly gave invited or contributed conference presentations, national and some international.

As mentioned, the new team is founded on productive recent collaborations between these two scientists, one working primarily on melanoma and the other working mainly on leukaemia. Continued collaboration with C3M team 1 is proposed, and a Medical doctor in the team will provide a clinical link and source of human tissue specimens. Both DR2 scientists list various ongoing external collaborations, some international (with groups in Canada, the USA, Spain and Germany). One would look for joint publications as a future outcome.

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

One PI has given a number of invited or contributed conference presentations, including 4 international, and was also invited for institutional seminars. The team leader has also given invited and contributed talks, recently several per year, at national level. Both review for international journals and for French or other research sponsors. This is a reasonable level of external recognition at this stage, though the team leader would benefit from increasing her participation at international level.

With 9 listed members in the proposed team, recruitment seems satisfactory at this stage, though further expansion will be desirable. Probably the recruitment was not from abroad, since the aim is expressed of improving this. The team should recruit more postdocs and (as proposed), tenured researchers.

Both DR2s have been successful in obtaining external funding. The team leader has obtained 4 grants since 2005 (ARC or INCA); also a new grant is listed for 2011-12 for Team 6.

No grant funding is listed specifically for collaborative or network research, but the participants do have ongoing national and international collaborations, as reported above, some over several years. One of the PI has co-organized one conference workshop and was co-ordinator of a research grouping of 5 French laboratories on SYK-family kinases (2005-7). More activities of this kind would be desirable – to improve European and international networking.

No patents listed. The team has had about 5 contracts in this period, of which two industrial contracts, both funding a PhD student.

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

This is new team. The two DR2s have both trained several PhD and many Masters students. One of the PI was jointly responsible for the PETC platform at INSERM U576, and was a team leader there. The team leader has been overseeing a research subproject within Team 1 at C3M.

- Appreciation on the project

The proposal: seems carefully designed, feasible and worthwhile, stemming from the two DR2s' complementary expertise in melanoma and onco-haematology. They have collaborated productively up to now. When working on two types of malignancy at once, ideas from each field could benefit the other, and generate findings with broader validity for cancer. Focusing on interactions with the lymph node, a common growth site for both cancer types is logical.

Study of transendothelial migration seems a valuable idea for understanding metastasis, with establishment of proposed model systems allowing comparison between lymphatic and blood-vascular endothelial cells. These experimental models seem appropriate and original; they could be useful to other groups too. It may be challenging to isolate primary lymphatic endothelial cells, but they have an immortalized line also. This group has also developed animal models that will be used in the project: Syk floxed and Sparc transgenic mice. The Sparc study follows logically from previous work.

The study of SYK function also seems valuable. The researchers have contributed to showing that SYK can act as a proto-oncogene for leukaemia and yet a tumor suppressor for melanoma; elucidation of why this is by analyzing interactions with other tumor-associated pathways in cells and genetic studies of its function in the mouse both appear worthwhile.

The proposed research seems novel and original, the work on transendothelial migration particularly so. Besides testing the roles of candidate molecules, it might also be valuable to develop more global genomic or proteomic approaches to establishing the molecular requirements for this transmigration, for example use of an siRNA library to test for inhibition of the migration in melanoma and leukaemic cells, or microarray comparison of sets of cell lines that cross or do not cross each type of endothelium.

- Conclusion:

  - Summary

This proposed new group is based on a fruitful past collaboration and proposes some interesting and original future research ideas, which make good use of available experience and technology at C3M.

  - Strengths and opportunities

Added value may be expected from the combination of studies of two different malignancies within the common theme of cancer-host interactions. Both DR2s in the proposed new group have very good track records for publications, productivity, recruitment/funding and training of researchers, and have worked well together in the past. The group should (and does) now aim to expand, especially focusing on international recruitment, though obviously more technical support would also be valuable.

  - Weaknesses and threats

The team leader needs to improve her international visibility. Networking at this level could be improved by initiating network-type grant applications with groups in other countries, and by more participation in international societies or interest groups, and organization of workshops or conferences. It will be important to maintain a clear common focus and avoid the group's falling into two separate sections (melanoma, leukaemia); however such a separation does not seem likely.

  - Recommendations

Overall, the committee supports the strategy proposed for the new group and the proposed project.

Team 7: Cellular and molecular pathophysiology of obesity and diabetes

Team leaders: Jean-François TANTI and Mireille CORMONT

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5 (4.15ETP)	5 (4.15ETP)
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 of the application file)	3	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	3
N7: Number of staff members with a HDR or a similar grade	5	5

- Appreciation on the results

The activity of the team is focused on the study of the cellular and molecular mechanisms involved in adipose tissue alterations in obesity and diabetes, and more particularly on the role of inflammatory and hypoxic stresses, and on the association between obesity/diabetes and the occurrence of cancer. The team is recognized for its leading position in the study of the relationships between insulin sensitivity and inflammation in adipose tissue.

Over the period considered the team provided a number of important contributions in the field:

- The implication of the MAPK pathway in cytokine-induced insulin resistance, namely the role of ERK1 and MAP3KA8 (or Tpl2).

- The role of Rab4b in Glut4 trafficking.

- The role of HIF and REDD1 in hypoxia-induced insulin resistance.

- The efficiency of targeting cellular metabolism by the combination of Metformin and 2DG to selectively block prostate cancer cell proliferation.

The scientific production is very good. During the last 4 years 42 papers were published, 19 in collaboration, including 10 with other teams of the C3M) in the best journals of the discipline (Diabetes, Diabetologia, JBC, Cancer Res, Oncogene, Endocrinology, Mol Endocr, Autophagy, …).

3 PhD theses have been defended in the considered period, 3 are ongoing (for 4-5 permanent researchers).

The majority of the publications are signed by several, if not all, permanent team members, reflecting complementarities and an excellent collaboration inside the team.

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

Very good recruitment of PhD and master students. One of the PhD obtained the « Prix de l'Université de Nice Sophia Antipolis in 2010.

2 post-doc were recently recruited on grants already obtained (ANR and INCa), and 3 have been working in the team during the 2007-2010 period.

The different members of the team exhibit a strong capacity to successfully obtain grants from the ANR, INCa and associations to support their project. They are also part of an FP6 European Grant that ended in 2010.

They have numerous national and international collaborations.

The team leaders and the other PIs have only few invitations for plenary lecture in international meetings.

- Appreciation on the scientific strategy and the project

The scientific program is meaningful and well-funded, in the continuation of the results obtained in the past few years. It is focused on new aspects of adipocyte metabolism and adipose tissue function: adipocyte and inflammation, adipocyte and hypoxia, the role of Rab4b in Glut4 translocation, obesity and cancer. It involves an increasing number of transgenic mice models, due to the availability of the animal facilities.

Two original and promising new axes are proposed, on the role of miRNA in adipocyte function and in inflammatory stress-induced insulin resistance, and on the dialogue between adipocytes and prostate cancer cells.

Almost all projects are supported by ANR, INCa or charity grants, and the members of the team are coordinators in a number of them. These grants allowed recruiting 2 post-docs and 2 engineers.

- Conclusion :

  - Summary

It is a very good team which has generated important advances in the field of adipocyte metabolism. The projects are regularly supported by competitive grants (ANR, INCa), and the results published in the best journals of the specialty.

The force of the team comes from complementarities of its members and their fruitful collaboration are attested by their joined signatures on papers.

  - Strengths and opportunities

The team has a long lasting expertise in the study of adipocyte metabolism and signaling, and is a leader in the field of the molecular mechanisms linking insulin sensitivity and inflammation.

As a whole, the project addresses important new aspects of adipocyte metabolism and of the deregulation of adipose tissue function in obesity (inflammation, hypoxia, cancer).

The collaboration with team 8 will facilitate to validate their basic findings in adipose tissue from obese patients.

  - Weaknesses and threats

Permanent members are all senior researchers. The recruitment of a young researcher will allow strengthening the development of the scientific project. Attention should be paid to the number of developed projects in order to remain competitive in a highly competitive field.

  - Recommendations

The team has an excellent national visibility, but efforts should be made to improve its international recognition.

Team 8: Hepatic complications in obesity

Team leaders: Albert TRAN and Philippe GUAL

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	8 (2ETP)	6 (1.5ETP)
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3 (2.25ETP)	3 (2.5ETP)
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	2
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
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	7	6

- Appreciation on the results

The research of this team over the past four years has been focused on the identification of factors involved in the progression of steatosis towards NASH (non alcoholic steatohepatitis). This project was developed through two main axes : (i) one devoted to the identification of predictive markers for NASH, (ii) the other analyzing the contribution of adipose tissue proteins in the alteration of hepatic functions.

The main contributions of the team were:

The constitution of a large cohort of 500 liver biopsies from morbidly obese patients.

The identification of putative biomarkers of NASH by joining genomic/proteomic strategies and clinical approaches.

The discovery that several well-known hepatic proteins (hepcidin, C Reactive Protein and hepatocyte growth factor) are also produced by adipose tissue and could contribute to hepatic alterations in obese patients

The research strategy of the team is excellent combining the identification of potential hits in human tissues by large screening procedures and the study of their functions in cellular and animal models.

The team has a very good scientific production. During the last four years, the work has led to 34 published articles mainly in specialist journals (J Hepat, Hepatology, Diabetes). Among these 34 papers, 15 were directly the production of the team and 19 were obtained in collaborative studies. Of these 34 papers, 6 have been published in journals with an impact factor of greater than 7.0 (Hepatology, Gut, Diabetes), 13 in journals with an impact factor ranging from 4.0 to 7.0 (Diabetologia, J Hepatol, Plos One, Am J Transplant).

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

The attractiveness of the team is very good with the recruitment of a young permanent researcher at INSERM, three PhD students and permanent positions for two engineers.

The team has attracted a lot of funding in the past four years.

The clinical research is very well funded with numerous clinical trials with industrial partners.

Participation to the Hepadip European network (ended in 2010), and numerous national and international collaborations.

Only few invitations in European and international meetings.

Participation of the team to an EU consortium (Hepadip) and to an ANR (French Research Agency) grant.

A project which is in total adequation with the mission of INSERM and which has really clinical perspective in the treatment of NASH. The cohort of liver, adipose tissues biopsies and plasma of obese patient has been transferred from the Hospital of Nice to INSERM.

- Appreciation on the scientific strategy and the project

The project is well structured, associating translational and basic aspects. It is divided into three major aims, two of them being in the direct line of the recent data obtained: 1- developing a non invasive index predictive of NASH; 2- studying the mechanisms leading to the progression from steatosis to NASH, focusing on the role of osteopontin and on adipose tissue dendritic cells. There is a considerable clinical interest in establishing a non invasive index of NASH. The advances already made by the team and the strategy developed are both guarantees for future progress in this field. The study on the development of hepatic complications induced by obesity will be developed using various adequate genetic and nutritional mice models. This evolution of the project is enabled by the availability of the mouse facility, and all models are available.

The new third project concerns the role of autophagy and ER stress in hepatocyte cell death associated with NASH. A reciprocal role of autophagy and ER stress on insulin sensitivity was recently reported, but nothing is known concerning their role on the fate of hepatocytes. This last part is based on cellular and animal models as well as on the use of available human liver samples. It will benefit from the expertise on ER stress of the young researcher recently joining the team.

The clinical part of the project is well funded through different PHRC and clinical trials. Two grants recently obtained (Société francophone du diabète, Société nationale française de gastroentérologie) will allow to support the fundamental part of the project for the forthcoming years.

The projects afford a number of original aspects: the cohorts, the role of osteopontin in the progression of liver disease, a domain where the team has a leading position, a role for dendritic cells in adipose tissue inflammation in obesity, an exciting area which has not been yet explored, and the control of hepatocyte cell death by autophagy and ER stress in an obese context.

- Conclusion :

  - Summary

A very good team that provided important progress in the comprehension of the mechanisms involved in the development of hepatic complications in obesity.

  - Strengths and opportunities

The cooperation between clinicians and scientists on a major problem of public health in the same team provides a unique environment to have access to important cohorts and allows an excellent opportunity for basic and clinical science to progress in parallel. In addition to the morbidly obese cohort the establishment of complementary cohorts, that already begun, will be a major strength of the team.

  - Weaknesses and threats

The project is evolving towards inflammation and immunology, requiring adequate skills in the domain. The recruitment of an immunologist or a tight collaboration with such a team will be important in a near future.

Although the relevance of the co-direction of the team by two team leaders did not seem evident to the committee, the management of the team is efficient as attested by the quality of the scientific production.

  - Recommendations

The team needs to go from an excellent national recognition to a more evident international visibility.

Team 9: Pathophysiological aspects of adaptative responses to metabolic challenges and dysfunctions

Team leader: Paul GRIMALDI

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		0.7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		3
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	1
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	2
N7: Number of staff members with a HDR or a similar grade	0	3

- Appreciation on the results

The new team 9 is an association of one researcher working on the role of PPARß in muscles, another one working on the mTOR pathway in adipocytes and a recently recruited young scientist with a good background in inflammation. The results of each member are presented independently.

The group working on PPARß has developed animal models allowing overexpression or invalidation of PPARß in skeletal muscle (SM). In the past, these models have allowed to demonstrate the crucial role of PPARß in the shift from glycolytic to oxidative metabolism.

In the last four years, this group showed that treatment with a specific ß agonist promotes an aerobic-like exercise remodeling skeletal muscle and heart. They also showed that activation of PPARß (overexpression in muscles or pharmacological activation) induces the myonuclear density of SM.

The other project aimed to determine the role of the mTOR pathway in adipocytes and the possible implication of this pathway in pathologies such as diabetes and sarcopenia. Several results have been obtained but so far remain unpublished in peer-reviewed journals.

The last project is managed by a recently recruited CR1 at Inserm. Most of the results described have been performed during his postdoctoral stay in San Diego. When he arrived in the Inserm Unit in 2007, he has developed a project aimed at characterizing the leukotriene synthesis pathway in adipose tissue from obese patients and the possible involvement of this pathway in obesity-induced inflammation and development of insulin resistance. The publication of these results is expected in 2011.

Overall, the team has an important scientific production (48 papers and reviews since 2006). Among these papers, 7 were directly the production of the team (authors in first or last position) and the other are more collaborative studies. Most of these papers have been published in specialist journals, mainly in the field of nutrition and physiology. The average impact factor is around 4.0 (5.9 (Cardiovascular Res) 3.6 (Pfluger archives), Am J Physiol 4.3)). One researcher has not published.

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

Several fundings from ANR (2) and the Conseil General have been obtained. Most of them have ended in 2010. A very substantial funding fom Fondation Cœur et Arteres is still running but it is now important to apply to other european or national fundings

- Appreciation on the scientific strategy and the project

The description of the projects starts with the tools, which are more or less the same as those developed by the team leader in 2000. Since 10 years, new approaches have been built that might give more flexibility in terms of explored materials, and which should produce new type of information.

Characterization of the PPARß effects in muscle and T cells: It is somehow difficult to understand why it is still needed to perform again a full characterization of PPARß in muscle as many things have now been published since 10 years, particularly by the team leader. The work proposed on mitochondrial density and metabolism carry quite some redundancies with previous reports from the group of Evans et al. Thus, the expectancy in terms of novel findings can be considered as low. Exploring T cell metabolism along each of these lines is certainly more innovative and should be considered as a priority in the new project.

Signaling pathways affected by PPARß in muscle and T cells

Various approaches are proposed to explore the links between PPARß activity and mTOR and insulin pathways. Animal models are planned to be used, but we are still in need of understanding which in vivo challenges will be performed to unravel the altered regulations in mutant animals.

The so far less explored pathways in terms of regulatory activity of PPARß (calcineurin/NFAT for example) are certainly of interest, albeit most of the work is planned in Jurkat cells, which limits the interpretation of the results that will be obtained.

Thus, the feasibility is very high, but the relevance and interest are dampened by the fact that it looks quite re-doing what has been done before, even though different pathways will now be explored, and different materials (T cells versus muscle cells) will be assessed. The description of the project clearly lacks being embedded into an in vivo characterized physiological model where such observations would gain significance.

- Conclusion :

  - Summary

A reconstituted team around three full time researchers with various and complementary expertise in different fields. The project has been refocused on the role of PPARß in metabolism, oxidative stress and inflammation in muscles and T lymphocytes.

  - Strengths and opportunities

All the modified cells and genetic animals to study PPARß in muscles and T lymphocytes are already available in the team.

The recruitment of a young investigator with a strong knowledge in inflammation opens new avenues for this research field. In particular, a link between regulatory mechanism involved in metabolism and in inflammation is presently a very exciting question.

  - Weaknesses and threats

The novelty of the research is rather low, except for the possible new development towards T cells. However, the discussion with the PI highlighted the difficulties that this new development will face (in particular lack of expertise).

It is important to increase the levels of funding and international visibility.

The recruitment of post docs and PhD is essential. The quality and the quantity of the publications must be improved.

  - Recommendations

The project should be reviewed, such as emphasizing the exploration of the links between metabolism and inflammation. This is attempted in the introduction of the report, but is lost in the description of the tasks. However, this new focus would also require establishing tight collaborations with experts in the field of inflammation.

Team 10: Microbial toxins in host-pathogens interactions

Team leader: Emmanuel LEMICHEZ

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	4
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	6	5
N7: Number of staff members with a HDR or a similar grade	4	4

- Appreciation on the results

After 7 years of existence, the team now comprised of 5 staff scientists (DR2, CR1, McUPH and 2 PUPH), 2 postdoc, 5 Ph.D students and 4 research assistants is at a productive stage.

The team is interested in the mechanisms of action of bacterial toxins during host cell infection with an emphasis on toxins targeting host Rho GTP-binding proteins.

One earlier significant finding of the team was the discovery that Cytotoxic Necrotizing Factor CNF-1, which is associated with most uropathogenic Escherichia coli (UPEC) strains, modifies Rho GTPases leading to the accumulation of a constitutively activated form of Rho. This in turn triggers ubiquitin-mediated proteasomal degradation of Rho. This work pioneered subsequent studies by other groups that demonstrated that ubiquitination of Rho is an important general physiological regulatory mechanism of Rho GTPase activity such as during the epithelial-mesenchymal transition.

A follow up has been to look for specific ubiquitin ligases of Rho GTPases using a siRNA based approach. This has led to the identification of the E3 ubiquitin ligase for Rac1, which represents a real breakthrough in the field. The team leader has initiated some productive collaborations both within the institute and outside leading to the identification of the RING finger protein Unkempt as a novel Rac1 downstream effector involved in transcriptional regulation. Evidence for a novel pathway for regulation of Rac1 activity by the tetraspanin protein CD9 downstream of alpha2 integrin has been provided. A biochemical cascade linking ubiquitinated activated Rac1 to the endocytic machinery through the ubiquitin-binding protein Tollip and the clathrin-binding protein Tom1 has been demonstrated with consequence for Rac1-dependent invasion of host cells by UPECs.

Another provocative finding was the observation that in endothelial cells, the EDIN exotoxins of Staphylococcus aureus, which ADP-ribosylate and inactivate RhoA, induce the formation transcellular tunnels allowing exposure of the underlying extracellular matrix and bacterial adhesion. EDIN-dependent mechanisms of entry could be studied in a mouse model of infection using bioluminescent S. aureus strains. A follow-up of this study led to the demonstration that the anthrax edema toxin is also able to induce the formation of transcellular tunnels and to the characterization of the underlying mechanism.

The results implicating S. aureus EDIN in transcellular tunnel formation in cultured HUVECs in vitro have been published in J. Cell Biol in 2006. The roles of EDIN in vascular permeability and in a mouse infection model were published in Infect Immunity in 2009 and 2010. The work on anthrax LT in endothelial cell cytoxicity was published in Cell Microbiol. in 2010. Collaborative projects also led to co-authorship in several publications including the interaction between Rac1 and Ukempt (FEBS J. 2010) and Rac1 ubiquitination (FEBS J. 2008), regulation of Rac1 association with membranes by alpha2 integrin (J Cell Sci. 2010). In addition, more recent studies that led to the identification of the Rac1 E3 ligase and the mechanism of anthrax edema toxin-mediated formation of transcellular toxins, respectively, are in revision process in very high impact factor journals. All together, members of the group published more than thirty peer-reviewed articles including several reviews with high impact (Nat Rev Immuno. 2010).

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

The group leader has established an excellent national and international network. He is invited to international conferences (ELSO 2008 (co-organizer of a session), EMBO meeting 2008,...).

The group appears to be an attractive place for predoc and PhD students.

The PI has been successful in raising external funds from local (InfectiopoleSud) and national agencies (ANR, ARC, PHRC).

The team has collaboration with foreign groups and has established a very good network with national and international groups.

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

The excellent young, energetic investigator has a strong leadership potential.

The team members all have clearly defined projects.

The research is really original and the projects are clearly cutting edge.

- Appreciation on the project

The research team will focus on two broad topics related to UPEC-encoded CNF1 as a Rho activating toxin and the mechanisms underlying S. aureus' Edin-mediated formation of transendothelial macroaperture.

Project 1. Role of CNF1 in infection by UPECs. The team will investigate potential interplay between CNF1 and UPEC-encoded proteins including alpha-hemolysin (HlyA) toxin, which may antagonize CNF1's role in bacterial persisitence in the blood by targetting macrophages, and the ABC-transporter ATPase HlyB known as the HlyA transporter. In addition, candidate E3-ligase for Rho proteins have been identified through a siRNA-based screen, which will be further characterized for specificity and function.

Project 2. Mechanisms underlying EDIN-induced macroaperture formation. The formation of transcellular tunnels induced by EDIN toxins raises several interesting questions such as the mechanism underlying the generation of negative curvature and a potential role of the cortical actomyosin cytoskeleton that will be explored in collaboration with biophysicists.

The proposed projects are clearly cutting edge and original.

In addition and not directly connected to the main expertise of the team, MDs who are affiliated to the team will be involved in developing projects both in the virology and parasitology fields. These include projects on the pro-tumorigenic property of the E6 sequence of human papilloma virus, and on the mechanisms underlying persistence of the parasite Leishmania infantum.

- Conclusion:

  - Summary

A young, dynamic team combining modern cellular microbiology and biochemistry to ask relevant fundamental questions concerning host-pathogens interactions and mechanisms of cell infection.

  - Strengths and opportunities

The leader has proven an excellent scientific leadership. He has a clear vision on how to run his research program, asks original questions and applies innovative and multidisciplinary approaches.

The project is exciting and ambitious. The leader was able to establish a very good network.

  - Weaknesses and threats

It is the only team working on host-microorganism interactions within C3M that may be limiting. However this point should tempered owing to excellent scientific production of the team during the past period.

  - Recommendations

The recommendation of the committee is to continue in this excellent direction.

Team 11: miR-155 biogenesis and function in macrophages

Team leader: Mr Michele TRABUCCHI

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
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)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)		
N7: Number of staff members with a HDR or a similar grade		

- Appreciation on the results

The project leader is an Italian scientist of 40 years old. After his PhD defended in 2002, he spent 2 years at the University of Genoa, (Italy) and then 7 years in an expert laboratory in California at UCSD, first as a post-doc and then as an Assistant Project Biologist. His application for an ATIP/AVENIR grant has been selected and M Trabucchi will join the C3M in 2011.

Good track record with 20 publications in peer reviewed journals. 1 Nature in first author in 2009, 1 FASEB J and 1 Cell Death Diff in co-first authors and 1 PlosBiol in second author

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

M Trabucchi has successfully been granted an ATIP/AVENIR grant as Young group Leader (2011-2014)

The group leader has been invited at several international meetings to give a presentation.

Collaboration with his former UCSD laboratory, another group at Scripps, (San Diego) and other groups, either in C3M or abroad.

- Appreciation on the project

The research program is the continuation of the project the team leader has developed in his former laboratory. His investigation has led him to discover that the RNA-binding protein KSRP binds specifically to the terminal loop of miRNA and participates with the Drosha and Dicer complexes to the biogenesis of a subpopulation of miRNA. Among these miRNA, KSRP is required for the maturation of miR-155. Previous work has provided evidence for the role of miR-155 in the immune system, since miR-155 knock out mice are immunodeficient, due to a defect in B and T cell functions. Furthermore, a series of results suggest that miR-155 plays also a role in macrophage. Consistent with these observations, M Trabucchi has reported that LPS treatment promotes the binding of KSRP to miR-155 in macophage. Based on these findings, the project will comprise 4 main research lines devoted to the role of miR-155 in this cell type :

1) Characterization of the molecular complexes involved in miR-155 biogenesis

2) Identification of the post-translational modifications that are required for the switch between the repressor and activator complexes controlling miR-155 maturation

3) Delineation of the signaling pathways regulating the transition between repression and activation of miR-155 upon inflammatory signals in macrophages

4) Identification of miR-155 mRNA targets

The project is well focused, the questions are sound and the experimental design is carefully thought.

The question of the molecular mechanisms that control miR biogenesis in response to extracellular signals is an emerging theme that is certainly going to provide novel insights on the relations between environment and genome expression. Thus, this project is relevant, focused, and well defined an opportune.

- Conclusion :

  - Summary

A promising group leader who has been granted an ATIP/AVENIR contract. The research project is timely, well focused, deals with an important question and the expertise to develop it is either part of the past experience of the team leader or will be carried out in the frame of collaborative projects with expert groups, either in C3M or abroad.

  - Strengths and opportunities

Strong expertise of the leader project in this biological domain. Good track record of the applicant.

Quality of the scientific project

This project will find logical collaborations with C3M groups, such as Team 7 and Team 4.

  - Weaknesses and threats

Like each team leader in the position of setting up his own group, the team leader will have to face a delicate transition period during which he will have to hire competent collaborators, secure his own position (CNRS or INSERM or MCU ?) and develop his research project in a competing field. However, this is not a weakness but rather the challenging situation that every new team leader has to cope with.

  - Recommendations

It is important to secure a technical support from C3M (technician or engineer) which should help this team setting up its scientific activity.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
CENTRE MEDITERANNEEN DE MEDECINE MOLECULAIRE	**A**	**A**	**A**	**A**	**A**
CELL DEATHS, DIFFERENTIATION, INFLAMMATION AND CANCER [AUBERGER-AUBERGER]	A	A	Non noté	A	A
BIOLOGY AND PATHOLOGY OF MALANOCYTIC CELLS: FROM CUTANEOUS PIGMENTATION TO MELANOMA [AUBERGER-BALLOTTI]	A	A+	Non noté	A+	A+
ENVIRONMENT, REPRODUCTION AND HORMONE-DEPENDENT CANCERS [AUBERGER-BENHAMED]	A	A	Non noté	A	A
PATHOPHYSIOLOGICAL ASPECTS OF ADAPTATIVE RESPONSES TO METABOLIC DYSFUNCTIONS [AUBERGER-GRIMALDI]	B	B	Non noté	B	B
HEPATIC COMPLICATIONS IN OBESITY [AUBERGER-GUAL-TRAN]	A	A	Non noté	A	A
MICROBIAL TOXINSIN HOST PATHOGEN INTERACTION [AUBERGER-LEMICHEZ]	A+	A+	Non noté	A+	A+
INFLAMMATION, CANCER AND CANCER STEM CELLS [AUBERGER-PEYRON]	A	B	Non noté	B	B
METABOLIC CONTROL OF CELL DEATHS [AUBERGER-RICCI]	A+	A+	Non noté	A+	A+
CELLULAR AND MOLECULAR PATHOPHYSIOLOGY OF OBESITY [AUBERGER-TANTI]	A	A	Non noté	A	A
MICROENVIRONMENT, SIGNALING AND CANCER [AUBERGER-TARTARE]	A	A	Non noté	A	A
MIR-155 BIOGENESIS AND FUNCTION IN MACROPHAGES [AUBERGER-TRABUCCHI]	Non noté	Non noté	Non noté	A+	A+

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

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

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

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
  - **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
  - **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
  - **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
  - **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
  - **SVE1_LS5 Neurosciences**
  - **SVE1_LS6 Immunologie, Infectiologie**
  - **SVE1_LS7 Recherche clinique, Santé publique**
- **SVE2 Ecologie, environnement**
  - **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
  - **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
  - **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

Présidence et
Services Centraux

Université Nice SOPHIA ANTIPOLIS

Nice, le 11avril 2011

Affaire suivie par :
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N/REF : 2011-1757

AERES
M. Pierre GLORIEUX
Directeur de la section des Unités
de recherche
20 rue Vivienne
75002 – PARIS

Ref : Rapport d'évaluation S2UR120001732 - Centre Méditerranéen de Médecine Moléculaire - 0060931E

Monsieur le Directeur,

Faisant suite au travail effectué par le comité de visite de l'AERES et du rapport d'évaluation émis sur l'Unité de Recherche « Centre Méditerranéen de Médecine Moléculaire » portée par l'Université Nice Sophia Antipolis, vous voudrez bien trouver ci-joint la réponse que nous désirons apporter à ce rapport.

Celle-ci comporte à la fois quelques éléments correctifs factuels et des observations de portée générale visant à apporter des réponses globales aux recommandations très positives faites par le Comité de visite que nous remercions pour son travail constructif et détaillant ces réponses au regard des activités de chacune des 11 équipes de recherche concernées.

Vous en souhaitant bonne réception,
Je vous prie de croire, Monsieur le Directeur, en l'expression de mes sentiments distingués

UNIVERSITE DE NICE - SOPHIA ANTIPOLIS
1.1.1996

Pour le Président de l'Université de Nice-Sophia Antipolis et par délégation,
Le 1er Vice-Président

Pierre COULLET

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Réf : C3M/ /2011/001

Nice, 4/4/11

Dear Madam, Sir, to whom it may concern,

Please find enclosed our answer to the evaluation report raised by the AERES committee regarding the centre Méditerranéen de Médecine Moléculaire (INSERM U895/C3M).

I would like to express our sincere thanks to all the members of the AERES committee for the impressive work they made regarding this evaluation and their detailed report.

You will find first in the forthcoming pages the answer regarding the general evaluation of the center (pages 1 to 3) followed by the specific comments of each of the 11 applying teams (pages 4 to 10).

We thank you in advance for your consideration and are looking forward to hearing from you soon

Yours sincerely,

Patrick Auberger

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Université Nice SOPHIA ANTIPOLIS
FACULTE DE MEDECINE

OVERALL EVALUATION OF THE C3M

The direction of the Centre Méditerranéen de Médecine Moléculaire (C3M) thanks the AERES committee for the positive feedback and pertinent recommendations they gave us regarding our project.

The committee made a series of relevant points and recommendations to the institute, that we would like to discuss below. i.e

1)- the fragility of the third topic essentially due to the fact that it will comprise only two teams
2)- the need to clearly identify the respective domains of investigation of C3M and IRCAN
3)- the fact that although most of the projects are well thought-out and address relevant questions only too few programs are cutting-edge
4)- the recruitment of new groups at C3M
5)- the coming of team 9 to C3M did not appear as a priority for the committee members
6)- the completion of the animal facility at C3M.

In addition, 4 other points have drawn our attention

i) increase the level of publication in very high impact factor journals
ii) stimulate the participation of C3M in European networks
iii) organize an international meeting at C3M
iv) encourage the team leaders to hire foreign post-doctoral fellows

Main points

1) The recruitment of a new team to reinforce the « Inflammatory and Infection » topic will be one of the main priorities of C3M. As mentioned in the document, an international call will be launched in July 2011 to attract a foreign team (likely on an AVENIR/ATIP contract). At this occasion, a special care will be made to limit the gender bias noted by the committee, but it should be noted that in the last call most of the answers were from male. Together with the arrival of new team 11 this will constitute a solid base for the development of this important and highly efficient topic of C3M. In the same line, the «Metabolic Diseases » topic will have to be also strengthened in the future (please see also point 5).

2) This is indeed a crucial point. At present, we are not sufficiently aware of the projects of all the teams of IRCAN and it is worthwhile to remember that when C3M was created in 2008, there was no plan for a future Cancer Institute at the Pasteur site. Eric Gilson and I met a first time in January 2011 to discuss about the future development of the platforms in Nice. We have also decided to create common meetings gathering researchers, post-doc and docs of both centers to better identify who is exactly doing what within both institutes. This will allow to minimize the risk of thematic overlap and to promote the best synergy between the centers. To our knowledge there is no evident overlap regarding the cancer themes at C3M and IRCAN. Regular meetings between both directors will be a guarantee against possible problems and also the occasion to develop collaborations between both institutes.

3) We agree that cutting-edge programs would increase the national and international recognition of C3M. The question here is who is going to develop risky projects. In any events it cannot be PhD students since we don't want them to be at risk to have no publication during their PhD. Therefore each team is expected to recruit post-doctoral fellows that will be able to take sufficient risks to develop original and cutting-edge projects. Ideally, in case of sufficient critical mass the project of a team should

be a pertinent balance between well-thought classical approaches (PhD) and more risky research (Post-docs and PIs)

4) This relies to point 1. As mentioned in the project we will have to recruit one or two national or international high-level professional investigators in a near future. The call we published and which was successful in recruiting M Trabucchi aimed at reinforcing themes 2 and 3 essentially.

5) We noted that the AERES committee has important concerns about the scientific project of team 9 (team 9 has wished to answer these criticisms, please see pages 9 and 10 of the present document) and that the committee does not recommend the coming of this team in C3M as a priority. The coming of this team was an opportunity to gather teams working on metabolic diseases in Nice at C3M. Our institutions (INSERM and UNS) favored this logical opportunity to regroup the metabolism field at C3M. Further the arrival of team 9 should compensate the lack of success of the Avenir group working on glucose transporters (which thus decided to leave Nice) to avoid the weakening of the « Metabolic Diseases » topic. However, due to the relatively negative evaluation of team 9 by the AERES committee, it is likely that this team will not be created by INSERM. If it is indeed the decision of our institution, the steering committee at C3M has decided that the coming of team 9 at C3M will not be possible. Indeed, our internal policy does not recommend to give a financial support to a team with an unfavorable evaluation. The researchers of team 9 were aware of this rule when they applied to join the C3M. However, we have already met some of them to find adequate solutions for their integration in C3M existing teams, if it is their wishes. We also agree with the recommendation that the recruitment of one or two non-local teams has to be preferred in the future to strengthen both the « Inflammation and Infection » and « the Metabolic Disease » topics (Please see also point 1).

6) The new development of the animal facility at IRCAN early in 2012 will necessitate that C3M welcomed all the mice currently housed at the Pasteur site during a 18 month intermediary period. Therefore, as highlighted by the committee, it is a priority to finalize the equipment of the C3M animal facility in order to welcome the 4000 mice currently present on the Pasteur site site. The local and national institutions are aware of this problem. The recruitment of a full time engineer (UNS) is occurring in 2011.

Other points:

i) As recommended by the committee all the teams will eagerly try to increase their level of publication in high impact journal. This supposes to be able to take risks in some of the themes of the center. This could be achieved by launching cutting-edge programs and developing new animal models and original technological approaches. Of note, some teams at C3M have currently papers in favorable revision in high impact journals (Nature, Gene Dev and Dev Cell).

ii) This is doubtless a goal to attain in the future. Some teams at C3M have already obtained European contracts and/or have international contacts for training of foreign students. Efforts will be made by the direction and the team leaders along this line.

iii) As stated in the document, this point was a strong wish of the direction. It will also be a priority of the new direction team. Our goal is to organize the first international C3M meeting in 2014.

iv) The group leaders would be delighted to attract post-doctoral fellows. However, it should be stressed that it is not an easy task, and the international call that team leaders recently did in nature (Team 7 for instance) was not successful in providing good quality foreign postdocs. The French candidates undoubtedly presented with higher quality. This should change in a near future with the expected increase in the international visibility of C3M.

TEAM COMMENTS

TEAM 1 : Biology and pathology of melanocytic cells : from cutaneous pigmentatioon to melanoma

Team leader : Robert Ballotti, DR1, INSERM

I would like to thank the committee members for their constructive discussion and valuable comments that we will obviously take into account.

I just want to clarify three points.

First, contrary to what is mentioned in the report, we did not abandon the project on senescence. We continue this line of research by focusing on the senescence-associated secretome of melanoma cells. Indeed, we have a manuscript in revision, showing the pro-tumor effects of senescent melanoma associated secretome.

Second, we fully agree that it would be stimulating and beneficial for our group to recruit foreign researchers and participate in international networks. To this aim, we are involved in a European application comprising groups from UK, Iceland, Finland and France (PEOPLE MARIE CURIE ACTIONS-Marie Curie Initial Training Networks (ITN)-Call: FP7-PEOPLE-2011-ITN: PhenoMel, Phenotype Switching in Melanoma).

Third, it should be mentioned that Thierry Passeron, a young PU-PH in Dermatology who is currently working in team 1 has been preselected for an AVENIR/ATIP position in March 2011.

TEAM 2 : Cell death, differentiation, inflammation and cancer

Team leader : Patrick Auberger

We thank the AERES committee for the thoroughness of the evaluation of our team and also for its pertinent recommendations. As recommended, we will be particularly vigilant to all the points stated by the committee. We would however like to offer already some comments on several points raised in the committee report.

Appreciation on the results

1- Publications are regular and in solid journal (EMBO J, Cancer Res x 5, Leukemia x 3, Oncogene x 2, Cell Death Diff x 2, Autophagy x 2, Faseb J, Haematologica….).
The total number of publications authored by one or several members of the team is 55. As stated 39 publications emanate from the team's work, a very good score since our team is relatively small compared to other teams at C3M. I would also like to mention that at the beginning of this quadriennal in 2006, I was the only researcher present in the team. On a total of 39 publications produced during the 2006-2010 period, 18 had an impact factor between 7 and 9 (49%) and 14 between 4 and 7 (36%). In addition, these numbers dont take into account the manuscripts published by members of the team outside of the team in the same period of time (Cell, Mol Cell, Blood, PNAS). As suggested, we will do our best to increase further the quality of our publications in the future, by introducing a dose of risk in our research (mainly via the characterization of original and promising animal models of human diseases such as psoriasis and multiple myeloma) as highlighted by the commitee.

Appreciation on the strategy, management and life of the team

1- It is not clear whether besides the team leader, members communicate/participate to meetings.
As mentioned, team 2 comprises two young researcher : one CR1 INSERM, recruited in 2007 and another one recruited in 2010. Both have participated to international meetings (ICDS, Pekin in 2008 and ASH, Orlando in 2010 for the first) and (ICDS, Rio de Janeiro in 2006, ICDS, Nice in 2007 and the Cell Death Meeting, Luxembourg in 2010 for the second one). In addition, the first one was the recipient of the Joseph Amalric prize from the Ligue Contre le Cancer in 2007 and the second one, the recipient of the Charles Grupper prize from the French Society of Dermatology in 2010.

2 - Special care must be taken to reinforce the team in experienced researchers
We do agree with this recommendation. Team 2 has been effective in recruiting young scientists (3 in the 2004-2010 period) which attests of the attractivness and the solidity of projects developed. Arnaud Jacquel is currently applying for a CR position to secure one more researcher on the first aspect of the project (Topic 1), as recommended the committee.

3- The team leader has made a very important contribution to the organization of C3M
As stated by the committee, managing both the C3M and Team 2 will be an important challenge but such a situation is common in nearly all institutes (please see the governance of IBDC, IPMC and IRCAN in Nice for instance, where all the institute directors are also team leaders). In addition, the institute is now well structured and also benefits from the presence of an administrative director and a scientific deputy director who will be both highly implicated in the governance and management of C3M.
Regarding team 2 organization's it is expected that each of the three topics will be strengthened by the presence of a PI in 2012. This is already true for topics 2 and 3. In September 2011, team 2 will also benefit from the arrival of 2 new PhD students (for topics 1 and 3) and an engeneer for 3 years (FRM funding of 250kE in 2011-2013) regarding topic 2.

Appreciation on the project

1- A solution will be the recruitment of experienced post doctoral fellow
It should be noted that team 2 comprises 2 post-docs (not mentioned in the staff member table of the AERES report). Nevertheless, we do agree with the suggestion of the committee and will try our best to secure at least one more post-doctoral fellow (preferentially from abroad) (please, see also point 2 above).

2- The three research lines have little in common
Obviously, we do think that there are strong connections between topic 1 and 3. Topic 2 is more related to inflammation and is also connected to the first topic (study of the role of Src kinases). Indeed, two of the three topics (the CML and Bcl-B themes) are actually investigating the role of cell death, autophagy and differentiation in leukemogenesis using CML or multiple myeloma mice models, with very close conceptual and technological approaches. The second topic on Lyn also benefits from the work made on the role of Src kinases (Fyn, Lyn in CML) and investigate the role of the tyrosine kinase Lyn in inflammation and skin homeostasis.

Conclusions
Weaknesses and threats
The productivity (especially when taking into account the size of the team) and impact factor of team 2 are among the best of C3M. Regarding funding, the team has collected more than one million euros in the 2008-2011 period. Nevertheless, we do agree with the committee that we have to publish part of our work in high impact factor journal and to increase our international visibility. Please also refere to point 1 «appreciation on results».

TEAM 3: Metabolic control of cell deaths
Team leader: Jean-Ehrland Ricci, CR1 INSERM

We would like to thank the committee for their evaluation and for their nice recommendations.

TEAM 4: Inflammation, cancer and stem cells
Team leader: Jean-François Peyron, DR2 INSERM

We thank the members of the AERES committee for their evaluation of the team. This letter intends to give additional elements on several issues raised in their report.

Appreciation on the quality of the links with international partners :
There are few collaborative papers with international partners
Most contacts with international groups concern ongoing projects which explains the few joint publications to date.

Appreciation on the project :
NFkB activation has been proposed to be involved in the resistance of CML cell lines to Bcr-abl-targeted therapies. For reasons that are not explained, focus will be put on the role of SOCS1.
As it was presented, we observed in 2 imatinib-resistant cell lines and in several imatinib-resistant patients samples, a lack of expression of SOCS1, a major negative regulator of NFkB, which could explain the abnormal and excessive NFkB activation, supportive of the enhanced leukemic cell survival. We have experimentaly ruled out several obvious “classical“ possibilities that could have explained the absence of SOCS1 (gene silencing, excessive degradation of the protein) and we are now exploring the potential implication of a deregulated miRNA species, that we believe is an interesting cutting edge possibility.

The functional screen to identify rescue pathways to NFkB-induced cell death….essentially alluted to without details of the role of the team and how the identified pathways will be followed up.
The experiments performed on a reporter cell line that dies upon NFkB activation (engineered by the ANR partner) will start with the arrival of a new postdoctoral fellow (ANR grant). The team has previously largely demontrated that it has all the skills, tools and knowledge to study the functions of any new NFkB regulator.

The proposed genetic investigation of the function of the NFkB pathway in PTEN-/-ALL is more solid, but also presents caveats….The proposed cross to RelA conditional mice could very well lead to no phenotype due to redundancy with other NFkB members….
NFkB exerts clear important survival functions in PTEN-/- ALL as we observed an intense induction of apoptotic tumor cell death upon pharmacological inhibition of NFkB. This mouse model is used to study the participation of NFkB to transformation and constitutes a tool to identify the NFkB target genes that are involved in transformation. We have set up 2 different mice crosses to block NFkB activation (invalidation of IKK2 and RelA). Reported KO studies of the different NFkB family members showed a high specificity. For instance, invalidation of RelA induced a strong apoptotic death of liver cells that was not compensated by other NFkB proteins. More originally, we are also genetically activating the NFkB pathway in vivo (deletion of IkBalpha gene), in order to accelerate transformation and facilitate the identification of the driver molecular events. We are confident to get clear marked phenotypes of the double KO mice that will bring valuable data on lymphoma generation, agressivity, metastasis and ability to engraft secondary normal mice (a fundamental property of cancer stem cell).

It is proposed to use the PTEN-/- mouse model of ALL to look for genes deregulated transcriptionally….that sustain the leukemogenic process…
Using a transcriptomic approach we are searching for new therapeutical targets by :
(i) analysing the potential of several genes/proteins already suspected to support cancer (CD98/LAT1, carbonic anhydrase 12). For this we are not using *poor specificity inhibitors*, but rather a selective LAT1 inhibitor as well as isoform-specific CA small molecule inhibitors (collaborative projects).
(ii) going deeper into the transcriptomic analyses to identify new original targets. We develop bioinformatic analysis, in particular GSEA and compative studies between mouse and human data to identify the deregulated signaling pathways as well as the crucial cancer-driver genes that are conserved between the species.

…the conditional knock-down cellular model…in K562 has been used to identify a Bmi-dependent signature. It is proposed to study its relevance. This is interesting but represents in itself a major task.
We believe that we have defined an interesting niche of opportunity with the original discovery that Bmi-1 favors leukemic proliferation of K562 cells by repressing cyclin G2, a negative cell cycle regulator. As the gene is frequently downregulated in cancer cells we will explore its potential tumor suppression function and dissect its yet unknown mode of action. A collaboration with an international partner has been set up. An application for a grant from INCa, if successful, will reinforce this project with funds and a postdoctoral fellowship.

There is an absolute need to redefine priorities in the numerous objectives…
We fully agree with the committee on that point. The search for leukemic stem cells, the screen for Bmi1 inhibitors and the use of double KO mice PTEN-/- Bmi1-/- which are major tasks by themselves, won't be performed.
All our efforts, strengths and team's resources will go to the study of two major items : the analysis of the PTEN-/- cancer mouse model and the deciphering of Bmi1's mode of action. Each project involves a new PhD student (both started in november 2011, one is from Nice and the other one comes from Paris). The size of the team is increasing by the arrival of 2 postdoctoral fellows (Infectiopôle Sud, ANR) and a grant proposal has been selected for evaluation by INCa for an additional postdoctoral fellow.

TEAM 5: Environment, reproduction and hormone dependent cancers: epigenomic mechanisms

Team leader: Mohamed Benahmed, PUPH

We are grateful to the AERES committee for their evaluation of our project, comments and recommendations.

TEAM 6: Microenvironment, signaling and cancer

Team leader: Sophie Tartare-Deckert, DR2 INSERM

We thank the committee for its detailed and positive analysis of our project and its helpful recommendation for our proposed new team. We would like to bring the following comments on some points raised in the report.

General comment on the conclusion: We agree that the international visibility of the team

leader is a key issue. To answer the committee, we believe that her official independency as the leader of Team 6 should bring opportunities for international networking and participation to workshops or conferences. Also, her full independency should improve our international recruitment. In addition, the team has currently an excellent candidate for applying for a tenure position. This will help expanding the group. As recommended, we will be vigilant to maintain our project as a whole.

Specific comments:

1. In this period 5 research students obtained their PhD degree.
As stated in the original document, 6 students obtained their PhD degree, one of whom being a MD.

2. *Both DR2s have been successful in obtaining external funding. The team leader has obtained 4 grants since 2005 (ARC or INCA); also a new grant is listed for 2011-12 for Team 6.*
As stated during the oral presentation, Team 6 has now secured 2 grants for 2011-12 (ARC and Laurette Fugain).

3. *The team has had about 5 contracts in this period, of which two industrial contracts, both funding a PhD student.*
The team leader has been recently engaged in a non-disclosure agreement with Valocor Therapeutics (Vancouver, Canada) to evaluate new small compounds on melanocyte and melanoma biology that will reinforce our industrial partnership.

4. *Besides testing the roles of candidate molecules, it might also be valuable to develop more global genomic or proteomic approaches to establishing the molecular requirements for this transmigration, for example use of an siRNA library to test for inhibition of the migration in melanoma and leukaemic cells, or microarray comparison of sets of cell lines that cross or do not cross each type of endothelium.*
We totally agree with the committee and we will carefully follow these helpful suggestions.

TEAM 7: Cellular and molecular pathophysiology of obesity and diabetes
Team leaders: Jean-François Tanti, DR CNRS and Mireille Cormont, DR INSERM

We would like to thank the members of the AERES Committee for the positive evaluation of the team and for their constructive comments. We will devote the next 4-5 years to improve our international visibility as recommended by the Committee. We will also pay attention to the numbers of projects that will be developped in order to remain focussed in the team and competitive in the field.

In the AERES document, the boxes of the table (p 25) corresponding to engineers (N5) and Ph.D students (N6) for the future appear as black box without number inside. We have for the future 2 engineers without tenured position and 3 Ph.D. students.

TEAM 8: Hepatic complication in obesity

Team leader : Albert Tran, PUPH and Philippe Gual, CR INSERM

We thank the AERES committee for its positive evaluation and appreciation of both fundamental and translation research axis of our team. We also thank the AERES committee for its constructive comments and recommendations.

As suggested by the AERES committee, we will reinforce collaborations with experts in the inflammation and immunology fields, while we already work with A Wakkach (Nice), an immunologist who has a solid background on interaction between T cells and dendritic cells and K Clement (Paris) and A Bouloumié (Toulouse), who have broad expertise in adipose tissue inflammation and insulin resistance.

We have maybe not been clear enough regarding the relevance of the co-direction of the team by two team leaders. This team is composed of fundamental researchers, which are under the responsibility of P Gual, and of a large number of clinicians (with Pr A Tran responsible for the clinical aspects of the project), which are all important actors in the development of the program. The co-direction of the team by two team leaders reinforces the synergic and the translational research of the team which is a main part of the program. This co-direction is effective and, as mentioned by the AERES Committee, efficient as attested by the quality of the scientific production.

As recommended by the AERES committee, we will devote the next 4-5 years to improve our international visibility.

Note that the team 8 has 2 Ph.D. students who will defend their thesis in December 2013 (instead 0 for the future)

TEAM 9: Pathophysiological aspects of adaptive responses to metabolic challenges and dysfunctions

Team leader : Paul Grimaldi, DR1 INSERM

The members of team 9 “Pathophysiologial aspects of adaptive responses to metabolic challenges and dysfunctions” are grateful to the AERES committee for their comments, criticisms and recommendations regarding our scientific project.

We would like to amend some mistakes in the report, probably related to errors and omissions in our written file.

Team composition:

. N6: Two PhD students are currently included in the team (E. Lendoye, MD, fellowship from UNESCO/L’Oréal and G. Zeanandin, MD, Department of Nutrition, CHU de Nice).
. N7: Three investigators have a HDR (P. Grimaldi, I. Mothe-Satney and S. Schneider)

Funding:

The report mentions funding levels as a weakness of the team but we have obtained two grants in 2011 which seem to have escaped the attention of the committee:
. Fondation pour la Recherche Médicale, FRM (04/2011-04/2014), 140 000 Euros « Roles of PPARbeta in adaptive responses to metabolic dysfunctions in muscle and T cells »
. Agence Française de Lutte contre le Dopage, AFLD (04/2011-04/2013), 46 000 Euros « Molecular mechanisms of PPARb actions on muscle and T cell adaptive responses to physical exercise »

The competitive FRM grant was judged fundable by experts in our field and funds the project as it was presented in our AERES file.

Publications:
The report states that 7 out of our 48 publications were directly the production of the team (authors in first or last position) and the others are more collaborative studies. However, we count 18 publications where team members were first or last author and these do not include another 4 external publications that indeed can be considered more collaborative studies. Furthermore, probably as a result of miscounting our publications, the report incorrectly states that one researcher has not published.

Refocus of project and lack of expertise and collaborations in the field of inflammation:
In line with the recommendation of the committee, we will refocus the project on the role of PPARbeta in T cells in the context of the link between metabolism and inflammation thereby also strengthening inflammation research (third topic) in the center. We feel that we incorrectly left the impression that our team lacks the expertise to pursue this line of research. As the report correctly points out in the list of strengths and opportunities, we have a "young investigator with a strong knowledge in inflammation" in our team. Furthermore, this same foreign researcher (Dutch origin) has an active collaboration with the team of Anne Bouloumié in Toulouse and kept strong ties with the lab of Jerrold Olefsky in San Diego; both labs that have a strong track record in this research field. It was already planned that this researcher would become the next team leader in 2014 when the current team leader retires. In light of refocusing of the project, we now propose that this young investigator will lead the team from the onset, to use his expertise and (inter) national connections to manage this reviewed project.

TEAM 10 : Microbial Toxins in Host Pathogen Interactions

Team leader: Emmanuel Lemichez, DR INSERM

We are grateful to the AERES committee for their very positive evaluation and their strong support of our projects.

TEAM 11 : miR-155 biogenesis and function in macrophages (AVENIR/ATIP)

Team leader : Michele Trabucchi, PhD

We are delighted that you found our expertise and network connections in a good shape to start a new very exciting adventure as new Group at C3M Institute in Nice. We are also very pleased that you have overall appreciated our project which could make a fine contribution to the gene expression field. Your encouraging evaluation review prompts us to work harder and diligently to strive in making original and broad meaning discoveries which could have an important impact on a broad scientific community.