Compartimentation et dynamique cellulaires

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Compartimentation et dynamique cellulaires

From the

Institut Curie

CNRS

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

May 2010

Research Unit

Name of the research unit : Compartimentation et dynamique cellulaires

Requested label : UMR CNRS

N° in the case of renewal : 144

Name of the director : Mr. Bruno GOUD

Members of the review committee

Committee chairman :

Ms. Jennifer Lippincott-Schwartz, NIH, Bethesda, USA

Other committee members

Mr. Malcolm BUCKLE, ENS Cachan, France

Mr. Robert CROSS, University of Warwick, UK

Mr. Rolf KEMLER, Max-Planck Institute, Germany

Mr. Jonathon PINES, University of Cambridge, UK

Ms. Sylvie URBE, University of Liverpool, UK

Mr. Frans van ROY Ghent University, Belgium

Mr. William VAINCHENKER, Institut Gustave Roussy, France

Committee members suggested by CoNRS

Ms. Claudine PIQUE, Institut Cochin, France

Observers

AERES scientific advisor

Ms. Anne PLESSIS

University, School and Research Organization representatives

Ms. Ursula HIBNER, CNRS

Mr. Vincent MOULY, Université Paris 6

Mr. Daniel LOUVARD, Institut Curie

Report

1. Introduction

- Date and execution of the visit

The site visit took place In Paris on the premises of the Curie Institute on March 15, 16 and 17th. It was conducted by an international evaluation panel of nine experts in the scientific fields represented by the thirteen teams evaluated. After a closed-doors gathering of the committee, the visit started by a very short introductive speech by the director of the Curie Institute followed by a presentation by the director of the unit of the activities and projects of the research unit. Each group leader presented the activities and projects of their team. The committee then separated into different groups in order to have separate closed-doors meetings with the different categories of personnel of the Unit (four meetings with the post-docs, students, technician/engineers and permanent scientists respectively).The principal activities of the various platforms were also presented (although not evaluated here). Posters were presented by the students and post-docs during lunch and coffee breaks. The committee also met with the representatives of the Curie Institute, CNRS and University Pierre et Marie Curie-Paris 6. The visit ended with a closed-door meeting with the head of the Research unit. One of the team leaders was absent, for health reasons. The time planned for the missing presentation was dedicated to discussions with different members of her team in front of their posters.

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

The UMR144 was created in 1995 in the Curie Institute which also hosts a hospital strongly centered on oncology. It is located in the center of Paris, in an old University district called the "Montagne Sainte Genevieve" characterized by a very high density of interdisciplinary schools and research centers.

The UMR 144 is composed of about 200 people in thirteen teams all dedicated to various aspects of cell biology (endocytosis, intracellular transport, cytoskeleton, signalling, cell division, migration and differentiation…) with a strong emphasis on interdisciplinary (especially with physics) approaches. A recurrent (major or secondary) theme of these teams concerns the fundamental cellular and molecular mechanisms involved in tumour development, tumour progression and metastasis. It also hosts two facilities (one dedicated to cell and tissue imaging and another for protein production).

- Management team

The research Unit will be managed by its current director, Mr. Bruno Goud, assisted by a team leader as the deputy director. The Unit is very densely populated but because of its reputation and track record continues to attract top level scientists at graduate, post graduate and senior scientist levels.

- 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)	33	31
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	41	40
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	21.60	15.60
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	26	15
N6: Number of Ph.D. students (Form 2.8 of the report and 2.7 of the project file)	27	27
N7: Number of staff members with a HDR or a similar grade	26	26

2 • Overall appreciation on the research unit

- Summary

The unit is in a highly inter-disciplinary environment with a remarkable cross-fertilisation between physicists, engineers and cell biologists that has yielded tangible results in breaking open new, exciting technologies and research directions. The unit can be considered to be one of the best places carrying out cell biology research in Europe. It comprises 13 teams and is headed by a director who makes final decisions on resource allocations, but in a consensual manner when possible. Individual teams are responsible for raising their own funds for research expenses but the institute's core facilities - animal house, imaging, antibody production -are made available for free or at a nominal cost. There is a mixture of new, young teams, some promoted from within and some recruited internationally, and older established groups. All groups are carrying out internationally competitive research. There is a commendable culture of collegiality that has produced many collaborative papers. The central imaging facilities (light and electron microscopy) are world-class and the technology development within these facilities produced a novel rapid FRAP module that has been commercialised. Novel hardware and image processing developments may also prove to be substantial advances in the near future. The institute has an antibody and protein production facility that exploits the single chain antibody technology developed in-house both to provide common antibody reagents and develop research antibody reagents in collaboration with individual research teams.

- Strengths and opportunities

- Inter-disciplinarity, strong interface between biologists, physicists and engineers.
- Excellent imaging facility that develops both hardware and image processing technology.
- Central antibody facility that exploits the single chain technology developed in house.
- Subsidized animal house allows animal models to be developed.
- Collegial culture with an internationally recognised director who is an acknowledged leader in his field.
- Very strong faculty with a number of internationally recognised groups.

▪ Links to the hospital provide the opportunity for medically relevant and translational research.

▪ International reputation of the institute attracts excellent group leader candidates.

- Weaknesses and threats

▪ Specific to the unit: The retirement of the institute director will release space for expansion but will have an unknown effect on the relationship between the unit and the institute.

▪ Lack of a canteen reduces the possibility for informal interactions between groups that are important to generating new ideas and directions and internal collaborations. Structural biology is under-resourced but will be increasingly important in the future.

▪ Systemic to the French research system: relatively unattractive salaries make the unit less attractive on an international stage for researchers at all levels. The bureaucratic nature of the research organisations funding the unit makes some resource and personnel issues difficult or impossible and makes the unit less flexible in adapting to changing circumstances.

- Recommendations to the head of the research unit

▪ Continue this open, consensual directorship that has fostered an excellent collegial atmosphere.

▪ Strengthen the structural biology effort of the unit.

▪ Continue to foster inter-disciplinary research that makes much of the research at the unit unique.

▪ Establish a means by which the graduate students can get to know one another quickly upon joining the unit. Provide more opportunities for students to meet invited speakers.

▪ Establish a post-doc mentoring program.

▪ Establish a mentoring program for the junior group leaders.

- Production results

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	32
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	70.60
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	100%
A4: Number of HDR granted during the past 4 years	4
A5: Number of PhD granted during the past 4 years	19

4 • Appreciation team by team

Team 1: Molecular mechanism of intracellular transport

Team leader: Mr. Bruno GOUD

- 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)	4,5	3,5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	8	8
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	6	3
N7: Number of staff members with a HDR or a similar grade	3,5	2,5

- Appreciation of the results:

This world class team is lead by the director of the unit who is an experienced senior scientist with an established international reputation as a cell biologist and extensive experience as both a group leader, and as a head of a large and successful unit. The team has an outstanding publication record with a total of 40 scientific publications many in high impact factor journals (Cell, EMBO J. PNAS, Nat. Met.). The team leader appears often as senior author and otherwise is often present in the list when a sub group member is senior author. The team also has 1 patent. The team is strongly compacted with overlapping and complementary areas of research all benefitting from the excellent facilities present in the Institute. The group also clearly benefits enormously from the presence of a Prof. Emeritus with whom the team leader has a close and fruitful interaction.

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

The team leader has been awarded the Grand prix Jaffé de l'institut de France, and he and members of the team have been invited to 41 national or international meetings of which 29 were international. A total of 16 posters were presented at national and international meetings, 4 general public lectures were given and the team leader was responsible for the organisation of an international symposium held in France. The team recruits many foreign post docs (5), has 7 Ph.D students and supported a sabbatical visiting scientist from another European country. The team has 6 staff scientists of which one is responsible for the imaging platform of the U. The team has raised around 1.05 M over the 4 year period with 9 grant awards of which the team leader was principal investigator (PI) in 5

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

The team leader has been responsible for this group for almost a decade and has reached a steady state with respect to the maturity of the scientific subjects and contacts with the international scientific community. The imaging platform also constitutes a large teaching platform for the formation and training of scientists in this field.

The team is well organised and communication between its members is excellent. The large number of invitations to international meetings is testimony to the communication policy of the team.

Project 1. Function of Rab GTPases in membrane trafficking and organelle biogenesis. The project requires the generation of k/o mice for the Rab6 isoforms identified by the group. The focus will then be on Myosin II, Myosin Vb and Rab6IP1 to address whether Myosin Vb connects the secretory and endocytic pathways via interactions with Rab 6 and Rab8. Thus, a search for putative partners will be instigated and crystallographic studies on Rab6/Myosin II and /or RabC/Rab8/Rab11/Myosin Vb will be carried out in collaboration with the crystallographic group in the UMR and external groups. Yeast chips have already been constructed to facilitate the identification of partners. The role of Rab11 in Langerin trafficking will be examined using the live cell imaging approaches well established in the group. Neither of these projects appears to present any great technical bottleneck and the tools and objects required seem to be present and accessible: clear results are to be expected. Finally, in collaboration with another team in the laboratory, the transcriptional level of some 500 genes coding for Rab and Rab interacting proteins in tissues from patients with bladder cancer will be assessed. Some proteins have already been identified and their role in cancer progression is being investigated. This is clearly clinically very important but also possesses the potential of a spin off in the development of specific arrays for diagnosis. Given the current status and potential of the project, funding is not expected to constitute a problem.

Project 2. Physical parameters underlying transport events. The project aims at continuing the project on reconstituted Arf1-dependent COPI coat binding on giant liposomes. Optical tweezers will be used to measure threshold tensions at which the COPI coat can deform a membrane. Since this technique is well controlled by the group there are few technical barriers expected. Having obtained in vitro quantitative estimations of this effect, in vivo analysis will be attempted by the injection of 0.2-0.5 mm beads into cells that will be coupled to the Golgi apparatus and then tugged and tweaked using optical tweezers in an effort to characterise physical parameters involved in membrane transport. Some technical problems remain to be resolved, but again, given the current expertise and proximity of groups with complementary know-how, this cutting edge project should at the least produce an original assay if not important data concerning membrane trafficking.

Project 3. Mechanisms governing the spatial distribution of endomembranes. There are two projects involved here. The first aims at elucidation of the spatial distribution of endomembranes and relies on a computational tool that has been developed by the group to visualise the global organisation of well-characterised endosomes. The team will attempt to identify factors involved in the steady state organisation of endomembranes. The second project is an attempt to quantify structure/function relationships between pre and post Golgi membranes. These projects whilst innovative only in the application of the in-house developed algorithms could however provide interesting data complementary and useful to other groups within the laboratory.

- Conclusion

  - Summary

The first project is a continuation of a well established study and although it uses well established techniques , it is expected to generate important information concerning the identity and nature of putative partners in the Rab/Myosin system, potential transcription signatures associated with bladder cancer and important tools for transcription analysis. There is no question of the team leaders proven expertise, the project is driven by scientific questions and adequately supported by the scientific means available. The second project is more technically driven and may encounter some problems especially with the transition to in vivo studies but again the overall means at the team's disposition and the collective expertise in the group give this project a high chance of success. The third project is less well defined and the goals less clearly articulated, the results are therefore difficult to assess or predict.

  - Strengths and opportunities

The team has a high international profile. It is well established and has repeatedly proven its worth. The projects are globally sound and are expected to provide results in continuation of the past output of this group.Overall the projects are ambitious, exciting and well grounded in the competence present in the team. The chances of success at least for the first two projects are very high. Resources are more than adequate and given the team's track record one expects high-level dissemination of results. The projects globally are a logical extension of

the huge amount of expertise built up in the group over the years and constitute an excellent way of moving this into unchartered territory as well as training young researchers in a challenging field.

– Weaknesses and threats

The only potential weakness lies in project 3 because of its lack of clarity, however one expects that the team leader will be able to assist the project and in so doing may consolidate the project incidentally providing useful on hand training for the young researchers involved in this project.

– Recommendations

The team leaders heavy administrative duties as head of the UMR may be considered to pose a threat to his capacity to push forward on the projects, however, each project involves talented young scientists who seem fully capable of operating alone so the committee recommends that they be given as much freedom as possible in the direction of these projects.

Team 2: Structure and membrane compartments

Team leader: Ms. Graça RAPOSO

- 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)	2	2
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	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	1,5	1,5
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

The group is working on the biogenesis and functions of Lysosome Related Organelles (LRO) through innovative imaging approaches. The main studied model of LRO is the melanosome and the goal of the team is to understand the biogenesis of melanosome, in particular the coordination between the early and late stages of melanogenesis. The team also investigated disorders of LRO such as Ocular Albinism and Hermansky-Pudlak syndrom.

The team provided important advances in the melanosome field by describing a new pathway for protein delivery to melanosomes, involving the KIF13A and the clathrin adaptor AP-1 (JCB 2009) and by presenting the first electron tomography observation of early melanosomes (PNAS 2008). The team also found that the ocular albinism type 1 (OA1) protein regulates melanosome composition and interacts with the melanosome protein MART-1 (Hum Mol Genet 2009). Recently, the team also presents new evidence for interplay between melanosome proteins

and the ESCRT sorting complex and characterized an unconventional sorting mechanism for the melanosome-associated protein Pmel17.

The productivity of the team in term of number and quality of publication is outstanding. Indeed, 66 articles were published in peer-review journals during the 2005-2010 time period, including 8 reviews and 5 articles in top level or very good journals (Immunity, JCB, PNAS, Hum Mol Gen, Mol Biol Cell) as first and/or last-authors. The team also published 21 articles as last but one author in top level (Cell, Nat Immunol, Immunity, Dev Cell, JCB, PNAS) and very good (Traffic, JI, J. Cell Sci, Hum Mol Genetic Mol Biol Cell) journals.

The team has solid long-standing collaborations with leader groups in cell biology both in France and abroad. The teams also established many other fruitful collaborative projects as demonstrated by the high number of joint publications.

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

The team leader is invited frequently to international meetings: 10 invitations, including 2 EMBO/ESF conferences, 1 EMBO workshop, 1 Gordon conference on lysosomes during the 2005-2010 period and 2 international meetings in Japan (20th IUBMB 2006 and 20th IPCC 2008) as chair and invited speaker.

One CR2 was recently recruited in the team (2008) and the team also attracted a post-doc from abroad.

The team has been very successful at obtaining both international and national funds. Four successive NIH grants have been obtained since 2002 (current ones 2007-2011 and 2009-2013). The team is currently a FRM (Medical Research Foundation)-associated team, which is a result of a highly competitive selection. As a result, they received significant grants from the FRM. As part of collaborative networks, the team also received significant grants from the National Research Agency (ANR) and the National Cancer Institute (INCA) and is also part of national ANR and INCA networks. Two patents have been obtained.

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

The team has been recently reinforced by the arrival of a young permanent scientist and also includes other dynamic young scientists. The team strongly contributes to the animation of the unit and is a driving force for the development of the imaging platform at Curie, which includes training of scientists from within and outside Curie. The team leader is also strongly involved in teaching by giving lectures at under-graduate and master levels.

- Appreciation on the project

The team leader is very competent and creative and dynamic young scientists are also in charge of the projects. The projects are well defined and are likely to be successfully achieved given the solid preliminary data the strong expertise of the team and the grants already obtained for the next three years. The team is currently developing new electronic microscopy approaches especially in electron microscopy/immunofluorescence correlation microscopy.

- Originality and existence of cutting edge projects

Results obtained during the last five years have paved the way for original and exciting studies of melanosome biogenesis in normal and pathological situations. The team will investigate the role of tetraspanins, especially CD63, in the ESCRT-independent sorting of Pmel17 and will try to identify the formation of pathological amyloid fibers. The identification of the functions of OA1 will be pursued. The crosstalk between endosome and melanosome and the influence of melanocyte-keratinocyte interactions in melanosome biogenesis will also be explored.

- Conclusion :

– Summary

The team provided important advances in the exosome/melanosome field and will pursue the development of exciting projects in this field. The team leader is recognized at the international levels. The team leader greatly contributed to the development of innovative electron microscopy approaches and provided highly valuable help to other scientists from Curie and other institutes. The prospect of the team appears excellent considering the quality of the project and the ability of the team to raise funds.

– Strengths and opportunities

- High international profile
- National leader in the exosome field and innovative electron microscopy analyses
- High productivity team in terms of publications and patents
- Excellent funding ability
- Long standing and fruitful collaborations with the main leaders in the field of exosome and strong interactions with other teams within the unit

– Weaknesses and threats

One possible threat could be the high number of collaborations and the community contributions of the team in training and new technological development. Given the outstanding productivity of the team and its strong motivation to engage in collaborative research, these diverse activities do not appear problematic currently.

– Recommendations

The team leader should be careful regarding the balance between the research activity in the team and its community contributions.

Team 3: Morphogenesis and intracellular signalling

Team Leader: Mr. Daniel LOUVARD

- 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)	6	7
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1.60	1.60
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	3	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	4
N7: Number of staff members with a HDR or a similar grade	5	6

- Appreciation on the results

This is a well-established team that is internationally highly recognized and has made important scientific contributions over the years. The team focuses on the study of epithelial cell polarity, intestinal tissue organization and tumorigenesis. During the last funding period the team has published over 55 papers of high quality, which appeared mostly in internationally well-recognized journals. The team leader and group members were invited to many national and international conferences and seminars.

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

This is a world-class team in their field. This is reflected in the various highly competitive national and international awards received by the team leader. Many former lab members obtained independent positions elsewhere.

Several group members obtained national and international grants, are connected to industries, and participates in national networks.

The team leader puts much effort in the dialogue between science and its understanding by the general public.

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

The team leader is a major driving force of the research unit.

- Appreciation on the project

The team is composed of several groups, of which three are led by senior project leaders and one by a more junior project leader. Those scientists are all experts in their field of competence.

Group 1: This group works on the membrane-cytoskeleton linker, ezrin which is a member of the ERM family. The goal is to determine how ezrin coordinates actin filament organization and membrane protein transport/stability/activity to regulate the assembly and functions of specific domains of the plasma membrane. New ezrin partners were identified that provide the molecular basis to understand its dual role in filament organization and membrane protein trafficking. With the recruitment of a new collaborator future research directions will concentrate on merlin, which is homologous to ERM proteins and is the product of the tumor suppressor gene Nf2. It is too early to comment on this new research direction and if this can lead to an independent group.

Group 2: One of its goals is to study the molecular mechanism(s) by which some of the motors associated to microtubules and some of the myosins contribute to membrane traffic along the endocytic pathway or during the biogenesis of melanosomes (lysosomes related organelles). The group is interested to determine whether the motor activity of myosin 1a is required for the role of this myosin in anchoring actin filament of the intestinal microvilli in the plasma membrane of enterocytes. They are also focused on the contribution of myosin II to the migration of E. histolytica in two and three dimensions. In the future the group aims to investigate the function of Myosin 1b (Myo 1b) in regulating the shape of endosomes and TGN and to dissect the role of Myo 1b on the morphology of these organelles. In addition the group found that Myo 1b interacts wit MAX-1 and that both bind to the EphB2 receptor. This opens the possibility to study Myo 1b and MAX-1 during cell signalling mediated by the interaction of EphB2 with ephrins.

Group 3: The group works on two parallel approaches to study intestinal epithelial cells: A cell biology approach to better understand the role of actin-binding proteins in filament organization of the microvilli found at the apical pole of digestive epithelial cells and an in vivo targeting approach to specifically express genes of interest in the intestinal epithelium, in a constitutive or inducible manner, using the villin promoter. This has allowed the analysis of essential signaling pathways in intestinal homeostasis and tumorigenesis, such as Wnt, Ras, Notch and p53 pathways. The group aims to continue with these lines of research to better understand the role of actin-binding proteins in the organization of apical cell polarity of epithelial cells, and to investigate which signaling pathways play a significant role in tissue morphogenesis, stem cell maintenance and tumorigenesis, by specifically targeting crucial

genes in the mouse intestinal epithelium, through the villin promoter. Overall this is a very important research project and the group leader received international recognition for the work.

Group 4: The broad objective addressed is how malignant cancer cells escape from a primary tumor, invade into the surrounding tissue, and migrate through the circulatory system to establish secondary tumors at distant sites. In order to escape from the primary tumor and invade adjacent tissue, cancer cells degrade the basement membrane using invadopodia, specialized protrusions for matrix degradation; and then migrate towards the circulatory system using filopodia as guidance organelles. Fascin is a key regulator of filopodia formation because of its ability to bundle actin filament allowing for efficient pushing of the membrane. High levels of fascin expression are reported in aggressive carcinoma of different origin, while being absent from normal epithelial cells. In human colon cancer, fascin is exclusively localized at the invasive front of the tumors. To further investigate the role of fascin in tumor progression, it is aimed to search for fascin binding partners and to establish mouse models to test if fascin expression in primary tumors is sufficient to promote cell invasion. Although this group is a rather recent recruitment, both the excellent science and the dynamism of the group leader are very impressive.

- Conclusion :

  - Summary

The team has international visibility and the group members have a strong track record.

  - Strengths and opportunities

Over the years the team has acquired a deep knowledge on the role of actin filaments and their interactions with the plasma membrane. The combination of state-of-the-art cell biology and the analysis of animal models are unique in this respect. The committee appreciated the excellent scientific leadership from the team leader.

  - Weaknesses and threats

None

  - Recommendations

With the retirement of several senior scientists of the group 1 some mentoring may be required.

After retirement of the leader of the group 2, the projects of this group should be affiliated with another team of the unit.

Given the out-standing track record of the team leader and the very high scientific performance of the team, support of this excellent team is highly recommended.

Team 4: Traffic, signalling and delivery

Team leader: Mr. Ludger JOHANNES

- 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)	4	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	3
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results

This is a young and dynamic team, excelling in highly original research that has already contributed to the emergence of several new paradigms in the process of membrane dynamics and protein sorting mechanisms, in particular over the last 2-3 years. Both subgroups are tackling important fundamental mechanisms (membrane scission and bending, and mechanosensing of caveolae).

Very productive partnership of team leader and senior scientist, with an impressive number of principal authorships in high quality journals, including Nature, Nature Cell Biol., J. Cell Biol. as well as invited reviews published in major general interest journals. Primary literature includes: 23 principal and/or corresponding authorships, 30 co-authorships. The citation record for the team leader includes a total of 1378 citations, 742 citations for articles published since 2005, with the most highly cited senior author paper (Romer, Nature 2007) from this period already tallying 66 citations.

Multiple partnerships set up as collaborations with local and international leaders in membrane traffic as evidenced by large number of collaborative publications.

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

This is a young team that has already made important contributions in the field of membrane traffic, with a steady and consistently solid publication record in well-respected international journal. Most notably in the last three years, the group has seen several publications in the top journals in the filed (Cell, Nature, Nature Cell Biology, J. Cell Biol.). The team leader and the senior scientists are well respected in the community as evidenced by invitations to present their work at major international conferences. Their publication record shows extensive collaborative efforts with leading groups all over the world, including USA, UK and India as well as local collaborations.

The team leader is one of a handful of leading figures in the area of retrograde traffic and has consistently made important and original contribution to this area. Over the last 2-3 years the team leader and the associated staff scientist have been invited to speak at several major international conferences including Gordon Research, EMBO, ESF and FASEB Conferences. The team leader is also a member of a large number of editorial committees of international journals including Traffic, Biology of the Cell, Developmental Cell Biology and the American Journal of Physiology.

The group is able to attract high quality scientists at all levels; it has so far hosted scientists from Germany, Japan, China, Morocco, Spain, India and USA, in addition to French compatriots.

The team is well funded for all aspects of the projects with national and international grants. The team leader was a cofounder of a Biotech spinoff company (ShigaMediX SAS) and has acted as a consultant to other Biotech companies in the area of therapeutic drug delivery.

This team is very well connected not only within its own Unit (collaborators Louvard, Goud, Raposo), but also at an international stage, as indicated by a large number of co-authorships (>30) in the last 5 years.

This team has pioneered research on the trafficking pathways used by shiga toxin, leading to the generation of a battery of tools now widely used in the cell biology community to probe the retrograde trafficking pathway between endosomes and the Golgi apparatus.

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

This team is composed of two closely collaborating groups, "traffic and delivery" (group a) and "traffic and signalling" (group b) with common interests in mechanisms of membrane traffic and membrane dynamics with particular emphasis on the endocytic pathway. The team leader and the senior scientist in charge of the second group share office space and contribute jointly to the intellectual framework of their joint output. Post-doctoral and technical staff as well as PhD students share office and wet lab space ensuring good communication between the two subgroups. A clinical scientist is imbedded in the team and is being trained in cell biology.

The portfolio of this team extends from basic cell biology of membranes to translationally and clinically relevant projects (intracellular delivery of therapeutic drugs and immunotherapy as well as discovery of inhibitors of toxins). Collaborations with chemistry departments and Pharma-industry (Glaxo-Smith-Kline) are in place to support this work, and the main underlying technology is supported by 7 filed patents.

The team contributes to teaching by training several PhD and master students and plays an important role in providing high level expertise in membrane traffic. The team leader is actively participating in undergraduate teaching by giving lectures and providing wet lab training at a joint annual cell biology course of the Institut Pasteur and Curie, as well as at a membrane biology course organised jointly by Instituts Curie and Cochin, on a masters course at the Ecole Doctorale du Muséum in Paris, and at the Pasteur Institut in Lille on a cellular microbiology course. The senior scientist is the founder of "Club Endocytose", a society of researchers and students with a common interest in membrane traffic, which organises an annual meeting with local national and international contributors. The senior scientist also contributes to teaching at neighbouring institutes and universities notably teaching on Master courses of Paris XI, Paris VI, ENS and Institut Pastuer on the subjects of membrane traffic and signalling. He is also responsible for teaching cell biology athe ESIEE Management, école d'ingénieurs de Biotechnologie (CCIP).

- Appreciation on the project

The projects are split into two major themes (corresponding to the two groups) with overlapping interests in fundamental mechanisms of membrane deformation through (a) shiga and cholera-toxin driven generation of protein lipid nanodomains inducing curvature and underlying a new mechanism of clathrin independent internalization also used by SV40 virus, and (b) the modulation of membrane tension by dynamic disassembly of caveolae under mechanical stress. Both groups are studying important aspects of differential endocytosis of cargo (toxins and interferon receptors (IFNR) via clathrin dependent and independent pathways, as well as requirements for differential sorting of proteins at the level of the early endosome (retrograde transport and ESCRT-dependent and independent sorting to the lysosome).

Major focus areas of group (a) are: 1) Mechanisms of membrane fission: very fundamentally important process that is still not well understood in biological membranes – this project is supported by a collaboration with chemistry and physics departments at the Curie Institute. 2) Genome wide screening for major regulators of Shiga toxin uptake based on an in cell trafficking assay developed by the team, 3) screening small chemical libraries for inhibitors of shiga toxin (direct action and inhibition of uptake), 4) proteomics of the retrograde trafficking pathway and 5) the use of shiga-toxin based technology as a high capacity delivery tool for therapeutic drugs in a transgenic model for intestinal adenomatosis and a human breast cancer xenograft mouse models; this project is clearly of great interest to the mission of the Curie institute.

The projects of group (b) span: 1) a long-term interest in the interplay of trafficking and signalling in the IFN pathways and two more recent projects relating more closely to the overall interest of the lab in lipid protein interactions in membrane trafficking: 2) mechanosensing functions of caveolae (with particular emphasis on mechanical stress in tumour cells) and 3) cholesterol trafficking.

The research described in the projects is highly relevant for our understanding of basic membrane biology, subcellular compartmentation, protein sorting but also has an important translational and therefore clinically relevant component. The projects are very ambitious, but based on the experience, funding and staffing of the team, the project is feasible and should provide important new insights. It will however be extremely important to ensure that priorities are set early on in view of several screening based projects that are likely to yield a large number of interesting leads.

These teams are pioneers in the study of shiga toxin trafficking pathways, and are proposing to build on this expertise and existing tools to a) generate a comprehensive inventory of the molecular machinery governing this trafficking pathway, b) establish shiga toxin derivatives that can be used as high capacity delivery tools for therapeutic anti-cancer drugs. Proposed work on the mechanisms of membrane invagination and scission as well as mechanosensing of caveolae are highly original and clearly at the cutting edge.

- Conclusion :

  - Summary

This is an excellent team that is highly productive and innovative, emerging as one of the leading teams in the field of membrane traffic. The work is technically accomplished and intellectually stimulating, with excellent publication record and lots of promise for the future.

  - Strengths and opportunities

This is a very dynamic and highly original and productive team, establishing new paradigms, using innovative approaches and having an important impact in the area of membrane dynamics and interacellular trafficking at the international level. The portfolio is wide ranging from fundamental aspects of membrane budding and scission, to the potential adaptation of shiga toxin as a drug delivery tool, with high relevance for the mission of the hosting Institute – fighting cancer. Success in the latter will depend to a large degree on the quality of interactions with clinical colleagues and pharma industry, and expected outputs need to be clearly defined. It is good to see that the team already has a clinician embedded in the team and continued close contact with clinical scientists will help to make this part of the project a long-term success.

  - Weaknesses and threats

No major weaknesses detected. Lack of space is in danger of stunting the natural expansion of this team. Care should be taken to avoid fragmentation of the team and focus on the common aspects to both subgroups. Prioritising key targets will be very important in view of several planned screening projects.

Team 5: Biology of centrosomes and cilia

Team leader: Ms. Renata BASTO

Due to major reason the team leader could not present the work of her team to the committee who had instead posters presentations by the different members of the team.

- 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)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	1
N7: Number of staff members with a HDR or a similar grade	0	0

- Appreciation on the results

This group was started one year ago. The team leader had a highly successful and productive post-doctoral period that generated two very high profile papers in Cell. Since establishing the group the team leader has begun to exploit the results she obtained as a post-doc and they have made significant progress on a number of fronts. It is too early to expect any publications from this new team since it began one year ago. The team has already established a number of collaborations in her institute and outside.

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

The team leader has been invited to a number of international meetings as a speaker and is clearly establishing herself as an important player in the field of centrosomes and cilia. This is amply demonstrated by the award of a highly prestigious ERC starting investigator award. The team is clearly attractive: in the short time since she started her grant the team leader has recruited several post-docs, including some from abroad, and a foreign PhD student.

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

The team all have clearly defined projects. The team is already emerging as one of the leaders in the field having generated a number of unique reagents that allows asking cutting-edge questions. The team leader has rapidly taken on an energetic role in promoting scientific interactions and culture at the institute.

- Appreciation on the project

The team has clearly defined projects, with funding in place, that ask important biologically relevant questions. The projects all centre upon the role of the centrosome and cilia in development and disease. They are taking a multi-pronged approach to this making use of a number of model systems. The main system is Drosophila melanogaster. They are exploiting the genetics and cell biology available to investigate the role for the centrosome in

asymmetric cell division in neuroblasts, and the consequences for development of the neuroepithelium - notably in the optic lobe, and in tumorogenesis using cell transplantation to the abdomen. They are generating mutants by EMS mutagenesis, by homologous recombination and by excising mobile genetic elements, using hypomorphic alleles, in vivo RNAi and GFP-tagging at the endogenous locus to investigate the function of a number of key centriole components and regulators including SAK, Sas4, and Asp. A particular emphasis will be to use the transplantation assay to determine the influence of centrosome number on tumorigenesis combining this with different mutant backgrounds to uncover the pathways by which abnormal centrosome numbers can generate tumours. These unique genetic tools developed by this team allow them to ask questions at the cutting edge of the field.

As well as their strength in the Drosophila system that stems from the post-doctoral work of the team leader, they are also using Paramecium to study the role of the centriole in generating basal bodies. This project involves collaboration with the team 2 ("Structure and membrane compartments") to study cilia structure at the EM level. Furthermore, this system is cross-fertilising with the Drosophila system because the group has identified a Drosophila homologue of a Paramecium centriole protein and found that depletion of this protein generates an uncoordinated phentotype in flies.

Finally the PI intends to begin a collaboration with a mouse lab to investigate the effect of altering centrosome number in mammals. In particular they will study the effect of overexpression of the PLk4, the mouse homologue of Drosophila SAK, on the mouse neuroepithelium.

- Conclusion :

  - Summary

A young, dynamic team exploiting powerful genetic systems to ask fundamental questions about centrosome and cilia biogenesis and relevance to cancer.

  - Strengths and opportunities

The team leader has an excellent track record and has already begun to be recognised in the field. The team is using unique, genetic tools to ask important questions.

  - Weaknesses and threats

The project using the mouse neuroepithelium as a model system, while clearly medically relevant and having the advantage of the opportunities of the environment of the institute, may not have the sufficient critical mass, or could dilute resources in the future if it is to compete with other, larger mouse laboratories.

Team 6: Biophysical and molecular basis of cell adhesion and migration

Team leader: Ms. Sylvie DUFOUR

- 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)	2	2
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)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	0
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

The research of this team can be split in two directions: i. biophysical analysis (mechanobiology) of cadherin-catenin mediated cell-cell junctions; ii. Molecular analysis of enteric neural crest cell (ENCC) migration into the gut tissue. With respect to the first part, cadherin-mediated cell-cell adhesion is extremely important for multicellular development, morphogenesis, homeostasis, and defects in it have profound pathological effects. The analysis of cell-cell adhesion by this group is diverse and fairly original. With respect to the second part, the findings of integrin-cadherin interplay in the migration of ENCC are very original. The relevance lies in cell migration being studied in intact mammalian tissues (KO mice) rather than migration of cells in culture.

The publication output is rather modest although. Original work by the team leader as senior author has recently been published in very good journals (Development, J. Cell Sci.). Invitations to present the research of the group at international meetings or institutes have been rather infrequent until now.

A few fruitful collaborations were evident. A long standing collaboration with the previous team leader, who moved abroad, is foreseen.

- 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 presently quite small (5 members) and needs to be strengthened or at least consolidated by additional fund raising. Until now, funds were mainly national and modest. Grant applications are ongoing. Success of grant applications will be critical for the future of the group. The group contains 2 postdocs, of which one is from abroad. So far there is limited international visibility of the team.

The research of this team aims at a better insight in cell-cell adhesion, cell-matrix adhesion, cell migration, and most importantly cross talk between these important phenomena. The latter aspect is especially challenging and worthwhile investigating. Moreover, various important diseases (cancer, Hirschprung's disease, …) can be attributed to defects in these phenomena and this makes the planned research highly relevant.

- Appreciation on the project

Some interesting animal models for cell migration in vivo as well as biophysical technology for analyzing the mechanobiology of cell adhesions are available. Given this expertise, which is not at all trivial, it makes sense to use them for addressing interesting biological questions.

Raising of appropriate and highly relevant biological questions is not so well elaborated at this moment. Experimental planning appears to be inspired more by available technology, animal or tissue models, than by solid hypotheses. Nevertheless, from discussions it became clear that the team leader is rapidly growing in her rather new responsibility.

The intended work is generally original. Whether this will lead to cutting edge projects is still an open question at this moment. There is potential though. The team should aim more at publication in high-impact journals.

- Conclusion :

  - Summary

Small group with presently limited resources is addressing complex and relevant biological questions in a rather diverse way. The team leader should pay more attention to defining hypotheses of high relevance. In view of the limited resources available at this moment, the team leader should consider focusing on one major topic instead of two or more.

  - Strengths and opportunities

Some very useful mechanobiological technologies on the one hand, and an interesting animal model to study ENCC behavior in vivo and ex vivo on the other. At least in bilateral discussions clear enthusiasm of the team leader for her ongoing and planned research.

  - Weaknesses and threats

The group might be too small to address all the questions raised. Moreover, questions raised seem to lack clear focus. Future of the group may be completely dependent on many ongoing grant applications and production of high-impact publications.

  - Recommendations

At least during a few upcoming years, the team leader should regularly receive strategic advice from other expert people besides the former team leader.

Team 7: Structural Motility

Team leader: Ms. Anne HOUDUSSE

- 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)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	3	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

The achievements of this team are exceptional. Over the review period, the team has successfully elucidated key aspects of the molecular mechanism by which myosin VI generates force. Myosin VI is unique in being the only minus-end directed motor in the myosin superfamily. The mechanism of myosin is well recognised as being a key problem in biology, being responsible not only for muscle contraction but also for many other aspects of biological motility, from hearing to cytokinesis. The latest work, describing the molecular mechanism by which myosin VI generates a long powerstroke (36nm) using an apparently short lever, is particularly exciting, revealing as it does that a myosin uses a stroke based partly on a forceful conformational change and partly on the reversible melting of a 3-helix bundle. A previously-unseen state of myosin has just been crystallised. In addition, a number of other crystal structures have been completed in collaboration with groups at the Curie and elsewhere, on proteins that are more or less related to or connected the activity and or control of molecular motors.

Over the review period, the team has been very highly productive, publishing in top journals including Nature / 2005, mech of directional reversal ; Cell / 2007 / structural basis of large powerstroke ; 2008 – EMBO J / post rigor structure ; 2009 – Mol Cell / 3 –helix bundle. Other papers are all in top-rank journals. Perhaps more importantly, each paper makes a distinct, original, and well-defined scientific contribution.

The PI has highly successful national and international collaborations, especially a long-standing on the myosin mechanism with a lab in the US. The collaborations are all active, productive, and with front-rank 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 has an international profile and has a very substantial and sustained record of contributions to the solution of a key problem in cell biology. The team has a substantial network of productive national and international collaborations.

In 2004, the PI was awarded the bronze medal of the CNRS. IN 2005, she was awarded the FEBS anniversary prize for outstanding achievement in structural biology. In 2009, she was awarded the EMBO/FEBS Women in Science Award.

The reputation of the team is reflected in 16 invitations to the team leader to participate as speaker, session chair or organizer at high-profile national and international conferences. Members of the team have given 4 oral presentations and four posters at international meetings.

The group is extremely well reputed and there are consequently no problems in recruiting high quality co-workers.

The team has raised funds from Curie, CNRS, HFSP, NIH, ANR, ARC, ESRF

They have an ongoing collaboration with Cytokinetics on myosin-directed drugs.

- Appreciation on the project

The team has an exceptionally exciting, cutting-edge program. Their proposal is to continue to focus on structural biology as a route into the myosin mechanism, but to broaden out to include kinesins, and in general to work more on the regulation of molecular motors and on the mechanisms of teamwork amongst molecular motors. All the proposed experiments represent powerful, often imaginatively conceived approaches to important, unanswered, biological questions. This is a model program.

- Conclusion :

  – Summary

The achievements and projects of this team are truly outstanding. The team leader is an international leader with an exceptionally strong record of successfully determining important structures and interpreting them to yield conceptual advances of wide cell biological significance.

  – Strengths and opportunities

The team leader is an established international figure, highly scientifically successful. Opportunities exist to further develop crystallography, especially of trapped conformational intermediates, within the section.

  – Weaknesses and threats

Losing highly trained staff to attractive offers elsewhere.

  – Recommendations

It would be important to get a stabilized position to replace the CR1 lost. Streamline, somehow, the protein production pipeline.

Team 8 : Dynamics of Intracellular Organization

Team leader: Mr. Franck PEREZ

- 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)	0	0
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	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

After 5 years of existence, this team, now comprised of 1 postdoc, 2 Ph.D students, two research assistants and one technical assistant, is at a productive stage,. The team's productivity during the review period has been high, with 17 articles published in high impact journals such as Science, EMBO J, JCB, MBC and JCS and two submitted patents related to strategies for antibody phage display and regulation of trafficking of target proteins.

The team's research interests into the dynamics of intracellular organization have broad applicability to the overall focus of the unit. In addition, the team's use of Antibody Phage Display and its production of antibodies is valuable to the Unit as a whole.

The team had a number of high profile publications, including 8 with the PI as last author. He has also been invited to a significant number of meetings demonstrating his high profile in this area of technology.

The team leader has also initiated a number of productive collaborations both within the institute and outside, some of which have already resulted in publications.

- 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 clearly establishing itself as one of the leaders in the use and development of new approaches to study organelle dynamics in live cells. This is reflected in the significant number of invitations of the team leader to international meetings and national seminars.

This is a rather small group but one that already has foreign members and appears to be a highly attractive place for PhD and post-doc applicants.

The team has been very successful in raising external funds from national research agencies (including ANR, Institute Curie and Institute Pasteur and INCa).

The team has numerous collaborations with researchers in France and in other countries, including the USA, Japan, Norway and Argentina.

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

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

The team is playing an important role in the overall environment of the Unit by serving to help coordinate the organization and distribution of antibodies and other approaches for targeting proteins with labels.

They are pioneers in the use of antibody display, microinjection of antibodies and use of FKBP protein for targeting proteins within cells.

The contribution of the team members to teaching and to the structuration of the research at the local level is commendable. The team leader is major organizer of a 1 week cell biology course held at the University of Paris with the Institute Jacques Monod head each year. He has also played a role in the development and international distribution of free software for biology.

- Appreciation on the project

The research team focuses on two broad topics related to intracellular organization, 1) the mechanistic basis underlying the Golgi's capacity to undergo shape changes and disassembly, and 2) the role of CLIP170 in the regulation of microtubule organization and dynamics. In addition to these projects, the team has spear-headed technologies relevant to their own and the Unit's needs that include the development of antibodies and binding assays. The team should continue to tackle important questions in the field of organelle biology while moving forward with technology development.

Project I Golgi organization and dynamics. The Golgi apparatus is the major sorting and processing station of the secretory pathway, consisting of hundreds of processing enzymes distributed across a stack of flattened cisternae. Despite its highly organized morphology, the Golgi is very dynamic. The team has been involved in describing these dynamics with the broader goal of understanding its physiological relevance and mechanistic control. One highly interesting discovery by the group is that Giantin, a large coiled coil protein is stably associated with the Golgi. Unlike Golgi enzymes, which in response to a photobleaching assay diffuse quickly into the bleached region, giantin does not, indicating it is highly immobilized on the Golgi. This suggests the protein plays a structural role in Golgi organization. Consistent with this idea, the team found that giantin remains associated with the old Golgi when the organelle undergoes reformation at ER exit in microtubule disrupted cells. The group is currently developing strategies to understand the specific function of giantin in Golgi activity. The team has further used photoconverted diaminobenzidine bound to an HRP substrate moving through the Golgi to inactivate the secretory functions of the Golgi. They found these results in the Golgi recruiting autophagic markers, a result they are following up in future studies. Another approach the team uses to study Golgi function is the FRAP/FKBP system to trap Golgi enzymes in the ER and release them to define the machinery involved in ER to Golgi transport of the enzymes.

Project 2. Microtubules play a critical role in controlling membrane transport among organelles, serving as tracks for motor driven movment of transport intermediates. The team has discovered several key properties of microtubules, themselves highly dynamic, that are relevant to answering the glogal control and organization of organelles. First, they found that CLIP170, associated with the tips of microtubule plus ends, helps control the localization of actin polymerization through recruitment of mDia1, and this plays a role in the regulation of phagocytosis. Second, they found important roles of kinesin protein KIF5B in prevening microtubule depolymerization at the plus end and in stimulating microtubule growth. Third, they discovered that along microtubule filaments there are GTP rich islands, suggesting the tubulin subunits along the filament are not al GDP-bound, as previously thought,with major relevance for microtubule structure and topology. This discovery was made possible by the team's ability to develop a GTP-tubulin specific antibody.

This outstanding team incorporates novel strategies, including photoactivatable fluorescent proteins, FKBP/FRAP trapping of proteins and antibody injection, to understand the dynamics of Golgi trafficking and structure, as well as microtubule behaviour and properties.

- Conclusion :

  – Summary

The team is without question a National leader in the field of membrane organelle biology and microtubules. Their innovative and relevant projects are of broad significance to the cell biology community.

  – Strengths and opportunities

Strong expertise in technology development allows cutting-edge questions to be asked.

  – Weaknesses and threats

Potential dilution of rigorous scientific efforts at the expense of PI's efforts at establishing/sharing novel imaging and marking technologies, balancing community contribution with rigorous science.

  – Recommendations

Help should be provided to support the platform technology development.

Team 9 : Systems Biology of Cell Division and Cell Polarity

Team leader : Mr. Matthieu PIEL

- 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)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	3
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

This group was established 2.5 years ago. Since then the group has capitalised on its biophysical approaches to study both the influence of extrinsic cues on mitotic spindle positioning and the migration of cells in confined environments. Due to the limited size of this team production analysis focuses on the leader activity the applicant is one of the pioneers in using micro-patterns to study the forces and cues influencing the position of the mitotic spindle and adapted the microfabrication techniques to study cell migration. Thus, he has established a relatively unique niche at present, although other groups are also adopting these approaches, and indeed the applicant has helped to

establish a spin-out company to fabricate these patterns. The impact of his research is in part reflected in the adoption of these techniques and approaches by other researchers. The relevance of the work to cells in the context of tissues is, however, less clear at present. The relevance of his findings on cell migration appears to be clearer since the deletion of one chain of the MHC receptor altered cell migration patterns in dendritic cells.

The team leader had a number of high profile publications as last author that stemmed from his work as a post-doc when he was establishing the techniques that he is now exploiting in his own laboratory. Since he only established his laboratory 2 years ago it is too early to expect any publications from the work initiated in his laboratory. Nevertheless he has contributed to several publications in international, high profile journals as a collaborator. He has also been invited to a significant number of meetings demonstrating his high profile in this area of technology.

The team has a number of productive collaborations both within the institute and outside, some of which have already resulted in publications.

- 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 clearly establishing itself as one of the leaders in the use and development of micro patterning to explore cell behaviour. This is reflected in the significant number of invitations to international meetings and to give national seminars.

The group is small but already contains foreign members. It appears to be an attractive place for PhD and post-doc applicants.

The PI has been very successful in raising external funds from national research agencies and from international funding bodies, plus has been involved in starting up a company to exploit the technology he helped to develop.

The team has a number of international collaborators.

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

The team leader is certainly one of the pioneers of the biophysical approaches that he is taking to study cell behaviour.

- Appreciation on the project

This team has a large number of interesting ideas to pursue to exploit their approach to altering the microenvironment of cells. These will likely produce interesting, novel insights into the biophysical properties of cells and subcellular structures. The relevance to cells in tissues remains less clear. The PI has a number of clearly defined grants funding specific projects. As explained above, many of the approaches are currently being pioneered by the group.

- Conclusion :

  – Summary

An excellent young, dynamic investigator with a highly interdisciplinary (interface between biology and physics/engineering) team exploiting relatively unique technologies to ask interesting questions about the biophysical properties of dividing and migrating cells. Global biological relevance of the research questions asked should however not be lost in the attractiveness of the technology.

  – Strengths and opportunities

Strong expertise in biophysics, technology development allows cutting-edge questions to be asked.

  – Weaknesses and threats

Biological relevance is not always clear.

Team 10 : Cell biology of tumor cell invasion

Team leader : Mr. Philippe CHAVIER

- 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)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	1
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	1	1

- Appreciation on the results

The team is led by a senior researcher, who has been working previously on phagocytosis and who has been very successful. He has switched research themes to the mechanisms of 3D migration and invasion. One of the main topics is focused on a specialized structure called invadopodia and on the delivery of a metalloprotease (MT1-MMP) and other compounds of this structure to degrade ECM. More specifically, the team has worked on the role of the exocyst in MT1-MMP recycling and on the mechanisms of actin assembly in invadopodia.

Several original outstanding results have been obtained concerning the role of IQGAP1 in the invadopodial extension, and of VAMP7 in MT1-MMP accumulation. In addition the team has worked on the role of formins in cell migration and has described a new but controversial mechanism of migration/invasion through contractility of the cell rear. The last project concerns ARF6 and its role in endocytic recycling during cytokinesis and in abscission.

The publication record of this team and of its leader is excellent with original papers as last author in Nat cell Biol, Curr Biol (3), J Cell Biol, PNAS and Cancer Research and reviews in Nat cell Biol, Nat Rev Mol Cell Biol, J Cell Sci, and Curr Op cell Biology. It has strong internal collaborations, with three teams, which led to several publications, such as in Mol Cell Biol, Curr Biol, PNAS and EMBO J. It has a long-standing collaboration with a group in the USA and another one with a French group.

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

During the last 5 years, the team leader has been invited to 13 international and 2 national conferences. At the time the team included 1 staff researcher, 3 Post-docs and 1 PhD student. The team leader is the PI of two national funding from the Inca/ARC (218 K€) and the ANR (ANR-blanc 2008)

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

The team appears well positioned within the Institut Curie taking advantage of the imaging facilities. The team leader also organizes a course between the Institut Curie and the Institut Pasteur.

- Appreciation on the project

The team has two main projects on the Invadopodia.

In the first project the investigators will study the trafficking of MT1-MMP through the endocytosis-recycling pathway to the site of invasion. The project is based on the characterization of the exocyst complex by using RNA interference coupled to TIRF microscopy to study the localization of MT1-MMP. In addition using the same approach the team will define the mechanism of vesicle fusion by depletion of syntaxins and the role of SNAP23 and its partners.

The second project appears more original and is based on the discovery by the team that ARF6 binds to JIP3 and JIP4 and controls the endosome transport along microtubules through a kinesin to dynein switch. As JIP3/4 are scalfolding proteins for JNK, ARF6 may influence tumour cell invasion through local regulation of JNK activity. This approach will be mainly focused on the possibility that ARF6 participates in JNK localization in the invadopodia. Two other sub-projects concern the role of HDAC6 and tubulin acetylation in tumour invasion and on the hypothesis that protein translation may occur at the invasive sites due to mRNA polarization.

The team has two important grants which allow them to carry out these two projects. In addition the core facilities of the Institut Curie will facilite this project.

The project is overall original based on previous results of the team and seems quite feasible since it is performed with cell lines with technologies already developed in the team. The use of TIRF microscopy can be identified as a cutting edge technology for this project.

- Conclusion

– Summary

This is a productive team capable of high impact research in cell biology and led by an internationally recognized team leader. The team has an excellent overall achievements and a very high potential working on a hypothesis driven research. The originality of the project is related to the fact that it is largely driven by previous original results obtained by the team and a great competence on ARF6 and the exocyst complex. The project has an important impact in cancerology an is extremely relevant to a Cancer Research Institute because it has as goal a better understanding of the mechanisms of invasion. However their projects will be even more relevant if it could be applied to other cellular models than cell lines, which currently appear as a limitation to this work.

– Strengths and opportunities

- Excellent scientific leadership
- Well structured team with young investigators
- Project well integrated in the UMR and on the major theme of the Institut Curie (breast cancer)
- Feasibility of the project
- Possible link with therapy (HDAC)

– Weaknesses and threats

- Project may be too classical
- No attempt to work on primary cancer cells or on more relevant cellular models.

Team 11: Molecular oncology

Team leader: Mr. Francois RADVANYI

- 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)	0.25	0.25
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	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 other engineers, technicians and administrative staff (Form 2.6 of the application file)	3	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results

The group leader is an experienced cancer cell biologist, focusing on the molecular genetics of mainly bladder and breast cancers. The relevance for cancer research is very high, as research is done on the real human disease instead of cell lines or animal models that quite often fall short when compared to the complex human pathology. The strategy is not really new, and many strong groups are following similar approaches. Nevertheless, the expertise of the group in molecular genetics of bladder cancer is established, and the extension to breast cancer for particular target genes or novel mechanisms of carcinogenesis or cancer progression is a logical one in view of the interaction with the Curie hospital. The embedding of bioinformatics in the group is excellent. One may wonder though whether this cancer-oriented group, which is active in an excellent cell biology department, forms a perfect fit. Opportunities for better integration, in terms of appropriate cell and animal models, could be more actively exploited. In view of novel oncogenes (e.g. TYRO3, p38alpha), novel mechanisms for carcinogenesis (MRES = multiple regional epigenetic silencing), or novel stratifications of bladder cancer patients (alternative pathways to generate Ta or CIS precursor lesions) the group executes innovative work, reflected at this moment by intellectual property (patents) and licensing (industrial agreements), rather than by publications. In terms of health improvement, impact of results in cancer research is usually difficult to predict. In terms of scientific advances, this group performs very well.

In the field of cancer research, this group publishes regularly in excellent (Nat Genet), very good (JNCI, Cancer Res, Hum Mol Genet, Oncogene) to good journals. Also in the field of bioinformatics, the publication output is excellent (Mol Syst Biol) to very good (Bioinformatics).

Partnerships with leaders in the field of both bladder cancer and breast cancer reflect quality. Especially for breast cancer, this is quite important in view of the many strong groups working on it. The stability of several partnerships is evident from co publications over a time span of several years.

- 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 is regularly invited to international conferences, for instance to a Gordon conference in 2008 and to Gordon and CNIO conferences in 2009. However, regarding visibility there is room for improvement (e.g. AACR meetings and awards).

Recruitment of post-docs is limited (presently only 1). On the other hand, the group has many PhD students. A particular advantage is the joining of a research clinician (Fabien Reyal), affiliated with the Curie clinic.

Fund raising is adequate, both at the national and the international level. Industrial interactions are elaborated whenever possible.

The team leader has productive collaborations with national and international cancer researchers of high reputation. The team leader is active in several multicenter studies. There is strategic access to annotated banks of human tumor samples.

As cancer encompasses a variety of diseases, which often remain difficult or even impossible to cure, any progress that leads to more efficient detection, better prognosis or even therapy represents a significant step forward. In this respect, this group is doing a very good job.

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

Good mixture of molecular geneticists, molecular cell biologists, bioinformaticians, medical scientist. There should be room for development of appropriate mouse cancer models. There appears to be a correct focus on cutting-edge projects (like MRES).

- Appreciation on the project

A long term (4 yr) scientific project has been presented by the team leader in a well structured and convincing way.

The team leader emphasized the need for a data manager with permanent position.

Three interesting projects were presented by the team leader.

The first project involves the identification of new therapeutic targets by means of a transcriptomic approach. Emphasis is put on 'druggable' targets: i.e. enzymes that can be inhibited, and proteins with an ectodomain that can be targeted without cell permeabilization. The FGFR3 receptor combines both features and occurs as constitutively active mutants in bladder tumors. The project aims at identifying and inhibiting tumor-specific downstream signalling of FGFR3 and synergistic oncogenic events (like TYRO3 activation).

A second project involves the genetic analysis of tumors, in particular breast tumors, by more classical means like transcriptomic and CGH analyses. Novelty is to be expected by use of novel ways of analyses (like Independent component analysis = ICA), by focus on particular amplicons, by comparison with oncogenic pathways characterized in bladder cancer, by analyzing multiple tumors from the same patients, and by patient stratifications using multiparameter analyses.

The third and most innovative project is the epigenetic analysis of cancer, more particularly early events in bladder and breast cancer. Focus lies on epigenetic silencing of whole chromosomal regions independent of DNA copy number (originally reported by this group: Stransky et al., Nat. Genet. 2006). Recent work by this team demonstrated the importance of such 'multiple regional epigenetic silencing' (MRES) phenotype in malingnant progression of bladder cancers (Vallot et al., JNCI, in press). Silencing was apparently due to histone modifications rather than DNA methylation. The ambitious aim is now to systematically characterize such silenced regions, to identify putative tumor suppressor genes therein, to analyze the mechanisms of formation of such regions, and of course to translate these findings to the clinic.

- Conclusion :

– Summary

The team is led by an established cancer researcher addressing the molecular complexity of particularly bladder cancer in a multidisciplinary and successful way. This project is highly relevant for human cancer. Several novel genes and even novel mechanisms of carcinogenesis have been discovered and are presently under further study.

– Strengths and opportunities

- Good mixture of molecular (cell) biology, molecular genetics, bioinformatics. Good interaction with the clinic, what increases strongly the relevance of basic cancer research.
- Good interaction with other cancer researchers worldwide.
- Good access to cancer biobanks.
- Innovative mechanisms and hypotheses.
- Realistic potential for industrial alliances.

– Weaknesses and threats

- Group may be too small to either remain competitive or to become really competitive with the strongest players in the cancer research field. This should however not be a problem at the national level. More post-docs may strengthen the group.
- Focus of the group may be too diluted to either remain competitive or to become really competitive with the strongest players in the cancer research field. As too many tumour types, too many genes, too many mechanisms appear to be under study, the group may gain in competiveness by focusing on their most innovative and exclusive findings only.
- Lack of appropriate cellular and animal models. This is an inherent problem due to the complexity of cancer rather than a wrong strategy of the group. Nevertheless, the group may consider opportunities to make appropriate cell and mouse models, better reflecting their innovative findings in human cancer patients.

Team 12 : Molecular mechanisms of the mammary gland development

Team leader: Ms. Marina GLUKHOVA

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

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)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

The team studies the molecular mechanisms of the postnatal mammary gland development in the mouse. The mammary epithelium is organized as a bilayer, with a luminal layer of secretory epithelial cells, and a basal myoepithelial layer. In functionally differentiated mammary gland, during lactation, luminal cells produce milk, whereas myoepithelial cells are contractile and serve for milk expulsion

The team has continuously published over years with one well recognized work published recently in Nat. Cell Biol.

The team has several national and internationally collaborations where partners mostly provide transgenic mice and the collaborative work resulted in publications.

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

The team has a well recognized expertise in mammary gland development and is well recognized on a national level. It is supported by national funds of the ARC, LNCC, and ANR. The team leader and the senior scientist of the group presented the work on national and international meetings.

- Appreciation on the project

During the period of 2005-2009, the projects developed by the team were focused on the analysis of the role of the interactions between basal epithelial cells and the extracellular matrix (ECM) in mammary development; the identity and characteristics of basal-type mammary stem/progenitor cells; and the cellular and molecular events at the origin of basal-type mammary carcinomas. Several compound mice were generated to delete integrins or to over express mutated ß-catenin in the basal myoepithelial layer and the resulting phenotypes were analyzed. This work will be extended by adding mutants for p53 and c-Myc and by analyzing the role of podoplanin in the basal-type of progenitor cells. Overall this is a solid research program.

The cellular and molecular mechanisms underlying the formation of the various mammary epithelial cell types are poorly understood. To characterize relevant signaling pathways, putative mammary stem cells, and their relationsship to mammary tumorigenesis is the long-term goal of the group.

- Conclusion :

  - Summary

This is a very focused and solid research project with clearly defined goals. It fits to the general mission of the Curie Institute.

  - Strengths and opportunities

The use of animal models for breast cancer is clearly in the interest of the Curie Institute.

  - Weaknesses and threats

A potential weakness is that the team uses the usual candidates in altering the development and the physiology of the mammary gland.

Team 13 : Cytoskeletal Architecture and Cellular Morphogenesis

Team leader : Mr. Phong TRAN

- 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)	2	2
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)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	0
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

The team is interested in the cell biological mechanisms by which the cytoskeleton impacts on the morphogenesis of living cells. Their work has so far focussed on the model organism S. pombe, which has a well-polarised interphase cytoskeleton. Key contributions have been made concerning the related roles of microtubule dynamics,actin dynamics, motor activity and filament crosslinking in setting up and maintaining the interphase

cytoskeleton, and on the molecular mechanisms by which the self-polarisation of the interphase cytoskeleton drives the polarised growth of the cell. In exciting new work done in collaboration with P. Nurse, two complementary mechanisms have been discovered that direct the S. pombe cytokinetic ring to assemble at the midline of the cell. Very recent work addresses the molecular mechanisms of stabilisation of the central spindle and of spindle pole body replication. All these experiments successfully address large and important biological questions in inventive and effective ways.

Publication record over the review period is exceptional: all publications are in high impact journals, including Nature (2009), Nature Cell Bio (2007, as an invited commentary and not research paper), Cell (2007), Dev Cell (2009), Curr Biol (2008,2009), PLoS ONE (2007). Each paper makes a distinct, original and well-defined scientific contribution.

The team leader and the senior scientist have long-standing and successful collaborations, including that with Nurse (Rockefeller) on cytokinetic ring assembly, Nedelec (EMBL) on modelling and simulation, and Sato (Tokyo) on spindle pole body duplication.

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

The team has an international profile and has a very substantial and sustained record of contributions.

The team leader received the 2005, MC McCabe young investigator award ; 2007, Michael Brown Young investigator award. The international profile of team is reflected in 8 invitations of the team leaderto international conferences. Coworkers have also been invited, and in particular large numbers of posters have been presented by coworkers at international meetings.

The group is extremely well-reputed and well connected and has no problems to recruit high quality co-workers.

Funds are provided by the UMR144, Curie, CNRS, and external grants from ANR, Mairie de Paris (Programme emergence), LNCC and ARC.

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

The team is successfully co-directed by the team leader and a senior scientist. The team leader chairs the advisory board of the Curie light microscopy imaging Platform. He is overseeing and advising on its development and ensuring its efficient usage.

- Appreciation on the project

The team proposes an exciting, cutting-edge proposed program. It has only been established for two years, and is already very successful. It is proposed to continue all three themes (specification of polarised growth. Sites, specification of medial cortex, mechanism and control of spindle pole body réplication). All the proposed projects address central biological questions, using creative approaches, including novel engineering-based approaches. It is proposed to add a fourth project, meiosis in the worm C. elegans. This last represents an especially creative new direction to go into.

- Conclusion :

– Summary

The level of achievement and the proposed program are both outstanding.

– Strengths and opportunities

The team leader is an established highly scientifically successful international figure.

– Weaknesses and threats

Downsizing from a US lab to join Curie. Many benefits but the team leader should be aware that resources may become limiting.

– Recommendations

Provide C. elegans facilities.

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

Team 1: Molecular mechanism of intracellular transport

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

Team 2: Structure and membrane compartments

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

Team 3: Morphogenesis and intracellular signalling

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

Team 4: Traffic, signalling and delivery

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

Team 5: Biology of centrosomes and cilia

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

Team 6: Biophysical and molecular basis of cell adhesion and migration

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

Team 7: Structural Motility

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

Team 8: Dynamics of Intracellular Organization

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

Team 9: Systems Biology of Cell Division and Cell Polarity

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

Team 10: Cell biology of tumor cell invasion

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

Team 11: Molecular oncology

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

Team 12: Molecular mechanisms of the mammary gland development

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

Team 13: Cytoskeletal Architecture and Cellular Morphogenesis

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

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Observations générales sur le rapport AERES

Overvall appreciation

We thank the committee for the overall very positive appreciation of the Unit. We plan to implement the main constructive recommendations for the Unit and for each individual team. In particular, special attention will be paid to establishing mentoring programs for post-docs and young group leaders.

However, we consider that the criticisms raised about Team 6 and Team 11 are not fully justified and detailed answers to the committee's comments are given below. In particular, we wish to emphasize that Team11 has developed state-of–the art system biology approaches devoted to cancer biology leading to the identification of several essential candidate genes for bladder cancer progression. The team leader is considered as one of the world leader in this field. Studies performed by this team are very important to strengthen cancer-related research in the Unit and to reinforce the links with the Curie Hospital. We consider this team as one of our major asset in our effort to bridge cell and cancer biology. Furthermore, the Head of Institut Curie Research Center fully supports this branch of activity of this team.

Team 1 (Bruno Goud)

We apologize for the lack of clarity pointed out for project 3. We have recently developed a computational imaging approach that uses the values from 3D automated image acquisition to describe the 2 or 3D organization of endomembranes with probabilistic density maps in micropatterned cells. This approach allows for the detection of even subtle changes in steady-state organization of endomembranes (Schauer et al., *Nat Meth* in press). We are not merely applying existing off-the-shelf quantitative analyses, but we are developing tailor-made analyses which requires the development of new statistical methods. This project will advance both biological and statistical/mathematical knowledge.

The main questions we want to address in the near future is to describe the spatial organisation of pre- and post-Golgi biosynthetic and endocytic compartments and to investigate the molecular mechanisms that position these membranes in response to polarity

clues. In particular, we will investigate the role of extra-cellular matrix (ECM) and the role of the nucleus-centrosome-Golgi apparatus connectivity on intracellular membrane organisation. The expected results are i) to understand how pre- and post-Golgi Rab-mediated transport cascades are spatially organized; ii) how biosynthetic and endocytic/recycling routes are interconnected; iii) the role of ECM geometry on post-Golgi compartments organization; and iv) the correlation between cytoskeleton organization and endomembrane positioning. Combining micropatterning with endomembrane density maps represents a powerful tool to address these issues.

Team 2 (Graça Raposo)

Given the specialized expertise in electron microscopy and intracellular trafficking it is in our belief important to share this knowledge by providing training and establishing collaborations. Nevertheless we agree that it is sometimes impossible to handle to many projects at the time with risks of impacting on the own research projects of the team. We will be careful in maintaining the balance.

Team 6 (Sylvie Dufour)

As mentioned by the committee, our team has addressed complex and relevant biological questions using original approaches. Our past studies revealed a crosstalk between adhesion receptors in the control of cellular mechanics in vitro and cell behavior in vivo. Our project for the next years is to provide a deeper insight into the molecular mechanisms underlying this crosstalk in vitro and also in vivo, during embryonic development. We think that this is an appropriate and highly relevant question of clear biological significance.

The various aspects of our project concern the role of adhesion molecules in the regulation cell adhesion and migration in response to environmental cues. While these aspects might appear diverse we included them in our project, because currently we are exploring various hypotheses concerning the molecular control of cell behavior with the objective to focus on the most promising one. We disagree than the project is derived form the access to specific techniques and biological materials and models available. We have developed and adapted some technologies and models in order to address our biological questions (and not vice versa).

We have only in our team a main topic, which is focused on the molecular mechanisms controlling development, and it includes in vivo studies. One permanent researcher, the team leader and an excellent graduate student are involved in this project. In addition, biophysical aspects of our project will be developed in close collaboration with biophysicists who will provide human resources for this work. We are convinced that the close interactions and collaborations in the course of the biological and biophysical studies will be fruitful and help our small team to successfully accomplish the project.

From 2003 to the end of 2007, I have been leading my own research group within the team of Jean-Paul Thiery at the UMR144. Since 2007, I conduct my research as an independent team leader in UMR144. Since 2003, I am the principal author (last and corresponding author) in all the papers produced by my group, including those published in very good journals as mentioned by the AERES committee. Some of the research projects that I initiated before 2007 still have to be accomplished, and therefore, for obvious reasons, to avoid redundancy or competition, I maintained my collaboration with the former team leader. Independently, I have developed several national and international collaborations with

developmental biologists that have an internationally recognized expertise. I am sure that a scientific exchange and collaboration with these laboratories will be an excellent support for our team in the future.

Team 9 (Matthieu Piel)

The main recommendation of the committee is the following: “biological relevance of the research questions asked should however not be lost in the attractiveness of the technology.”

I am well aware of the danger of working with cultured cells, and moreover with new tools that do not have a long history of validation. This is exactly why I think that a team like mine has to be embedded in a biology lab like UMR 144. It is also why I have several strong collaborations with other teams of biologists working on morphogenesis of yeast cells, or on migration of dendritic cells. The relevance of this work was acknowledged by the biologist community and our work was published in high profile journals (Current Biology and Science). I also plan to reinforce the work on in vivo validation of phenomena we described in vitro, in collaboration with developmental biologists on questions related to cell division. Nevertheless, I am convinced that the new experimental approached we develop, allowing to quantitatively manipulate the cell microenvironment, will allow, as live cell microscopy did on the last fifteen years, to deeply renew our understanding of cells. Many questions can only be asked in vitro in a first time, as physical and chemical parameters of the micro-environment are difficult to quantitatively modify in tissues, but it is of course compulsory to validate observations made in vitro on more physiological systems.

Team 10 (Philippe Chavrier)

We agree with the committee that we are applying classical concepts of modern cell biology to understand a biological process, *i.e.* the migration of invasive tumor cells, a field which until recently largely underestimated the contribution of membrane trafficking and cell polarization to the capacity of tumor cell to spread and disseminate. It is our opinion that recent reports documenting the importance of integrin recycling for invasion of ovarian cancer cells and the role played by p53 in this process, as well as our own work on the trafficking of MT1-MMP, a matrix metalloproteinase that is emerging has a major player during metastasis provide clear demonstrations that classical cell biology is perfectly relevant and will contribute significantly to the understanding of a complex phenomenon such as tumor cell invasion.

Team 11 (François Radvanyi)

We are quite surprised to notice some contradictions in the report concerning our Oncology Molecular Group leading to a confuse feeling about your appreciation. For examples, first in the Appreciation results “the strategy is not really new” but “the group executes innovative works”, then on one hand, it is mentioned in the Appreciation of the strategy that “there appears to be a correct focus on cutting edge projects” and on the other hand it is mentioned in the Weaknesses and Threats that “focus may be too diluted”. In general, we do not really understand the conclusions established in the Weaknesses and Threats in view of the overall report.

The main criticisms in this report section are that we are not enough focused since "too many tumor types, too many genes, too many mechanism appear to be under study" and the "lack of appropriate cellular and mouse models".

A significant proportion of the activity of the group is devoted to a systems biology approach to cancer using large-scale data. It is inherent in the nature of this approach, by contrast to reductionist approaches, to reason more in terms of groups of genes and pathways than in terms of individual genes.

Concerning the number of cancer studied we focus on two cancers in particular: breast and bladder cancer. We do also publish work on other cancers, but this work involves the occasional application of our expertise to a particular question and represents a very small part of our research effort. For bladder cancer, the strategy adopted is to work from human samples to animal models, identifying the genetic and epigenetic changes involved in tumour progression. This global approach to bladder cancer has proved highly fruitful. By contrast, for breast cancer, we focus on one subject, arising directly from our work on bladder cancer — regional epigenetic silencing, — a subject almost completely unexplored by other groups, despite the major international efforts devoted to breast cancer. Our work on breast cancer and similar studies on bladder cancer provide fertile ground for interaction, with each area of research benefiting from the other. We therefore see our decision to work on two different cancers as an additional strength, rather than a weakness. We have worked on bladder cancer for many years and have constructed national and international networks. Our work on bladder cancer is recognized worldwide. We may be considered newcomers in the field of breast cancer, but our relative lack of experience in this field is compensated by our decision to tackle very new topics in this cancer and by the collaborations we have established within the Institut Curie and with leading groups in the field of breast cancer at Institut Paoli-Calmettes in Marseille (Daniel Birnbaum) and at the University of Amsterdam (Marc van de Vijver), where one member of the team worked for one year.

Finally, concerning the criticism of lack of appropriate cellular and animal models (mentioned twice). This comment is not really fair. Concerning the cell lines, to study and mimic the Ta pathway of bladder cancer characterized by FGFR3 mutations, we were the first group to establish engineered cell lines and to identify epithelial human bladder derived cell lines expressing mutated FGFR3 which allowed us to demonstrate the oncogenic properties of this major oncogene in bladder cancer (Bernard-Pierrot et al., 2006). It should be noted that those models allowed us to collaborate with pharmaceutical companies. Concerning the mouse models, we have developed two mouse models to study the role of the FGFR3 oncogene in vivo. One enabled us to show that clonal oncogene activation was responsible for the occurrence of a benign tumour, sebborheic keratosis (Logié et al., 2005). It is true that the relevance of the second transgenic model to the human situation was demonstrated only recently and that no mention of this was made in our written report. We did show it in the oral presentation, but this was missed by the reviewer. We had also described in the presentation the use of a chemically induced model of bladder cancer that we had used to study synergy between carcinogen and mutated FGR3 and to study the role of lactadherin in bladder cancer development.

Team 12 (Marina Glukhova)

A potential weakness pointed out by the committee is that the team uses the usual candidates in altering the development and the physiology of the mammary gland.

We, therefore, would like to comment on our choice of the molecules whose role will be investigated by our team. We have chosen to perturb Myc and p53 pathways as they are

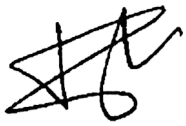
known to be altered specifically in basal-like carcinomas, the type of mammary tumors we are working on. Although the corresponding studies are numerous, currently, the data on the functions of Myc and p53 in the epithelial stem cells are either unavailable, or contradictory.

Roles played by specific integrins and, consequently, by their extracellular matrix (ECM) ligands in mammary development deserve to be investigated, as integrins are essential for adhesion, migration and associated signaling events, all crucial for epithelial morphogenesis. Further, cell-ECM interactions have been implicated in the maintenance of the mammary stem cell population (Taddei et al., 2008). We now would like to define contribution of specific integrins and their ECM ligands in the mammary stem cell niche.

Finally, podoplanin has been recently identified by our team as a new mammary stem cell marker. Although this molecule has been implicated in cell migration and tumor invasion, its role in mammary morphogenesis is completely unknown.

Team 13 (Phong Tran)

It is suggested that the team leader should be aware that resources may become limiting in his transition from the US to France. In fact, we are fully aware of the perceived differences in the scientific culture and practice between the US and France. Nevertheless, in the two years of starting the lab, we have successfully competed for external grants, and we have recruited very able students and postdocs. We are quite confident that we will be successful in launching our research program at the Curie in Paris.



Bruno Goud
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