Institut de biochimie et génétique 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

Institut de Biochimie et Génétique Cellulaires

From the

CNRS

University Bordeaux 2

May 2010

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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 : Institut de Biochimie et Génétique Cellulaires

Requested label : UMR CNRS

N° in the case of renewal : 5095

Name of the director : M. Bertrand DAIGNAN-FORNIER

Members of the review committee

Committee chairman

M. Michel KOENIG, IGBMC, Strasbourg, France

Other committee members

M. Jean-Claude MARTINOU, University of Geneva, Switzerland

M. J.-W. TAANMAN, University College London, London, UK

Mrs Evelyne DUBOIS, CERIA, Bruxelles, Belgium

M. Mick F TUITE, University of Kent, Canterbury, UK

M. Tomoyuki TANAKA, Wellcome Trust Centre for Gene Regulation & Expression, Dundee, UK

Committee members suggested by CNU, CoNRS, CSS INSERM, CSS INRA, INRIA, IRD

CoCNRS representative : Mrs Isabelle MUS-VETEAU,Nice University, France

CNU Representative : Mrs Monique LOMBARDY ALRIC, ERT, CIDAM, Clermont-Ferrand, France

Observers

AERES scientific advisor

Mrs Catherine DARGEMONT

University, School and Research Organization representatives

University Representative : Mr A. BLANCHARD (Bordeaux II)

CNRS representative : M. S. TOMAVO

Report

1 • Introduction

- Date and execution of the visit

The visit took place from November 5th, 9 am, until November 6th, 5 pm. It was subdivided in presentation of the AERES committee, overview by the director of IBGC, activity and projects presentation by the team leaders, parallel meetings with permanent scientists and post-docs, ITA (engineers, technicians, administrative assistants), students, meetings with past and future directors, with university and CNRS representative, and final discussion of the AERES committee. Ample time was given for questions after each team leader presentation.

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

The Institut de Biochimie et Génétique Cellulaires (IBGC) was founded by the CNRS on the campus of the University of Bordeaux II. It is an "unité mixte de recherche", UMR 5095, with two heading institutions: CNRS and Université de Bordeaux II. The "IBGC" building is run by the CNRS, but team 13 (future team 11) is located in the university building, at a short walking distance. The scope and focus of IBGC research activities was initially centered on yeast and fungi biology, with major fields of research on metabolism, mitochondrial biology and chromosome transmission. In the last years, new interests and research activities have emerged on cell death mechanisms and extension of the model systems to mammalian cell biology, still centered on metabolism, mitochondrial biology and chromosome transmission.

- Management team

The director is assisted for his director task by the « bureau », consisting of the leaders of the 13 other teams. Due to retirement of the actual director before the end of the next reporting period, the PI of team 4 has been proposed to take over the director position, from 2011 to 2014.

- 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)	**16**	**16**
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	**27**	**26**
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	**32**	**NA**
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	**23.9**	**23.9**
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	**0.8**	**0.8**
N6: Number of Ph.D. students (Form 2.8 and 2.9 of the application file)	**34**	**9**
N7: Number of staff members with a HDR or a similar grade	**28**	**27**

NA: non applicable

2 • Overall appreciation on the research unit

- Summary

The IBGC has a strong emphasis on mitochondrial research, metabolic and cellular regulations, and cell death mechanisms, by using as first models yeast and fungi systems. Teams from IBGC have made key discoveries in the fields of faithful chromosome segregation during mitosis and meiosis, of epigenetic determinants, especially prion proteins, in vegetative incompatibility and cell death, of regulations of purine pathways and their links with pyrimidine, histidine, phosphate and one-carbon metabolisms, of structure-function of mitochondrial complexes (mostly complex V), and of mechanisms of cellular quiescence and cell death by apoptosis, autophagy and mitophagy, which are important processes that play a role in cancer and degenerative diseases. Scientists from IBGC were the first to discover the existence of storage granules during quiescence, the first genes involved in mitophagy in yeast and the dimeric nature and structure of the mitochondrial complex V. This has resulted in very good publications during the last 4 years.

- Strenghts and opportunities

The originality of the institute is that many teams share the same model systems, including saccharomyces cerevisiae, Schizosaccharomyces pombe and Podospora anserina, and emergence of mammalian cell models. In addition, the institute is has leading equipements for structural biology, and metabolomics.

- Weaknesses and threats

The major weakness of IBGC is its low local and international visibility.

In addition, an important need to reorganize some teams has been initiated but should be pursued.

- Recommendations to the head of the research unit

Between the past and future reporting periods, four teams out of fourteen will disappear, either due to leave of the team leader (2 teams) or to integration of a team that has become too small or insufficiently productive (2 teams). The AERES committee members fully support these perspicacious restructurings, as well as the emergence of a new team (future team 5) by internal growth. The committee members believe that this restructuring should even go one step further, by merging the teams identified as weak (teams 8 and 13, future teams 7 and 11) with the most appropriate partner teams, in order to gain scientific and organisational visibility. The merging of the two teams working on prion proteins is also a serious option that should help to create momentum and gain visibility. Teams working on autophagy and mitophagy, two related projects, should work in close proximity. Overall, the institute needs a stronger lead from the top.

This restructuring should also help to organise a fairer distribution of staff and personnel accross the building and across teams.

The future director wishes to further develop the mammalian cell model systems and to introduce small animal models such as C. elegans system, in order to extend the breadth of relevance of the current scientific projects (molecular mechanisms of chromosome transmission, metabolomic studies, prions and cell death mechanisms). The AERES committee fully supports the further development of mammalian cell model systems and the introduction of small animal models such as C. elegans system, in order to extend the breadth of relevance of the current scientific projects.

Provision of common services was noted and were extensively used by the teams (electron microscopy, mass spectrometry, cristallography). These services need improved scientific supervision, to decide for priorities and management.

During the meeting with «ITA»s, the engineers and technicians have expressed the wish that the directors (past and future) establish a common policy for all teams and facilities with regards to inclusions of engineers and technicians among co-authors in publications. This is important as it may impact the individual careers. For more visibility of opportunities, the CNRS engineers and technicians have also expressed the wish to be proposed for promotion via an official « concours » and commission examination, as it is already the case for Administrative and university staff. As stressed by the director, CNRS and University staffs have unequal access to in-service training, with a more favorable situation for CNRS staff. This is also important since it also impacts the individual careers.

- Production results

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

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	38
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	33
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)] x 100	88,4%
A4: Number of HDR granted during the past 4 years	3
A5: Number of PhD granted during the past 4 years	23

3 • Specific comments on the research unit

- Appreciation on the results

The IBGC has a strong emphasis on mitochondrial research, metabolic and cellular regulations, and cell death mechanisms. The originality of the institute is that many teams share the same model systems, including saccharomyces cerevisiae, Schizosaccharomyces pombe and Podospora anserina, and emergence of mammalian cell models.

With the exception of 2-3 teams, there is a general lack of translational research.

Most teams of the IBGC have very good publication records. What is missing however, is a few more excellent publications (ideally published in high impact factor journals) for the sake of international visibility.

Overall, most teams do not have sufficient oral presentations at international meetings. This should be improved.

Over the last four years, the IBGC has trained a good number of PhD students. In order to meet the few more excellent publications, the IBGC need to increase the number of recruited post-docs. Teams that are unable to recruite high-profile post-docs should be merged with more internationally visible teams.

Some interesting patents, could be improved

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

In general, the number of invitations to international conferences is not sufficient given the size the institute. The institute has a very good recruitement from French scientists having done post-docs abroad. On the other hand, the number of post-docs is insufficient. Every attempt should be made to recruit non-French post-docs.

Many teams have secured funding by successful applications at the ANR (blancs) and Région Aquitaine agencies. For the sake of visibility, granting from European fundings should also be sought

The institute has participated to the establishement and development of the « Meetochondria » network. There is a very uneven distribution of international collaborations across the groups. Teams 1, 2, 3, 10 and 12 have very good international collaborations. This is much less the case for the other teams.

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

Between the past and future reporting periods, four teams out of fourteen will disappear, either due to leave of the team leader (2 teams) or to integration of a team that has become too small or insufficiently productive (2 teams). The AERES committee members fully support these perspicacious restructurings, as well as the emergence of a new team (future team 5) by internal growth. The committee members believe that this restructuring should even go one step further, by merging the teams identified as weak (teams 8 and 13, future teams 7 and 11) with the most appropriate partner teams, in order to gain scientific and organisational visibility. The merging of the two teams working on prion proteins is also a serious option that should help to create momentum and gain visibility. Overall, the institute needs a stronger lead from the top.

This restructuring should also help to organise a fairer distribution of staff and personnel accross the building and across teams.

Provision of common services was noted and were extensively used by the teams (electron microscopy, mass spectrometry, cristallography). These services need improved scientific supervision, to decide for priorities and management.

The IBGC has developped its activities mostly (but not only) along two major lines which are mitochondrial biology and structural biology of mitochondrial proteins. For the first line, the IBGC has made important efforts, both by equipments and by new team recruitements, to extend the expertise of yeast mitochondrial biology to mammalian (human) mitochondrial biology, which give to the institute a very comprehensive view over the mitochondrial biology filed and open the way to translational and medical research. This novel expertise in mammalian cell biology was also of direct benefit for the teams working on prion proteins and on cell metabolism and physiology. Equipements and access to large facilities for structural biology, which is one of the strong field of the institute, have been substantially strengthened during the last 4 year period. Scientific animation was limited. Seminars are sporadic and not on a regular scheduled basis

The institute employs 16 researchers with teaching duties, who make strong ties with undergraduate students of university Bordeaux II. All teams, irrespective of their teaching duties, have trained an important number of PhD students (34 over the last 4 years for the entire institute).

- Appreciation on the project

Most teams that are maintained for the renewal of the Unit have an excellent long term scientific project, sometimes slightly overambitious compared to the size of the team or to the available funds (as indicated in the details). Only the projects of teams 8 and 13 (future teams 7 and 11) were deemed unconvincing, given the high competition in their respective fields.

The future director wishes to further develop the mammalian cell model systems and to introduce small animal models such as C. elegans system, in order to extend the breadth of relevance of the current scientific projects (molecular mechanisms of chromosome transmission, metabolomic studies, prions and cell death mechanisms). The AERES committee fully supports this view, since expertise and equipements are very similar both types of developments. Molecular mechanisms of chromosome transmission, metabolomic studies, prions and cell death mechanisms were identified as very original and cutting edge projects. These projects should be strongly supported.

Each team has its own financial support. Purchase of general equipments and allocation of space and human resources are discussed by the « bureau ».

During the meeting with «ITA»s, the engineers and technicians have expressed the wish that the directors (past and future) establish a common policy for all teams and facilities with regards to inclusions of engineers and technicians among co-authors in publications. This is important as it may impact the individual career. For more visibility of opportunities, the CNRS engineers and technicians have also expressed the wish to be proposed for promotion via an official « concours » and commission examination, as it is already the case for Administrative and university staff. As stressed by the director, CNRS and University staffs have unequal access to in-service training, with a more favorable situation for CNRS staff. This is also important as it also impacts the individual career.

The directors, scientists and ITA are worried about the low renewal of ITAs positions from the heading institutions.

4 • Appreciation team by team

Team 1 : Molecular mechanisms of chromosome transmission

Team leader: M. Jean Paul Javerzat

- 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)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
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)	2	1
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

Team 1 members are interested in chromosome biology and they particularly study the mechanisms ensuring faithful chromosome segregation during mitosis and meiosis in Schizosaccharomyces pombe. They started to investigate the biological roles of heterochromatin in centromere function and their work revealed a functional relationship between heterochromatin and cohesion. This has led this group to focus on regulation of cohesins and Shugosin, both of which are involved in sister chromatid cohesion and in properly orienting kinetochore-microtubule interactions. They identified and characterized the key regulation of Shugosin by Bub1 during meiosis. They also identified novel regulators Ssl3 and Wapl/Pds5, which are involved in cohesin loading on chromosomes and in cohesin turnover during the cell cycle, respectively. These studies have revealed how cohesins and Shugosin are regulated to ensure proper chromosome segregation in mitosis and meiosis, making important contributions to the research field.

During the last 4 years, Team 1 published 3 papers, two in Current Biology and one in EMBO journal, all are in excellent international journals with high impact factors. In the past, they also published a relatively small number of papers in high-impact journals. All these papers have been highly cited. Thus this group seems to favour the quality rather than the quantity in publication. The committee positively supports this strategy because it helps to enhance international visibility of the group in this competitive research field.

- 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 4 years, the group members gave 4 invited talks in international research conferences, which also provides evidence that the works of this group are highly acknowledged in the research field.

At the present time, the team is composed of 6 researchers, mainly French scientists. The team is active and successful in training PhD students. For example, one PhD thesis has been recently defended.

Recruitment of suitable post-docs and PhD students from abroad may improve productivity of the group further.

This team has successfully obtained 3 grants for the last 4 years, which is far above the average. To hire new post-docs, it is preferable to acquire more grants.

The team 1 leader has established strong international collaboration with experts in the research field.

Because the basic regulatory mechanisms for chromosome segregation and sister chromatid cohesion are well conserved from yeast to vertebtares, it is likely that research outcomes from this team would reveal the mechanisms in human cells. Therefore the research of this group has potential medical relevance.

- Appreciation on the project

The team 1 proposes to investigate the roles of Wapl/Pds5 in cohesin turnover as well as functions of cohesins in gene expression. This group has already obtained interesting results along these lines, which establishes this lab as one of the most active groups studying the role of Wapl/Pds5 in fission yeast. His results showing regulation by cohesins of sub-telomeric gene expression are also exciting and may indeed reveal novel roles of cohesins in gene expression and silencing. All these projects are indeed feasible using the current expertise in this lab and based on already-established international collaborations. On the other hand, these are research subjects currently under fierce competition. To make greater contributions to the field, it will be crucial to consider how fission yeast can be uniquely useful to address these subjects, compared with budding yeast and vertebrate cells that are already used by many research groups.

The proposal contains several orginal and innovative ideas. If the project is successful, they will identify novel substrates of Eso1 acetyl transferase, which would give new insights into mechanisms for establishment of sister chromatid cohesion. The regulation of sub-telomeric gene expression by cohesins is also exciting and may indeed reveal novel roles of cohesins in gene expression and silencing. However according to the team leader's presentation, it appeared that the approach proposed to confirm the attractive hypothesis that a trans-acting non-coding RNA might trigger the nucleation of heterochromatin will not be used. This could mean that this group will not continue to address this interesting problem establishing a link between cohesin and gene expression.

Team 1 apparently secured its ressources for the next years. No particular problems were brought for discussion during the meeting.

- Conclusion :

– Summary

Team 1 has published high-quality research papers in high-impact journals, making important contribution to the research field of chromosome segregation. The team leader proposes innovative research projects, which will be feasible based on their expertise. In the institute, this team is one of the most productive groups at least in terms of quality (rather than in quantity), delivering seminal research outcomes.

– Strengths and opportunities

In spite of fierce competition in the research field, the team leader has been maintaining very good international reputation. He has a good chance to improve his international visibility further by successfully conducting his excellent research proposals during the next 4 years.

– Weaknesses and threats

The team leader has several strong competitors who are working on similar subjects using budding yeast and other organisms. There is a risk that his discovery is scooped by his competitors even if he finds something very novel in the near future. It will be crucial to consider how fission yeast can be uniquely useful to address the subjects of his interest.

– Recommendations

1. Given that team 1 is one of the most productive groups in the institute, this team should be given high priority in resource allocation in the institute, for example, for lab space and access to various research services.

2. Recruitment of more post-docs and PhD students, especially from abroad, would further enhance productivity of the team and its international visibility.

Team 2: Non-self recognition in fungi

Team leader: M. Sven SAUPE

- 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)	2	2
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)	3	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)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	0
N7: Number of staff members with a HDR or a similar grade	3	4

- Appreciation on the results

The work carried out by this team has been focused on the genetic control of vegetative incompatibility (VI) in the fungus Podospora anserina and has had two distinct elements: analysis of non-allelic VI (Accelerated cell death in Podospora autophagy mutants/The HET domain as cell death effector domain/Extreme evolutionary plasticity of the het-e, het-d and het-r incompatibility genes) and the role of epigenetic determinants in VI, specifically the [Het-s] prion (correlation of structure and infectivity in the [Het-s] prion/ Role of Hsp104 in [Het-s] prion progression/Non-prion amyloids of HET-s/[Het-s] propagation in a foreign host/E,coli inclusion bodies of HET-S are prion amyloids). Few groups outside Bordeaux work with this particular fungal species and where they do, the focus is primarily as a model for cell senescence in fungi. The work being carried out by team 2 is therefore unique and is undoubtedly having an international impact on several fronts. The quality of the work reported is high and in particular the work on the [Het-s] prion has been recognised as being ground breaking, of wide significance and contributing to the emerging field of prion-based epigenetic inheritance. Although working on a fungal prion per se is not novel (there is considerable interest and activity in yeast prion research) neverthless this team's work makes an important contribution not least because it shows that prions are not restricted to one yeast species.

The team is composed of 6 permanent members (5 scientists and 1 TCE): Four of them have a habilitation to lead research (HDR). The team have produced a number of high quality publications in major peer-reviewed research journals over the review period, some of which have been in collaboration with other researchers in Europe or the USA. Journals where the research has been published include Molecular Cell, J. Biol. Chem, J. Mol Biol. and Nature. Three PhD students have successfully defended their theses in the period. The group – and espcially the team leader– have written a number of important review articles that will have been widely read. We also note a very good activity of publication for the PhD students and thepost-doc in this same period.

The team has been involved in a number of productive research collaborations over the review period primarily in relation to their studies on the [Het-s] prion. These have resulted in major publications and have allowed the team to broaden their approaches to the study of the prion by including structural biology/in vitro approaches to complement their predominantly in vivo approaches. There has also been a long term link with the group of Fons Debets in Wageningen in the analysis of VI in natural populations of P.anserina. The collaborations entered into therefore have increased the productivty and impact of the research being done by the team in Bordeaux. Several of the partnerships described appear to be ongoing and will continue through the next 4 year period

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

There is evidence that papers on the research have been presented at various national and international conferences – although perhaps not as many as one might have expected (3 invited lectures are reported). The team leader has been invited to speak at two major prion/protein misfolding conferences in 2005 and 2009.

A new staff scientist joined the team in 2007 following a period as a postdoctoral researcher in the UK. The quality of the current research team looks strong on paper.

Four research grants are listed as having been awarded during the review period but none of these run beyond 2009. In only one case is the PI/grant co-ordinator the team leader and the role of the team leader in the other three is unclear or what level of resource these grants provided the team with over and above that provided via CNRS funding

The team has been involved in a number of productive research collaborations over the review period primarily in relation to their studies on the [Het-s] prion, specifically with leader teams of the field at the ETH of Zurich. These have resulted in major publications and have allowed the team to broaden their approaches to the study of the prion by including structural biology/in vitro approaches to complement their predominantly in vivo approaches. There has also been a long term link with a group in Wageningen in the analysis of VI in natural populations of P.anserina. The collaborations entered into therefore have increased the productivity and impact of the research being done by the team in Bordeaux. Several of the partnerships described appear to be ongoing and will continue through the next 4 year period.

- Appreciation on the project

Their attempts to understand the molecular events associated with VI have thrown up as many intriguing questions as there have been clear cut answers. Of particular importance is their finding elaborated in the hypothesis that forms the basis of the planned work, namely that the VI system in P. anserina (and some other – but not all – fungi) may actually represent an evolution of a rudimentary host-pathogen defence system akin to innate immunity seen in higher organisms. The programme of research outlined does have an element of risk involved particularly since much depends on their identifying a suitable pathogen of this fungus, to rigorously test this exciting – and potentially groundbreaking - hypothesis. There are also plans to broaden their study on the ¤-helical amyloid fold and, importantly, they will also look in a second fungal species, namely Fusarium spp. Although a detailed description of the type of experiments that would be conducted is not presented, it is evident that the projects will build on what has been learnt over the last 4 years from their studies of VI in P.anserina.

There is no doubt that the work planned by this team for the next period is both original in conception and in execution. The hypothesis upon which the work on the evolution of the VI sysem is based, has the potential to have a much wider impact than simply on our understanding of a non-pathogenic, relatively under-resourced model fungus. For example, could there be a value in relation to identifying new 'druggable' targets for anti-fungal therapeutics ? That said, as the report recognises, the VI system under study is not universally found in fungi and may be restricted to a small evolutionary branch.

- Conclusion :

  - Summary

The team has carved itself a distinct niche in the highly competitive field of prion research and in addition has made major contributions to our understanding of VI. This in turn has led to the development of a significant new hypothesis that they now plan to put all their resources into testing. Their ability to translate their research into outputs is very good and they have fully embraced the opportunities afforded them of international collaborations which they have chosen wisely. The project for the next period is quite new and original and could have strong potential for practical application.

  - Strengths and opportunities

- A novel experimental system in which team 2 are world-leaders
- A new hypothesis built on earlier work which – if proven correct – will be of considerable and widespread significance
- A proven ability to translate research findings into outputs in high quality, peer-reviewed journals
- A strong international profile

  - Weaknesses and threats

- Threat : Failure to establish a suitable host-pathogen model system to test out their hypothesis.
- Weakness : No real 'back-up' plan evident should a model system not be established
- Threat : Obtaining sufficient external funding to support their research
- Weakness : Insufficient exposure at major international conferences
- Weakness : No collaboration with Team 3

  - Recommendations

Team 2 would need to recruite a collaborator with a background in immunology

Team 3 : Functional analysis of amyloids

Team leader: M. Christophe CULLIN

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

- Appreciation on the results

Team 3 has focused on two significant questions in relation to amyloids and their behaviour in disease: what makes them infectious and what makes them toxic? To answer these questions they have to date focused exclusively on a yeast-based model and have chosen to exploit heterologous amyloid proteins one of which is unique to this team, namely a highly mutated form of the Het-s prion protein from Podospora anserina (a protein also intensively studied by Team 2). Their approach has been a wise one, namely to combine in vivo genetic screens with in vitro/biophysical studies, although the latter is done predominantly in collaboration with other researchers outside the team. The findings have begun to appear in the scientific literature, although the wider significance of their findings remain to be established as is whether their findings can be extrapolated to other amyloid systems and hence inform research aimed at identifying suitable molecular targets for anti-amyloid therapies.

The work of this team has resulted in eight research papers, largely published in journals with a reasonable impact factor. Team members were principle investigators on six of the publications. In addition, one PhD thesis was produced during this period. Given the size of the group, a higher number of research papers might have been expected. The team have not published any reviews in learned journals.

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

Surprisingly, none of the team members appears to have been invited to give lectures or other conference presentations at either national or international level. It is unclear why this is so since the team have generated novel data over the last four years that has found its way into peer-reviewed journals and should be communicated prior to publication to an audience of peers.

The modest scientific output of group in combination with its dwindling staff number will undoubtedly have affected the group's ability to recruit high level scientists, post-docs and students, in particular those from abroad. Furthermore, the team will be also losing one of its key members and it is unclear whether this post will be replaced. In 2010, the team will be merged with the current team 5 (Structure and function of NDP kinases) and this will significantly strengthen the work on relating amyloid structure to toxicity.

The team has successfully applied for competitive funding with one research grant from ANR being listed as having been awarded during the review period (although this runs out in 2009). The PI on this grant is the team leader although the level of resource this grant provides the team with over and above that provided via CNRS funding, is not evident.

Collaborations with groups in Ireland and China have facilitated the team's in vitro studies and resulted in one joint publication. Whether these two collaborations are continuing long term (i.e. post-2009) is not evident.

Apart from the links with team 5, there is no evidence of any other productive collaboration within the IGBC which might be viewed as surprising, especially given the common interests shared by this team with those of team 2 in relating amyloid sequence/structure to infectivity in a fungal model.

- ## Appreciation on the project

With the departure of one critical team member who has been largely responsible for the studies on amyloid 'infectivity' it is evident that the group expects to wind down their research on the infectiousness of amyloids. Nevertheless, the team proposes to conduct a novel genetic screen that they hope will identify new genes implicated in prion maintenance. If no new genes do emerge then there is no indication of any other strategy to approach this question and presumably this project will be terminated.

The project on amyloid toxicity is much stronger and builds on their recent findings with a highly mutated form of Het-s (M8) and human A□. A genome-wide screen, the results of which have not yet been published, has pointed them towards membrane association/ damage being key to the toxicity observed. Several novel in vitro strategies to follow this up are in place and involve a new collaboration via the merger with team 5. The proposed work on A□ has considerable potential and it should be given the highest priority especially given the relatively small size of the team. This project also has the potential to be directly relevant to human disease (in this case Alzheimer's disease) and the proposed testing in cultured cells is the most exciting new aspect of the proposed programme for the next four years. The studies on both Het-s (M8) mutant and A□ will undoubtedly add to our knowledge of the relationship between amyloid sequence/structure and toxicity and the mechanism of amyloid-mediated toxicity.

The questions being addressed are not in themselves novel – indeed there is considerable activity in both areas – but the team do have some elements of novelty in both their chosen model system and in the leads they have on the mechanism of amyloid toxicity. It is pleasing to see that they plan to translate their findings in yeast to a mammalian cell context. This is essential for this work to be competitive and to have any impact on the amyloid field. Although this work is likely to yield publishable results, it is important that the team increase the rate of their outputs and attendance at conferences in order to significantly increase their international reputation in already very crowded and competitive field.

- ## Conclusion :

  - ### Summary

Over the past four years, this team have made some novel contributions to the amyloid field and in particular in probing the mechanism of amyloid toxicity using a simple yeast model. Although not matched by a prolific output, nevertheless they have published several good quality research papers. However, the relevance and impact of the research would have benefited from a more translational focus, e.g. the functional analysis of amyloids that play a role in human disease. It is therefore important that the group fully develops their new line of research in the field of amyloid toxicity that will attract external funding. The proposed research on the Alzheimer's disease-associated peptide A□ is an important development. Whether this proposed research can inform our understanding of the molecular basis of neurodegeneration and death in the case of Alzheimer's disease remains an open question. Their identification of membrane damage as a potential and critical effector of amyloid toxicity is an important step forward and, should their hypothesis be proven, this will attract considerable attention from others in this highly competitive field.

  - ### Strengths and opportunities

- Development of a novel in vivo assay for amyloid toxicity
- Translating findings made in yeast, to cultured mammalian cells
- Definition of a new mechanism for amyloid-mediated toxicity

- Weaknesses and threats

- Low international profile in a highly competitive field
- No presentations (invited or otherwise) at major relevant conferences
- Obtaining sufficient external funding to support their research
- Failure to fully develop collaborative projects with other teams in the IGBC

- Recommendations

The team is encouraged to focus their efforts on the A¤ project and should ensure effective transfer of their findings made in yeast, to cultured mammalian cells. Because of their role in human disease, amyloids are of great medical importance and, therefore, the best funding opportunities for the team will come from targeting the interface between basic amyloid research and its applications to human diseases. To be internationally competitive such funding will be a necessity.

Team 4 : Genetics of metabolic pathways

Team leader: Mr Bertrand DAIGNAN-FORNIER

- 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)	5	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	6	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)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	1
N7: Number of staff members with a HDR or a similar grade	4	2

- Appreciation on the results

Since the creation of the laboratory in 1996, this group is interested in studying the purine pathways and their links with the pyrimidine, histidine, phosphate and one-carbon metabolisms in Saccharomyces cerevisiae.
This group has developed a high expertise in knowledge of metabolism and cell physiology. When we analyze all the publications issued from this group, the most striking observation is that the starting point was always the purine metabolism. From an observation made by a member of the group or reported in the literature, a new study began and always led to a nice work with clean and clear data allowing a publication of high quality. In some cases this new study led to the development of completely new research topics.
Starting with the observation that two genes involved in GTP synthesis were down regulated, when cells shifted from proliferation to quiescence, this laboratory was able to produce six papers in high impact factor journals and containing major observations about quiescent cells. Some of them described the mechanisms involved in the degradation of yeast adenine deaminase upon transition from proliferation to quiescence. The others shed light on

what happened in quiescent cells (identification of actin bodies, formation of proteasome storage granules, polarized growth in the absence of F-actin in yeast exiting quiescence). It is worth noting that this beautiful research resulted from their great expertise in physiology, metabolism and cell biology.

The second major contribution of this group stressed the importance of the purine balance and the identification of crosstalk between pathways, which is crucial to maintain homeostasis. This study led to 5 publications whose one in the high impact factor (14.8) journal, Gene and Development. The major conclusions of these studies were the following ones:

- ATP shortage led to a strong induction of phosphate utilization and AMP biosynthesis genes
- ATP and GTP shortage did not reveal a common transcriptional response
- GTP over expression was highly toxic for yeast cells and led to arrest of proliferation and massive cell death
  AICAR was a strategic metabolite allowing maintaining purine-phosphate homeostasis
- AICAR played a role in the interaction between the regulator Pho2 and the two specific regulators, Pho4 for phosphate metabolism and Bas1 for purine biosynthesis

The success of this research resulted from the combination of the genetic and biochemical approaches allowing to determine the impact of mutations on the production of metabolites and consequently on the expression of many genes. The introduction of the HPLC technique in the laboratory was essential to the measurements of metabolite intracellular concentrations. These small metabolites appear more and more as major players in the control and the crosstalk of many metabolic pathways.

For these last 4 years, the scientific production of this group (11 publications for which the team members have been the principal investigators and 10 publications resulting from collaborations of one member of the team with another research group) is significantly greater than the mean production of the IBGC groups. Among the publications not in collaboration, only one is in a journal with an impact factor below 4. One publication is in J.Cell.Biol.(IF 9.6) and one in Genes and Dev.(IF 14.8). It is worth noting that it is exceptional to publish, in such a high level journal, a study about metabolism in a microorganism. This reflects the great quality and the originality of the work of this team.

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

This team has obtained several grants from ANR providing the funding for their research and for hiring post-docs. This laboratory seems to be attractive since it has welcomed 2 post-docs between 2006 and 2008, 4 new post-docs in 2008-2009 and 3 PhD students. Members of the team have participated in many international meetings as invited speakers (5) or with poster presentations (9).

- Appreciation on the project

The project is in continuity with the most original observations obtained during these last 4 years. Since the previous team will be split into 2 teams to create a new group studying the quiescence (see team5), this group will be focused on the study of the role of small molecules in cross-pathway regulation. They will pursue the study of the role of AICAR in Saccharomyces cerevisiae but also in other organisms such as mammalian cells, Schizosaccharomyces pombe and C.elegans for the following reasons. AICAR and SAICAR accumulation in human are associated with 2 monogenic disorders leading to severe mental retardation. AICAR has shown anti-diabetic properties in rodents and this molecule can improve endurance in mice in the absence of training. Since AICAR accumulation can physiologically and pathologically affect multiple unidentified effectors, the aim of this project will be to identify these effectors and to understand the underlying mechanisms in several model organisms. To begin this work, the proteins interacting with AICAR will be identified with AICAR affinity chromatography columns. The work on C.elegans will be performed in collaboration with a group at Université Bordeaux 2 which is an excellent idea to acquire the expertise necessary to manipulate a new organism.

A second work will be based on the study of another central regulator, the metabolite PRPP. The starting point of this research is the reported observation that a mutation in the biosynthetic pathway of PRPP led to a small cell size phenotype. This suggests that PRPP could be involved in the control of growth acting as a general metabolic sensor. I think that this group possesses all the tools required to undertake this new topic. They have the expertise in multiple strain constructions, in genetics, in determination of intracellular metabolite concentrations by HPLC. They have acquired the equipment for cell volume measurements and they plan to collaborate with a group with expertise in PRPP measurements.

The last topic proposed by this team is based on the observation that a small non-coding unstable transcript was most probably involved in the transcriptional regulation of IMD2, which is a favorite gene of this team. It was also observed that this gene was down regulated upon entry into quiescence. It will be tested if this small non-coding transcript is involved in this control and the mechanisms and the partners required for this control will be identified. Finally the group proposes that this regulation would be more general and they present an attractive hypothesis. They speculate that the role of these small transcripts could be to maintain chromatin in an open state at specific loci during quiescence and this last hypothesis is worth being tested. To confirm this hypothesis the team will work in collaboration with two other groups.

The research project plans to study the role of small molecules such AICAR and PRPP in cross-pathway. Moreover they plan to extend their study in other organisms such as mammalian cells and C. elegans. Their study should lead to very innovative discoveries for several reasons. In the study of the signaling pathways, the nature of the small molecules triggering the modulation of the pathway as well as the mechanisms by which this control is exerted, are very often the last and the most difficult steps to solve. Since AICAR accumulation can physiologically and pathologically affect some higher eukaryotic organisms, it is very interesting for this group to use their expertise to undertake the same study in these organisms. The idea that PRPP could be involved in the control of growth acting as a general metabolic sensor is especially attractive.

- ## Conclusions

  - ### Summary

Thanks to their excellent knowledge of metabolism, genetics, cell biology and physiology, this group has developed a very original research leading to an excellent scientific production for these last 4 years. Their results largely contributed to improve the understanding of quiescence in Saccharomyces cerevisiae and to identify crosstalk between metabolic pathways which is crucial to maintain homeostasis. The research program of this team is original and ambitious. Since this group possesses the expertise required to shed light on the different raised questions, there is no doubt that this work will lead to very innovative discoveries. Moreover, the idea to extend their study to other model organisms is excellent. Of course, it will be indispensable to establish contacts with laboratories able to transmit their competence in the manipulation of these new organisms. Although the present team is excellent intellectually as well as technically, the 3 topics requiring a lot of work, the future recruitment of post-docs or PhD students will be crucial to manage this research program.

  - ### Strengths and opportunities

Their high expertise in knowledge of genetics, metabolism and cell physiology. Their experience in using the HPLC technique allowing the characterization and quantification of metabolites which is a crucial step in the understanding of the role of small molecules in cross-pathway regulation.

When it is required, this group always finds the means to increase their chance of success either by initiating appropriate collaborations (group expert in the study of C.elegans or group with expertise in PRPP measurements) or by obtaining grants allowing the purchase of the appropriate equipments.

  - ### Weaknesses and threats

The 3 topics requiring a lot of work, the future recruitment of post-docs or PhD students will be crucial to manage this research program. It will also be indispensable to take care to the competition especially when the group will begin to enlarge their study to higher organisms.

  - ### Recommendations

To augment the international visibility of the group, it would be useful to increase the number of oral presentations in international meetings.

Team 5 : Cell biology of quiescence

Team leader: Mrs Isabelle SAGOT

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

- Appreciation on the project

For the last 4 years, the project leader has developed a very interesting research in within team 4. Research of this team led to increase the knowledge of quiescence cell biology. The major observation was the identification of two markers of the quiescent cells namely the Actin Bodies (AB) and the Proteasome Shortage Granules (PSG). Future research will be mainly based on the study of the mechanisms involved in the formation, the maintenance and the dissociation of these structures.

The main research question of this group is whether quiescence is merely a consequence of a drastic decrease of the overall cell metabolism or whether quiescence is regulated by specific and active programs. To understand the quiescence state, they will use several approaches combining the methods in genetics, cell biology and biochemistry.

This group proposes to purify the ABs, which would allow to identify their components by mass spectrometry. In parallel, they plan to analyze the role of some putative proteins present in the ABs. This kind of experiments requires an excellent knowledge of biochemistry. It is thus a good initiative to undertake collaboration with a group expert in yeast actin biochemistry.

In the second topic, the challenge is to characterize the composition of the PSGs, to determine their activity and to identify their role for cell survival in quiescence. The purification of these PSGs will be initiated. If this group succeeds in identifying the components required for PSG assembly, there is no doubt that they will be able to answer to the very interesting question: e.g. are PSGs essential for cell survival in quiescence?

The last topic aims at understanding whether quiescence is a committed state involving a specific cellular program. Some observations led to conclude that it was possible to trigger the disassembly of ABs and PSGs even under conditions where cellular proliferation could not occur. Since it was observed that glucose alone could provoke this disassembly, the mechanism by which glucose induces it, will be studied. It has also been proposed to perform an HPLC analysis of the metabolic changes in the cells upon exit from quiescence. It appears that for this part of the project, the competition could be hard.

- Conclusions:

  - Summary

To sum up, this research project is very exciting and ambitious, it aims at deciphering the signals at the basis of a quiescence program using as tools the 2 markers, ABs and PSGs. This project is challenging. Since this group possesses an excellent expertise in cell biology but also in biochemistry, this project could be a real success and bring a major contribution to the understanding of quiescence cell biology.

  - Strengths and opportunities

Team 5 (Future) leader gave an excellent presentation during the meeting with the committee, convincing the committee members that the group leader is able to deliver the proposed projects and that the projects will address important biological questions.

The following points are also strengths of this team: excellent expertise in cell biology, 3 post-doctoral researchers with expertise in genetics and biochemistry, and a Collaboration with a world leader in yeast actin biochemistry.

  - Weaknesses and threats

It might be safer not to be too focused on ABs and PSGs until their crucial roles in quiescence are proven experimentally. It will be sensible to keep alert to other aspects of quiescence as well, as discussed in the third plan. It is crucial to continue the search for remodelling of other cellular structures.

  - Recommendations

Team 5 (Future) leader is an ambitious and intelligent young group leader, who will address a challenging and very important biological problem. The PI has obtained an ANR young researcher grant to conduct her research program. These research projects should be supported further in high priority by the institute for allocation of space and budget as well as access to various research services.

Team 6 : Mitochondrial organization and dynamics

Team leader: M. Manuel ROJO

- 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)	0	0
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	1	1

- Appreciation on the results

The team leader jointed the IBGC in Bordeaux as team leader in March 2008. The team studies an exciting but highly competitive field. Whilst part of the team of another team in Paris, the team leader initiated some highly original work of great importance to our understanding of mitochondrial fission and fusion. Recently, the impact of the team leader's work has diminished somewhat, possibly because he lost out to competing research groups. It is important that the team keeps its momentum going.

Between 2005 and 2008, the team leader published six articles as result of his work in Paris. On four of these articles the team leader was last author, two of these were published in high impact journals. In the short time this team is active at the IBGC, the team leader was co-author on a publication by a Spanish group.

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

Over the past four years, the team leader received six invitations to conferences and symposia, including three international invitations.

The team leader has a good reputation in the field of mitochondrial dynamics and is starting a new group at an attractive institute. Therefore, this team should be able to recruit high level scientists, including post-doctoral fellows from abroad.

The team has already secured a modest grant from the AFM to fund laboratory consumables, and the team leader is co-investigator on two other grants with collaborators.

The team leader has used his first year in Bordeaux to develop new research ideas and partnerships. The team has now established several collaborations within the Institute, and with other research groups in France and abroad. Some of these collaborations are with key players in the field and will be critical for the success of the team in the coming years.

- Appreciation on the project

In the next four years, this new team needs to make significant scientific contributions in order to establish itself. The four proposed research projects are attractive, original, appear feasible and have the potential to make an important impact. However, to be able to execute its research plans, this small team needs to grow and collaborate closely with others. A number of collaborations have already been set up, but it is essential that this team obtains significant competitive funding for post-doctoral researchers.

- Conclusion :

  - Summary

The team leader established his international reputation with earlier work in another lab in Paris. In 2008, he started his own group at the IBGC in Bordeaux. The team leader has used his first year at the Institute to nurture internal, national and international collaborations and develop an attractive research plan for the next four years. The field in which this team has chosen to work is fascinating, but also highly competitive. Thus, the team runs the risk of losing out to the competition. However, the team has carefully chosen four research projects where it may have an advantage to other groups. Nevertheless, in order to maintain its reputation, it is essential that the team secures funding for post-doctoral research fellows, so that it is large enough to withstand the competition and carry out the entire project.

  - Strengths and opportunities

- Strong expertise in mitochondrial dynamics, and techniques to approach the mechanisms of fusion and fission of mitochondria
- Good internal collaboration with team 10 to study how mitochondrial dynamics can impact mitochondrial bioenergetics.
- High international profile.

  - Weaknesses and threats

- Small team starting competitive projects with some delay relative to other, larger teams. (A delay that could be explained by the move of the team leader from Paris to Bordeaux).
- Collaborations are required to achieve the four sub-projects. There is the danger that the required collaborations (even though collaborators are identified) may exacerbate the delay.
- Obtaining sufficient external funding to support their research

  - Recommendations

Given its current size, the team has to be careful not to take on too many projects. The team needs to recruit post-docs and, hence needs to secure competitive funding. To be internationally competitive such funding will be a necessity.

Team 7 : Cell energetic metabolism

Team leader: Mrs Anne DEVIN

- 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)	2	2
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)	1	0
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)	4	1
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

The team is interested in processes involved in the regulation of cellular energetics, especially in mechanisms involved in the mitochondrial content adjustment and oxidative phosphorylation regulation. The team has acquired a great expertise in the characterization of bioenergetic parameters, which allowed the development of several productive research topics. Of particular interest is the study in which it was clearly demonstrated that besides its role in the control of glycolysis, the trehalose pathway regulates the mitochondrial enzymatic content involving hexokinase 2 and cAMP. The contribution of this work is important since it is the first time that a pathway involved in sugar storage is shown to regulate the mitochondrial enzymatic content. Another significant achievement by this group concerns the understanding of the Crabtree effect. It was demonstrated that fructose 1,6-biphosphate was able to inhibit mitochondrial respiration only in mitochondria isolated from a Crabtree-positive yeast strain. Furthermore, the team has published the interesting observation that in the absence of Tpk3, one of the three A kinase catalytic subunits, there is a significant decrease in cellular mitochondrial content especially in the amount of cytochrome c. The team subsequently unravelled the mechanisms involved in this decrease. They observed an increase of ROS production in the tpk3¤ cells, which is reversed in the presence of an antioxidant or when Hap4 was over-expressed.

During the last four years, the scientific production of this team has been fair. The team had ten publications of which the team members were the principal investigators and seven publications resulting from collaborations with another research group. Nine publications had an impact factor between 4 and 6. Among the ten publications directly from this team, the future team leader was first author on three papers and last author on two. The current and future team leaders also wrote two book chapters. Two PhD students presented their thesis.

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

The current and future team leaders have participated as invited speakers at six meetings (three local). The number of international invitations is considered relatively low for a team of this size. Although the team published a reasonable number of papers in journals with an acceptable impact factor, the limited number of international invitations will hamper their ability to recruit high level, international post-docs

This team obtained five grants from ANR for the funding of their research, three as co-investigators in collaboration with others. In addition, the team received one regional grant. The funding allowed the team to employ one post-doc. The team also benefited from the input of several PhD students.

The team has developed collaborations with three French and two international groups, which is considered appropriate for a group of this size.

- Appreciation on the project

The project of the team aims to shed light on three different problems, all involving their expertise in the characterization of bioenergetic parameters. In the first sub-project, the team intends to compare the energy metabolism of hepatoma cells versus hepatocytes. The committee deems this sub-project too broad and possibly too ambitious. The team proposes to test the effects of energy metabolism inhibiting drugs on normal and hepatoma cells, to establish a metabolic cancer therapy and to test it in vivo. This idea is not new and the committee is not convinced that this group possesses the expertise to undertake this study and will successfully compete with other research groups that are established in the field of metabolic therapies for cancer. In contrast to the written report, during the oral presentation, it seemed that the team only wants to compare hepatocytes and hepatoma as model of cells preferentially using oxidative phosphorylation or glycolysis. This discrepancy needs to be clarified. The committee is not persuaded by the importance of this new model to study the Crabtree effect.

The second question raised is the following one: what are the mechanisms responsible for the electron competition? This work is a continuation of the experiments that led to a publication in J. Biol. Chem. in 2005. The team proposes to use various yeast mutants to solve the question. Although the planned experiments may indicate the mechanisms responsible for electron competition, the committee wonders why the team waited four years to continue this work.

The remaining three sub-projects all concern the reactive oxygen species (ROS)-mediated regulation of mitochondrial biogenesis. These studies are based on the hypothesis that ROS acts as a sensor of the mitochondrial functional state and that, over a certain threshold, the organelles give a signal to the nucleus through regulation of the activity of transcription factors. Several approaches are proposed to further the understanding of this ROS signalling pathway. It is proposed to test if Hap4 is the sensor of oxidative stress, to identify new kinases controlling the ROS production, and to identify their targets and sites of phosphorylation required for the regulation of mitochondrial ROS metabolism. This work could be very interesting but again this project is not sufficiently defined. It is difficult to evaluate whether the researchers have the expertise to undertake all the experiments proposed, which require high competence in biochemistry and proteomics. Moreover, after the oral presentation, the committee was not convinced that this team has sufficient know-how of ROS signalling.

- Conclusion :

  – Summary

Over the past four years, this team has made some novel contributions to the field of regulation of cellular energetics. Although there has been a steady output of papers with a reasonable impact in the past, the committee is worried that the proposed project will not be as productive. The tumour therapy sub-project is considered too broad, and an in-depth study of the tumour therapy and ROS sub-projects are considered beyond the expertise of this relatively small group. Moreover, the committee thinks that both sub-projects will meet with stiff competition from better-positioned research groups.

  – Strengths and opportunities

Good expertise in the characterisation of bioenergetic parameters

Satisfactory track record of published papers

Ability to attract competitive funding

  – Weaknesses and threats

Low international profile in tumour metabolic therapy and ROS signalling

Proposed project too diverse and too ambitious for the size of the group

Insufficient expertise to conduct some of the sub-projects

– Recommendations

The committee is not convinced that this project warrants continuation in its current form. If the team and its project do continue, then the first priority should be to secure funding in order to be able to attract high level scientist with proven expertise in tumour metabolic therapy or ROS signalling.

Team 9 : Energy transducing systems and mitochondrial morphology (SysTEMM)

Team leader: M. Daniel BRÈTHES

- 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)	2	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	2
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	2
N7: Number of staff members with a HDR or a similar grade	2	6

- Appreciation on the results

The current team 9 (Cellular and molecular physiology -) will merge with the future team 9 (Energy transducing systems and mitochondrial morphology (SysTEMM) -) in the next period.

Over the past four years, the current team 9 studied structure-function relationships of the yeast adenine nucleotide translocator and alkyl hydroperoxide reductase 1. Unfortunately, their protein crystallisation efforts met with little success. As a result, the team has made little impact in the field.

The current team 9 published seven papers, including four papers of principle investigator in journals with an average impact factor. The team produced one PhD thesis. These numbers are low.

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

Disappointingly, apparently no invitations were received to conferences of symposia, but the team did organise several national meetings. The team has probably a reasonable national reputation, but will struggle to recruit international post-doctoral scientists.

The current team 9 received one grant to fund a post-doctoral scientist over the last four years. Again, this is not enough to maintain an international reputation.

The current team 9 collaborated with scientists in Greece and Russia, and hosted some national visitors.

- Appreciation on the project

See elsewhere: future team 9 (Energy transducing systems and mitochondrial morphology (SysTEMM) -)

- Conclusion

See elsewhere: future team 9 (Energy transducing systems and mitochondrial morphology (SysTEMM) -)

Strong points:

The team got its international recognition from its work on the structure of the ATP synthase. There is no doubt that the team has the appropriate expertise to be competitive in this domain. A new major observation of the group is the role of ATP synthase dimerisation in the formation of cristae.

– Weaknesses and threats

Declining international visibility because difficult projects coupled to a slow progress by the field.

– Recommendations :

Project of former team should be stopped and team members should profit from joining the scientific core topics of new team N° 9

An important part of the project will be to understand how the ATP synthase could regulate the morphology of cristae and whether this process that has been primarily discovered in yeast, can be extended to mammalian cells. The group will address these questions through biochemical, biopysical and genetic approaches. Finding how ATP synthase achieves this new function will be challenging. It is important that this group recruits post-docs to accelerate the progression of the work.

Team 8 : Molecular genetics of mitochondrial systems

Team leader: M. Jean-Paul DI RAGO

- 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)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	0
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)	2	1
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

During the past 4 years, team 10 has worked on a varied but well-focused research programme, involving structure-function and assembly studies of yeast complex III and V, in order to gain a detailed knowledge on the mechanism of these important enzyme complexes. They have used genetic tools to decipher the role of several subunits of complex V and of proteins necessary for its assembly. For this, they have made mutants of F1alpha, F1beta, F1delta, Atp11p, Atp12p, Fmc1p, Atp14p and Atp6p. Of particular interest, they have used an elegant rescue system using ARG8m to obtain viable strains lacking Atp6p and showed that this strain has only minimal mtDNA defects but a severe reduction of complex IV by failure to synthesise Cox1p. They have taken advantage of this model to over-express Atp6p with missense mutations corresponding to common mutations found in human mitochondrial diseases such as Neuropathy, Ataxia, and Reinitis Pigmentosa (NARP) and Leigh syndrome (a severe form of encephalopathy) in order to precisely understand the mechanism of the disease and to search for suppressors with the powerful yeast genetics tools. Of particular interest, a mitochondrial carrier, Odc1p, was shown to rescue the disease phenotype, and will be tested in mammalian cybrid cell lines, in order to explore the potential of this novel therapeutic approach. In addition, the team is contemplating to use their yeast model for screening of drugs for human mitochondrial cytopathies and set up human cell culture facilities for validation.

The work has been innovative and has produced a steady output of quality research papers

Over the four-year period, the team published 17 papers, including eight for which team members were principal investigators, of which again five were in journals with impact factors above 5 (which is very good). This number of articles is appropriate for the size of the team. One PhD thesis was produced and defended in June 2007 and one will be defended in December 2009.

The group has published a number of additional publications as part of national and international collaborations, often several publications with one partner.

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

The group contributed to many meeting abstracts and posters.Team members received four national invitations to conferences or symposia, and eight invitations to give seminars, including four international seminars. One would expect some international invitations to conferences, but the number of international invitations to seminars compensates for this to some extent. The team was awarded the " Troophées INPI de l'innovation 2008, lauréat region aquitaine, catégorie Laboratoire de Recherche".

The team has a good recruiting record, including one CNRS CR2 recruited after a three years post-doc, two PhD students and two M2 (Bachelors) students, and one post-doctoral fellow who was employed from 2006 to 2008 and obtained excellent publications. This is a team with a good international reputation that should be able to attract post-doctoral fellows from abroad.

The team has been quite successful with their grant applications. Five regional or national grants were awarded totalling over €750k. One ANR grant runs until 2012

The team maintained stable collaborations with colleagues at the Institute, with other groups in France and with five international groups. All international collaborators have a first-rate scientific reputation. These collaborations contributed for an important part to the achievements of the team. The team is also part of a collaboration aimed at screening of libraries of small molecule drugs for the treatment of mitochondrial diseases.

The team has submitted two patents; one has led to the development of a start-up. In addition, one patent on a small molecule therapeutic approach is under submission.

- Appreciation on the project

For the next four years, the team intends to study various molecular biological aspects of mitochondria using ingenious genetic techniques. Much of the work will be a continuation of their previous studies of yeast ATP synthase, but the team also plans and to extend their studies to the assembly of the chloroplast ATP synthase of the green algae Chlamydomonas reinhardtii and of the human enzyme. In addition, a study of mitochondrial-nuclear cross-talk is proposed involving allotropic expression of Podospora anserine ATP synthase subunit Atp9p in yeast mitochondria. This is a carefully considered, original research plan that builds on the successes of previous years. However, to be able to carry out the six different sub-projects the team needs to ensure that there are sufficient team members to do the work. The group is currently developing mammalian hybrid cell culture systems in order to transfer their knowledge in yeast genetics of mitochondrial function to mammalian systems with human disease causing mutations.

The team has already secured ANR post-doctoral funding until 2012 for one of the sub-projects, but additional funding will be necessary to complete all parts of the project.

- Conclusion :

– Summary

The team has an internationally recognized expertise in the study of major basic biological processes, such synthesis of ATP by the respiratory chain complex V, and a strong commitment to translational research aimed at understanding mitochondrial genetic diseases and developing screening methods for the identification of novel and innovative drugs for the treatment of these diseases. The research plans of the team build on a strong record of published papers and successful grant applications. They are a logical continuation of previous investigations. The fact that the methodology is largely developed provides the confidence that most, if not all, of the proposed work is feasible. The group has already obtained funding for a post-doctoral fellow to carry out one of the sub-projects, but it is thought that further external funding is required for the successful completion of all research plans.

– Strengths and opportunities

Strong basic research and medically oriented translational research.

Strong interaction with other teams of the IBGC and the team is, therefore, a strong component of the institute.

Good track record of publications

Good track record of competitive grant funding

Stable international collaborations with key players in the field

– Weaknesses and threats

Many projects for a relatively small group.

Apparently no invited presentations at major relevant conferences

– Recommendations

Further external funding is required for the successful completion of all research plans.

Team 9 : Energy transducing systems and mitochondrial morphology (SysTEMM)

Team leader: M. Daniel BRÈTHES

- 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)	4	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	2
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)	4	2
N7: Number of staff members with a HDR or a similar grade	5	6

- Appreciation on the results

The current team 11 (Structure-function of mitochondrial ATP synthase) will in the next period become team 9 led by a new PI. The current team 9 (Cellular and molecular physiology -) will merge with the future team 9.

The current team 11 has a good track record in the field of structure-function studies of yeast ATP synthase. Especially their work on ATP synthase dimerisation and cristae formation dated from 2002 is well-known. Over the past four years, this relatively large team predominantly continued with their studies on structural aspects of yeast ATP synthase. The research was original and of acceptable quality, although the committee felt that their crystallography results added little to the current knowledge.

The work of the current team 11 led to the publication of 25 research papers, including nine papers as principle investigator in journals with a reasonable impact factor. The number of papers published as principle investigator is a little bit disappointing for a group of this size. The team produced three PhD theses.

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

The current team 11 received one national and one international invitation to a conference or symposium. A single international invitation is disappointing for a group of this size. On the other hand, the team organised three national meetings.

This is a team with a good international reputation that should be able to attract post-doctoral researchers from abroad.

The team was pretty successful with their competitive grant applications: the work was supported by five regional or national grants.

The team collaborated with six other groups, including two within the Institute, three other French groups and one in Germany.

- Appreciation on the project

The merger between the current teams 9 and 11 will create a large, new team 9. The future team 9 intends to continue their structure-function studies of yeast ATP synthase and the adenine nucleotide translocator. In addition it proposes to develop a new research sub-project concerning structure-function relationships of the yeast type II NADH dehydrogenases.

Previous results of the structure-function studies of the adenine nucleotide translocase have been disappointing. Therefore, the committee feels that this work should now be terminated. The proposed studies on ATP synthase are a carefully thought through and attractive plan that is in part a logic extension of previous work. It is particularly sensible of the team to venture into human cell models to study cristae formation. The crystallography work on ATP synthase, however, runs the considerable risk that the group loses out to competing groups. It is, therefore, wise that the team also proposes a structural analysis of type II NADH dehydrogenases where competition may be less fierce.

The success of the project will in no small part depend on the progress that will be made with the protein crystallography. Past experience has shown that this work is risky; however, the ultimate rewards may justify the danger of failure.

One sub-project is supported by external funding. It is essential that the group secures further funding to support the other sub-projects.

- Conclusion :

  – Summary

The international reputation of the team is for a large part based on their previous work concerning the relationship between yeast ATP synthase oligomerisation and mitochondrial cristae formation. It is expected that the greatest opportunities for research lie in this area. It is sensible that the group now plans to extent this work to cristae formation in human cells. The protein crystallography part of the ATP synthase studies is technically challenging. Nevertheless, this work has the potential to be very rewarding. The structure-function studies of the adenine nucleotide translocase have been unsuccessful in the past and warrant no further studies. The new research sub-project on type II NADH dehydrogenases proposed by the team fits well with the other sub-projects, but appears rather understaffed. Although one of the sub-projects is supported by external funding, the team needs to seek further funding to guarantee the success of the project.

– Strengths and opportunities

The team has obtained international recognition from its work on the relationship between ATP synthase dimerisation and cristae formation

The team has the appropriate expertise to be competitive in this domain.

Reasonable track record of publications

Reasonable track record of competitive grant funding

– Weaknesses and threats

Declining international visibility, because technically challenging projects are coupled to slow progress by the field.

Structure-function relationships of ATP synthase is a highly competitive field

Few invited presentations at major relevant conferences

– Recommendations

The sub-project of current team 9 (adenine nucleotide translocase) should be stopped and team members should profit from joining the scientific core topics of the new team 9.

The merger of the two teams is hoped to produce synergy between the group members, but to facilitate this, special attention should paid to the management structure of the new team 9.

An important part of the project will be to understand how the ATP synthase could regulate the morphology of cristae and whether this process, which has been primarily discovered in yeast, can be extended to mammalian cells. Finding how ATP synthase achieves this new function will be challenging. It is important that this group recruits post-docs to accelerate the progression of the work.

Team 10 : Mitochondria, stress and cell deaths

Team leader: M. Stephen MANON

- 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	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	0
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)	2	2
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results

This group is subdivided into three subgroups, each investigating a project with overlaps between the 3 projects: 1) role of Bcl-2 family members (mainly Bax) in the permeabilization of the outer mitochondrial membrane, a process that occurs in apoptosis; 2) role of Bcl-2 and Bcl-x in autophagy; 3) role of UTH1 in mitophagy. Apoptosis, autophagy and mitophagy are important processes that play a role in cancer and degenerative diseases.

The work on Bax is performed on yeast. Since several years, this group has used this system to study how Bax can be activated to permeabilize the mitochondria. This is a risky approach since Bax is not naturally expressed in these cells. Nevertheless, the group has found interesting data that appear to be relevant for mammalian cells. In particular they have published a role of the phosphorylation at S163 and 184 in the activation of Bax (i.e a conformational change allowing its translocation from the cytosol to mitochondria). An advantage of the yeast system is that it allows to study how BH3 only proteins interact with anti-apoptotic or pro-apoptotic members of the Bcl-2 family. In collaboration with a group in Nantes, they have been able to show that Puma is a Bax activator.

Very intriguing is the effect of Bcl-x and Bcl-2 in autophagy, in mammalian cells. These proteins were known to act as autophagy inhibitors through inhibition of Beclin. This group now shows that Bcl-2 an Bcl-x can promote autophagy independently of Beclin. Importantly depletion of Bcl-x inhibited starvation-induced autophagy as does for example depletion of Atg7. Deamidation of Bcl/x could regulate this new function of Bcl-x. These data are novel and interesting.

The project on mitophagy is a very hot subject at the moment in particular because proteins involved in familial forms of Parkinson's disease, such as Parkin and Pink1, seem to promote mitophagy. Several years ago, the group identified UTH1 as a protein responsible for the selective elimination of mitochondria. How this protein works is still unknown. There is no homolog of UTH1 in mammalian cells, suggesting that part of the mechanisms of mitophagy is different between yeast and mammals. Interestingly, they have now reported a role of ROS in autophagy due to a decrease in glutathione after nitrogen starvation.

The group has published 8 publications and members of the group have participated in 16 publications with collaborators. Most papers are published in journal with an impact factor between 5 and 9 (Cell Death and Differ., JBC). This is a very good rate of publication given the average size size of the team.

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

The group has recruited a CR2 in 2007 and a MCU in 2009 from abroad. The team has recruited 2 PhD students and 1 post-doc. The number of post-docs in the lab is clearly low during the past 4 years.

This team developped many collaborations with external groups, the strongest and the most fruitful with teams in Nantes.

They have been invited 6 times to participate in national and international meetings mainly in meetings on apoptosis but with a yeast specificity.

Members of the groups were PI on all successful applications. The team should obtain funds that would allow the group to recruit post-doc and students.

- Appreciation on the project

Projet 1 on Bax: The team plans to obtain the 3D structure of active Bax. This is an interesting, but risky, project. Several teams have been trying to get this structure for many years but unsuccesfully. The committee does not see in their approach something that others have not tried. Another part of the project will be based on their previous observation of interactions between Bax and Tom 22; Bax-puma; Bax phosphorylation. The fact that Bcl-x can trigger a change in the conformation of Bax and form a complex with it is interesting. This system then allow to test compounds such as ABT737 that can displace this interaction, allowing Bax to oligomerize and permeabilize the mitochondria. This system should be exploited further to identify new Bcl-2 or Bcl-x inhibitors.

Project 2 on Mitophagy : The group will continue to investigate the role of UTH1. In particular they plan to search for UTH1 patrners. They also plan to test the involvement of the TOR kinase pathway in mitophagy. These projects are feasible.

Project 3 on Autophagy : The team will investigate further the interaction between Bcl-x and Rab7, that plays a role in the maturation of the autophagosomes. Yeast two hybrid will be used to understand in detail how these proteins interact. In addition, the team will test the role of the KRAS oncogene in the control of auophagy. This work will be done in collaboration with a team in Portugal.

- Conclusion :

  - Summary

The group works on hot topics (Bax and apoptosis ; mitophagy ; Bcl-2 and autophagy) and has to face a strong competition. Its specificity is to work on yeast, except for the work on autophagy.

  - Strengths and opportunities

The research performed is well known in the fields of apoptosis and mitophagy. They were the the first to have worked on mitophagy (identification of Uth1) and to discover the first gene involved in this process, in yeast.

They developped a strong, complementary and fruitful collaboration with teams in Nantes.

- Weaknesses and threats

Not enough post-docs to reinforce the axis of mitophagy.

No funding indicated for the next period

– Recommendations

Apply for funds, recruit post-docs and PhD students and focus on one or two topics at most. Teams working on autophagy and mitophagy, two related projects, should work in close proximity.

Team 11 : Regulation of Rho proteins

Team leaders: M. François DOIGNON & M. Didier THORAVAL

- 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)	3	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2.2	2.2
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)	4	1
N7: Number of staff members with a HDR or a similar grade	3	4

- Appreciation on the results

Team 13 is working on the regulation of polarized growth in yeast. The team showed in the past that Rgd1p is the GTPase activating protein of the S. cerevisiae Rho GTPases homologues Rho 3p and Rho 4p.

In the last 4 years, the members of the team studied the GTPase activating protein Rgd1p and its action on the small GTPases Rho 3p and Rho 4p in the yeast S. cerevisiae. They showed that:

– RGD1, encoding a RhoGAP involved in low-pH survival, is an Msn2p/Msn4p regulated gene in Saccharomyces cerevisiae.

– Synthetic lethality between RGD1 and MID2 depends on low pH.

– The cascade of MAP Kinases from the PKC pathway is essential for the response to low PH.

– The Rho3 and Rho4 small GTPases interact functionally with Wsc1p, a cell surface sensor of the protein kinase C cell- integrity pathway.

– Phosphoinosides affect both the cellular distribution and activity of the F-BAR-containing RhoGAP Rgd1p in yeast.

– The modules Rho3 / Rgd1 and Rho4 / Rgd1 are conserved in the human pathogenic yeast Candida albicans and have a role in filamentation.

The yeast is a model organism that presents many advantages including availability of strong genetic tools. The team has a good experience in the research field and in yeast genetics. The obtained results are interesting.

The team recruited and formed 4 PhD students, two supported their thesis in 2005, one will support its thesis by the end of 2009 and one begins its 2nd year of thesis.

The team published 5 articles in international journals on the team thematic since 2005 with modest impact factors between 2.8 and 5.8 (in Eucaryotic Cell, Gene, Microbiology-SGM, J. Biol. Chem. and in Communicative and Integrative Biology) and 1 review. Five other articles have been published in collaboration with other labs (one article with an IBGC team) .

We can underline that several publications of the IGE present in this team since 2007 were performed in collaboration with another group on a different project.

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

Members of this team have been invited only once in French meetings and once in a European congress held in Bordeaux. They participate to several national and international congresses but without to be invited.

The team recruited 2 french ATER between 2004 and 2007, and 4 french PhD students since 2002 (2 defended their thesis in 2005, one will defend by the end of 2009 and one begins his second PhD year).

The group leaders did not indicate either successful applications for fundings in the period 2005-2009, or for the next 4 years.

Projects have been achieved during the last period and will be done in the next period through collaborations with teams mastering some specific technical approaches necessary for the projects but the committee noted that these collaborations are mainly with teams from IBGC or at least Bordeaux.

The understanding of the role of the Spitzenkorper in hyphal formation and in pathogenicity of C. albicans, and the identification of new proteinic targets proposed in one of the team projects could allow the elaboration of new drugs against C. albicans.

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

During the last 4 years, the 3 permanent researchers of the group had teaching duties. Their publications in collaboration with other groups from Bordeaux show that these researchers are strongly involved in the structuration of research at the local level.

- Appreciation on the project

In the report, the team presented two projects for the upcoming period in the continuity of its research work on polarized growth in yeast:

1/ In vivo and in vitro study of the role of the F-BAR domain of the Rho GAP GTPase Rgd1p in the yeast S. cerevisiae as a model for mammalian proteins containing F-BAR and Rho GAP domains involved in the polarization process during neuronal migration. Members of the team have a strong experience with the yeast model and established collaborations that ensure the success of this project. A CNRS permanent researcher will join the group in January 2010 to contribute to the realization of this project.

2/ Study of the role of the Spitzenkorper in the hyphal growth and the pathogenicity of the yeast Candida albicans. This project will be carried out in collaboration who has a strong experience with this kind of yeast. The presented tools and strategy seem to be adapted to the proposed goals. The identification of new therapeutic targets and the elaboration of new drugs against C. albicans, which is a human pathogen of major interest involved in nosocomial infections, could be of interest for medical research.

This team is one of the rare groups working on the relationships of F-BAR and RhoGAP domain in yeast. The group initiates a new project on the study of the role of a very special yeast structure, the spitzenkorper, in pathogenicity of C. albicans. Very few groups work on the study of spitzenkorpers.

However, during the oral presentation and the following discussion, the relevance and feasibility of the team project did not appear clearly. The originality and usefulness of the project have not been really demonstrated and the strategies to find financial supports and international collaborations have not been clearly exposed.

- ## Conclusion :

  - ### Summary

On the basis of the report, the quality of the work done during the last four years is correct and the projects proposed are in the continuity, one of the two projects for the next period could lead to interesting applications for human health. However, the oral presentation did not convinced the AERES committee members of the feasibility of the project in the context presented : the relevance of the projects have not been really demonstrated and strategies to find financial supports and increase national and international visibility have not been exposed..

  - ### Strengths and opportunities

The members of the team have a good experience with yeast genetics and the tools necessary for the development of their projects. The collaborations already established at the local level reinforce the feasability of their projects. The arrival of a CNRS permanent researcher in January 2010 could strengthen the team. The teaching duties of 3 members of the team should allow attracting students in the team.

  - ### Weaknesses and threats

No fundings obtained in the last 4 years nor for the projects proposed apart from the CNRS and the University. The results of the team have been published in international journals but with average level. This team has only a low national and international visibility.

  - ### Recommendations

The presentation of the project for the next 4 years has not convinced the committee members. Due to 1/ the average level of the publications, 2/ the absence of fundings, 3/ the very low international visibility, 4/ the fact that the team does not seem to have collaborations with the other teams from the IBGC, 5/ the team is not localized in the IBGC building, the committee recommends to this team to join another group of IBGC or another laboratory.

Note :

During the past 4 years, the Institute included a team that worked on the structure and function of NDP kinases. This team will cease to exist in 2010. The team leader, who will retire in the near future, plans to join team 3. It is noted that over the last four years team 5 has not been very productive with only a modest output of publications and hence this merger may also be of benefit to team 5 both in terms of impact and outputs. Although, team members were invited to international conferences or symposia five times during this period, only three research papers with team members as principle investigator were published in journals with a modest impact factor. One PhD student successfully defended his thesis in December 2007. The committee agrees with the move of the team leader to team 3 and hopes that this transfer will strengthen the research of team 3.

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	B	B	A

Team 1: Molecular mechanisms of chromosome transmission

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+	non noté	A+

Team 2: Non-self recognition in fungi

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	non noté	A+

Team 3: Functional analysis of amyloids

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

Team 4: Genetics of metabolic pathways

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+	non noté	A+

Team 5: Cell biology of quiescence

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: Mitochondrial organization and dynamics

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	non noté	A

Team 7: Cell energetic metabolism

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

Team 8: Molecular genetics of mitochondrial systems

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	non noté	A+

Team 9: Energy transducing systems and mitochondrial morphology (SysTEMM)

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

Team 10: Mitochondria, stress and cell deaths

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	non noté	A

Team 11: Regulation of Rho proteins

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

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Comments on the report of the visiting AERES committee

We would like to thank the Committee members for their evaluation work that we thought was of good quality although we wish to answer to a number of points listed below.

1. General comments of the directors (current and future)

- In the report, specific analyses devoted to each team are very heterogeneous in length, content and level of detail. In addition, publications in the same journals are not consistently given the same value in the different team evaluation reports. A better homogeneity in the report form would contribute to a fairer notation process.

- We felt a lack of expertise in the Committee for bioenergetics.

- The report under its present form is written confusingly and should be improved before it is made publicly available. In particular, identification of the teams is confusing : teams 4 and 5 are mixed under a single heading; team 9 (2007-2010) and team 9 (2011-2014) are not clearly separated, conclusions in page 24 should be moved to page 28 and replaced by the proper conclusion for team 9 (2007-2010).

- The remark about "limited scientific animation" should be nuanced since from 2006 to 2009, 127 lecturers were invited to give a conference in the Unit. Seminars were held almost every Friday of each academic year.

- Repeatedly, in the different team evaluation reports, the committee states that funding and human resources for the 2011-2014 were not always secured. Since evaluation was carried out in 2009, at that time the teams obviously had little visibility concerning human and financial resources for 2011-2014.

- Two teams that have left the unit during the past four years have not been evaluated.

2. Specific responses of the project leaders

** Team 7(2011-2014) : Cell energetic metabolism*

The committee wonders why the team waited four years to continue the work concerning the mechanisms responsible for the electron competition: it was clearly shown both in the written report as well as during the oral presentation that this work was in progress and, as part of a PhD thesis defended in December 2008, led to the discovery of the active leak process (Biochim Biophys Acta, 2010).

Regarding the sub-projects relative to the reactive oxygen species (ROS)-mediated regulation of mitochondrial biogenesis, the team leader clearly showed during the oral presentation that, in light of data established by the group, HAP4 was the target of mitochondrial ROS and that the amount of this transcriptional coactivator was downregulated by H2O2. Hence the project proposed to further study the HAP4 mediated oxidative stress sensing. As far as the knowhow of ROS signalling goes, both project leaders of the team have significant experience acquired in this field as evidenced by their papers in peer-reviewed journals both in the past but also in the four-year report; see (ACL91, ACL95) and a recent paper in the J Biol Chem. 2010.

Regarding the proposed project too diverse and too ambitious for the size of the group; the size of that group has been similar for the past four years and that group has been steadily publishing in the fields of the proposed projects that are in the continuity of our scientific activities.

Regarding the insufficient expertise to conduct some of the sub-projects such as cancer cells metabolism see ACL54 [The crabtree effect (i.e. the origin of cancer cell metabolism)] and as stipulated during the oral presentation the team/project leaders recently published a review in a high impact factor journal (10.28) : Biochim Biophys Acta. 2009.

** Team 9 (2007-2010) : Cellular and molecular physiology*

The project of team 9 (2007-2010) is described as dealing with the ATPase, which is very confusing and does not correspond to what was presented during AERES examination.

Page 23 of the AERES report : " Over the past four years, the current team 9 studied structure-function relationships of the yeast adenine nucleotide translocator and alkyl hydroperoxide reductase 1. Unfortunately, their protein crystallisation efforts met with little success. As a result, the team has made little impact in the field. ".

About Ahp1p, we obtained crystals that diffracted. We then encountered technical problems that are closed to be resolved. This project will stop at the end of 2010.

About the mitochondrial ADP/ATP carrier, we recognized that all our efforts were not devoted to obtain crystals. However, we got some, and though they diffracted poorly, this is a very encouraging result. This is described in our report.

Crystallization of membrane proteins is a cumbersome process. Nowadays, the atomic structures of only 18 membrane transporters, not taking into account the ABC transporters, are solved. Membrane transporters are characterized by their ability to swing from one conformation (with an aqueous cavity open to one side of the membrane), to another conformation (the cavity open to the other side of the membrane). In all cases, only one conformation was obtained. Getting the 3D structure of the BA conformation supposedly open to the matrix would be a tremendous progress in the field of the membrane transporters and would help understanding precisely the transport mechanism, which is lacking so far in the field of membrane transporters.

Fully aware of the low number of researchers in the current team 9, we decided to join the future team 9 to take benefit of their skills in the field of structure studies.

It took many years for the 3D structure of the CATR conformation to come out. Should a project be given up just because it may take time before results are obtained ? Should only the research projects for which results are obtainable with an absolute certainty be supported ?

Page 23 of the AERES report: "The current team 9 published seven papers, including four papers of principle investigator in journals with an average impact factor. The team produced one PhD thesis. These numbers are low."

We don't agree with this statement considering the size of the team working on the ADP/ATP carrier.

** Team 9 (2011-2014) : SysTEMM*

The Committee considers that the contribution of crystallography was low and that the structure of ATP synthase provides little information. The team denies such remarks on crystallography since it is the first

real structure of the sub-complex F1C10. The crystal structure of the F_1c_{10} sub-complex of the F_1F_0 ATP synthase solved by the current team 11 provides a novel Mg.ADP-inhibited form of the F_1-sector with an ADP molecule in two highly closed catalytic sites. In the c_{10} rotor ring, the electron density maps reveal the apolar environment of the conserved carboxylate at the proton binding site that cannot rule out the involvement of a hydronium in H^+ transport. It is a significant advance in the face of a fierce competing group in the field.
The members of the team complain that :
- since the paper published in EMBO in 2002, the work done has not been taken into account
- the report on the team is succinct and collaborations are not taken into account.

* ***Team 10 (2011-2014) : Mitochondria, stress and cell deaths***
About the project to obtain the high-resolution structure of Bax, the committee claimed not to see the originality of our approach, as compared to previous unsuccessful attempts by others group.
Our originality does not lie in the approaches that will be undertaken, but in the objects that will be studied. Other groups tried to resolve the structure of native Bax (i.e. cytosolic and inactive) that has a very flexible conformation (as shown by NMR) and tends to aggregate, making it difficult, if not impossible, to form crystals.
Instead we will use constitutively active mutants previously characterized in our team (JBC, 2004; JBC 2007). Being membrane-inserted and active, they recapitulate the behaviour of activated Bax, and display the physico-chemical properties of genuine membrane proteins. The investigator in charge of this project has sound expertise in the biochemistry of membrane proteins, as she achieved the first determination of the high resolution structure of a mitochondrial carrier. These elements allow us to be confident in the successful outcome of this project.

* ***Team 11 (2011-2014) : Regulation of Rho proteins***
The committee has written : "The team published 5 articles in international journals on the team thematic since 2005 with modest impact factors": In its report, the committee referred to the Internet document giving criteria for identifying researchers and research professors "in producing research and valorisation." This document lists a number of major journals of high ranking including The Journal of Biological Chemistry, journal in which we published an article in 2008. 'The group leaders did not indicate either successful applications for fundings in the period 2005-2009, or for the next 4 years.' Of course we will make some applications for fundings in the future years, applications have already been filed or are under writing.
The committee noted that team 11 had collaborations mainly with teams from Bordeaux. The project leaders would like to stress that they have the ability to work with one of the best NMR team which is located in Bordeaux and that this collaboration also involves a very good team in Lille. Team 11 also works on immunofluorescence microscopy with a team in Paris-Sud Orsay and RhoGAP activities in the presence of phospholipids were carried out with a team in Budapest.
The project leaders would like to stress that they have heavy teaching duties.
At last, the project leaders do not understand why their location in a university building situated close to the IBGC instead in the IBGC itself is a negative point.

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