Institute for research on cancer and ageing of Nice

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Institute for Research on Cancer and Ageing of Nice

From the

University of Nice Sophia-Antipolis

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

February 2011

Research Unit

Name of the research unit: Institute for Research on Cancer and Ageing of Nice

Requested label: UMR CNRS

Name of the director: Mr Eric GILSON

Members of the review committee

Committee chairman

Mr Patrick MEHLEN, University Claude Bernard, Lyon, France

Other committee members

Mr Serge BOITEUX, CEA, Fontenay-aux-Roses, France (CoNRS)

Mr Cédric BLANPAIN, Université Libre de Bruxelles, Brussels, Belgium

Mr Hugues DE THE, Université Paris-Diderot, Paris, France

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Ms Urszula HIBNER, CNRS

Ms Chantal LASSERRE, Inserm

Report

1 • Introduction

- Date and execution of the visit

The on-site visit took place on February 15th and 16th 2011. Eric Gilson the director of the postulating center presented the IRCAN center to the committee that subsequently discussed with the 11 founding and postulating teams of this center. Visit had been prepared by a very well-organized and complete document and the evaluation took place under excellent conditions.

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

The IRCAN project reflects the wish of local institutions to create a research center dedicated to cancer and aging on the Pasteur campus in Nice. The unique setting of a university campus associated with two hospitals is definitely a great plus for IRCAN. The IRCAN should be led by Eric Gilson who was recruited PU-PH in Nice 2 years ago and currently gathers up to 11 teams, with quite different backgrounds, even though most teams could be identified as developing molecular and cellular biology.

- Management team

The IRCAN wishes to have a « classic » operational management team with a director, a deputy-director, a board composed of the team principal investigators and a scientific advisory board (SAB). The existing SAB is supposed to meet once a year and makes recommendations on the general scientific orientation. The director is a renowned international expert in the telomerase field and an EMBO member.

- 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)	19	19
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	26	20
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	34	31
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	23	21
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	14	
N6: Number of Ph.D. students (Form 2.7 of the application file)	22	
N7: Number of staff members with a HDR or a similar grade	36	29

2 • Overall appreciation on the research unit

- Summary

The appreciation of the research unit was on the overall positive. Major strengths include the talent of the director, the setting of the laboratory in the Pasteur tower, an ideal location to develop bench-to-bedside research in cancer and aging, and the obvious will of the local institutions to federate and support top-quality research in this location. The absence of external recruitment together with the fact that only some of the proposed groups actually work on cancer and/or aging must be rapidly corrected by making every effort to attract new group leaders with international visibility. This requires maintaining a sufficient amount of free space, rapid acquisition of a few missing equipments, the extension of the animal house, and a continued high level of support from local and national bodies.

- Strengths and opportunities

The evaluation committee has identified multiple strengths: most importantly, the scientific excellence of the director of IRCAN; then a few highly recognized senior researchers and some promising young principal investigators. The strengths also include good technical platforms, which appear to be in phase with the needs of IRCAN. It was striking for the committee to see how high the expectations for IRCAN are: there is a clear will of the Nice and regional institutions to support IRCAN, there was an effective support from INSERM, CNRS, Universities in terms of equipment, technicians, engineers over the past two years. Moreover, it appeared clear from the discussion with the various personals (staff scientists, ITA, post-doc and students), that there is a common wish from them to engage into a common project. Because IRCAN will need new talents to acquire visibility, the proposed « team nursery », an open space ready to welcome young small groups which need to mature before becoming identified teams, is an excellent project that should be realized.

The topic of cancer and aging is of course of major interest and there are no dedicated centers willing to link these two fields in France. Moreover, thanks to its close vicinity with the Nice public hospital and the anti-cancer center A. Lacassagne (CAL), the IRCAN may adequately develop high potential basic research but also a research which may be transferred to the clinic. Along this line, a clear support from University hospital and Centre Lacassagne (CAL) was given.

- Weaknesses and threats

The committee identified some significant weaknesses during the visit. The most obvious one is the geopolitical aspect. According to the Plan Cancer, it has been proposed to have only a few highly visible centers of excellence for cancer research in France. Nice appears to go in an inverse direction. Some good groups working on cancer in the Pasteur campus have moved to another location to be part of a laboratory developing a theme on cancer and metabolism (one of the strong themes developed in IRCAN with the presence of a world leader in this field). Also, the connection with groups working in the theme of development and cancer now located in Sofia-Antipolis appears to be lost with the separation from the Institut de Biologie du Développement and Cancer. The committee recognizes that it may be difficult to conciliate within the same town all the research groups addressing cancer research due to various considerations, but the committee expressed concerns that the national and international visibility of IRCAN may be limited and diluted because of the existence of three centers/institutes addressing cancer research in Nice.

Another identified weakness is that, so far, the 11 groups under the present evaluation were all from Nice. Even though the two founding words of IRCAN are cancer and ageing, there were significant concerns that forces on ageing and cancer were so far limited. As noted by the Director himself the future of the IRCAN and its attractiveness will also depend on the recruitment of new groups outside of Nice.

As a threat, the evaluation committee expressed concerns about the animal facility, which is so far limited in terms of space, but also in terms of experience and tools allowing exploration of animal models. As a side-practical recommendation, the project addressing the extension of the animal facility should receive counseling by experts in the field of animal models and facilities as concerns were raised on the danger to construct A1-A2-A3 containments within the same building.

Another possible threat as viewed by the evaluation committee is that following the opening of IRCAN, the center may face a decreased support from the region and the university.

- Recommendations

As a consequence of the above weaknesses and threats, the major recommendation lies in two words : attractiveness and excellence in the fields of cancer and aging. It is of key importance for IRCAN to attract young promising new groups, as well as more advanced senior groups. The possible venue, commented during the visit by the director of IRCAN, of a group leader developing a work on C. elegans and aging is a good indication of the ability of the IRCAN to become more attractive in this field. However, continued emphasis should be given to attractiveness (possibly independently of the ATIPE-Avenir programme). Along the same line, since two principal investigators for the most visible teams, are close to retirement, the next 6 years should be used to actively promote the emergence of leaders who will allow the continuation of the excellent research performed by these two groups.

As a side-practical recommendation, the project addressing the extension of the animal facility should receive counseling by experts in the field of animal models and facilities to ensure the building of a state-of-the-art animal facility.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	19
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	26
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	7
A5: Number of PhD granted during the past 4 years	30

3 • Specific comments

- Appreciation on the results

The IRCAN project is built around 11 teams working on different fields. The proposal described the aim to unify their strengths to build a center dedicated to cancer and aging. The different themes covered so far include:

-A basic research on telomeres in yeast and more recently in human cells which has been proven to be excellent headed by an internationally highly recognized leader –i.e., EMBO member, senior author in the best journals such as Cell-.

-A basic to translational research on cancer and metabolism headed by one of the most prestigious French biologists –EMBO member, president of the INCA SAB, member of the national Academy of Sciences.

-A basic to translational research on neutrophils and cancer led by a pathologist. This group with a long-lasting experience on inflammation and cancer attested by a large number of good publications developed a promising line of research on miRNA, which was recently acknowledged by a paper published in Nat Genetics.

-Two junior groups working respectively on the field of skin homeostasis and retrotransposition in human cancer. Both groups were recognized as promising groups having achieved extremely good post-doctoral works published in excellent journals –i.e., PNAS, J Clin Invest, J Biol Chem, J Cell Biol and J Biol Chem, EMBO J, Mol Cell, Nature Methods -. Projects were positively evaluated with a focused and well-conducted approach in one case and with a highly innovative project with great potential in the second case. Both principal investigators however need now to demonstrate by last author publications their ability to drive excellent research.

-A basic to translational research on diabetes with a clear wish to go towards diabetes and ageing research, performed by a renowned scientist in the field.

-different solid, but somehow less visible, research projects such as studying mitochondrial diseases and the stability of mt-DNA, the identification of gene mutations in key signaling pathways in sarcomas, the efficacy of anti-angiogenic treatments in renal cancers, the implication and role of cancer stem cells in glioblastoma and the relevance of cancer-associated fibroblasts in skin cancer.

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

The attractiveness of IRCAN has to be demonstrated, as this is a de novo creation. This is actually one of the main recommendations from the committee. However, it is important to note that there are already highly recognized scientists in IRCAN, who represent the stepping-stone of IRCAN. 2 PI are EMBO members, 1 is a member of the national academy of Science and is president of the INCA SAB. From the international visibility point of view, 3 PI are truly outstanding with a large number of invitations at international meetings. An important heterogeneity can be noted among the different team leaders, the core of the IRCAN is being held so far by 4 groups which clearly attract most foreign post-doctoral fellows. Most of the proposed teams have demonstrated their ability to obtain significant grant support, so that running costs should not be a major issue of the IRCAN.

- Appreciation on the management and life of the research unit

A major strength of the IRCAN is its director who is an outstanding scientist and appeared as a very capable and energetic director. The IRCAN presentation appeared like a coherent project with adequate scientific animation – weekly seminar, presence of a prestigious SAB-, adequate technical platforms, will to attract young groups, etc…-. Most PIs present their work in national and international meetings allowing the dissemination of the knowledge produced by IRCAN. 26 researchers have teaching duties within Nice-Sophia Antipolis University allowing the contact with undergraduate students and permitting the dissemination of the IRCAN research programs.

- Appreciation on the scientific strategy and the project

To link between aging and cancer is a timely and exciting project. It is indeed more and more clear that prevalence of cancer within the elderly population is very much increased, but the mechanisms are still unclear. Several institutions in the world have dedicated their projects to this aim. Therefore, the evaluation committee found it compelling to use cancer and aging as the leading words for IRCAN. The first merit of IRCAN will be that to attract scientists more and more interested in this field. However so far, no group recruited at IRCAN actually has presented a research program that indeed links aging to cancer. Thus, it will be a major challenge for the future of IRCAN to recruit new forces having their focus in such a project. It is however important to note that several key projects were presented harboring high potential in terms of both basic and translational research.

4 • Appreciation team by team

Team 1 : Telomere, senescence and Cancer

Team Leader : Eric Gilson

- Staff members

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

- Appreciation on the results

The team is composed of 18 persons: 6 researchers, 3 technicians/engineers, 6 post-doctoral fellows and 3 PhD students. The size of the team is coherent with the proposed research program. The high number of post-docs and students reveals the dynamics of the group. The team investigates structural and functional aspects of telomeres biology using budding yeast and mammalian cells in culture as models. The team has a leadership position at the international level in this highly competitive field of research. The scientific activity of the team is assessed by the publication of 52 articles in peer-reviewed journals (2006-2010). Every year, the team published in high ranked journals with E. Gilson or a team member as first/last authors: EMBO J (2006 & 2009), Current Biol (2006), NSMB (2006 & 2007), Nature Cell Biol (2009) or Cell (2010). They also publish important collaborative work with leader groups in the field, national and international. One should also note invited reviews in the best journals such as Nature Rev Mol cell or Mol Cell. The personal impact of E. Gilson is also assessed by invitations in major scientific events as speaker and chairperson such as AACR-Conference, Keystone symposia, CSH symposia. He also obtained important scientific awards in 2010: Eurocancer and Allianz-Institut de France. The team is strongly supported financially by national and European agencies, thus it has the possibility to develop its ambitious research program. The research project for the 4 next years is in the continuity of the past research and, in addition proposes novel issues. The research will be focused on the biological, biochemical and structural properties of telomeric proteins such as the telomerase complex (hTERT), TRF2 and APOLLO. The concentration of efforts on the TRF2 protein is certainly a very good issue. Several collaborations are developed with other IRCAN members in the field of cancer.

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

Attractiveness is obvious because of the quality of research achievements and project (see previous section). The high number of post-doctoral fellows and PhD students also points to attractiveness. The group is very well funded with national and European grants (ANR, EMBO, ARC, Label LNC). The group has national and international collaborations assessed by common publications with leading groups in Marseille, Basel (Switzerland) and Denmark.

- Appreciation on the scientific strategy and the project

The team strategy and the projects are ambitious and in good agreement with the financial and human forces in the laboratory. The projects are mostly basic research in molecular biology, but also translational in the fields of cancer biology and pharmacology. The integration in the IRCAN seems promising because of already ongoing collaborations. The project of the team focuses on fundamental research, which is essential for the team but also the IRCAN.

- Conclusion:

  - Summary

This is an excellent group at the cutting edge of the field. The projects are excellent and highly competitive. This is with no contest a leading team at the international level.

  - Strengths and opportunities

The quality of the results as assessed by publications in the best journals. The personal impact of E. Gilson as assessed by “invited reviews” in major journals and invitations to meetings. The composition of the group with several post-docs and students.

  - Weaknesses and threats

The only possible concern raised by the committee is the overload of administrative tasks in the context of IRCAN with at least eleven groups with very different aims.

  - Recommendations

The only recommendation for this group is to continue the excellence that this group has developed over the last past years. In the context of IRCAN, the committee thinks the recruitment of other strong basic research oriented groups (national and international) is mandatory. Basic research groups using other biological models such as yeasts (S. cerevisiae or S. pombe), nematode or drosophila should be associated with IRCAN in the future.

Team 2 : Retrotransposon and genome plasticity

Team leader : Gaël CRISTOFARI

- Staff members

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

- Appreciation on the results

This is a young research team starting 2010 with a very strong support by INSERM (CR1 position and AVENIR label) and ERC (young investigator). The team is composed of 9 members: 1 researcher, 3 technicians/engineers, 2 post-doctoral fellows and 3 PhD students. The results during the past four years are primarily associated with the team leader's post-doctoral period. In this laboratory, he investigated the homeostasis of telomeres in human cells and primarily the properties of the telomerase complex. He published papers in high ranked journals such as EMBO J (2006) (1/2), PNAS (2007) (2/6), Mol Cell (2007) (1/8). In Lyon, as an independent researcher (2008-2009), he developed research in the telomerase field with a paper in collaboration in MCB (2010). Since 2010, he initiated a new research program aiming to dissect the mechanisms of retro-transposition in human cells. The project was already presented two years ago (for the UMR creation with a 4 teams structure). The objective is to decipher the cellular pathways that control retro-transposition, and to understand how transposable elements participate in the normal and pathological (cancer) remodeling of the human genome. He will focus on L1 elements and their impact on genome stability using very recent and powerful global genome approaches. The results are not yet published. This can be easily understood because of the recent settlement of the laboratory. Recent results have been presented: i) identification of a potential L1 regulator protein, ii) development of an in vitro assay for retro-transposition. However, the functional impact of the L1-regulator candidate has not yet been unambiguously demonstrated. One paper is actually under review. Therefore, it is not easy to appreciate the recent results 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

It is too early to appreciate the impact of this new group in the field of transposable elements. The attractiveness is good assessed by the growing size of the group with 2 post-doctoral fellows and 3 PhD students. The impact of the group at the national and international level cannot be assessed because of the recent creation of the team.

- Appreciation on the scientific strategy and the project

The team leader has obtained two very strong supports from INSERM (AVENIR) and ERC (young investigator support for about 1.7 MEuros) and this is an overall very good strategy to attract collaborators and develop very ambitious projects. The project is highly competitive and addresses very basic questions in genome biology in human. This team proposes to understand molecular mechanisms of retro-transposition using in vitro and in vivo approaches. It also proposes to understand the role of transposable elements in genome plasticity and cancer. In term of strategy, the recent recruitment of an expert in bioinformatics was essential to analyze the huge amount of data generated.

- Conclusion:

  - Summary

This is a young promising team with a strong financial support from national and international agencies. The composition of the group is good with a bioinformatician, post-docs and students. Several collaborations are acknowledged in France and abroad. Together with the fact that the team leader indeed performed very well during his PhD and post-doctoral training, this group should then produce important results in the near future.

  - Strengths and opportunities

Very good post-doctoral publications in the field of telomerase. The new project on retro-transposition in human cells is attractive and ambitious. The financial support for 5 years is significant allowing recruitment of collaborators.

  - Weaknesses and threats

The group is young and will have to fight to exist in a highly competitive field. We do not know if the scientific environment is sufficient to develop such genomic project at the international level. Similar to Eric Gilson's group recommendation, the recruitment of other basic research oriented groups will be very helpful.

  - Recommendations

This is a young group with a great potential. However, the absence of production may be a problem in the near future. Thus, the team leader should focus and finalize one of his ongoing projects by a good publication in the next two years. Possibly, the research project should be reoriented at the light of the results obtained since the creation of the team.

Team 3 : Mitochondrial diseases and mtDNA stability

Team Leader : Véronique PAQUIS

- Staff members

	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)	/	/
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3 (1SC incl.)	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

The relevance and originality of the scientific results of this team are compatible with its small size. They are focused on diagnostic applications of mutation identification for different mitochondrial disorders for which the team has developed during these last 5 years appropriate techniques of biochemical and DNA analysis of mitochondrial respiratory chain defects. This work is therefore centered on the genetics of mitochondrial diseases and has been performed in direct collaboration with the laboratory of genetics and the Reference Center for Mitochondrial Diseases (CHU of Nice, Archet 2 Hospital). The link between the work done so far in the field of mitochondrial diseases and the proposed project is not clear.

The team presents a good number of cooperative clinical publications in the field of mitochondrial genetics, i.e. the PI presents 15 papers dealing mainly with diagnostic findings on mitochondrial diseases. The only published paper from the team which may be relevant for cancer research deals with the role of hMSH5 in the regulation of hMSH4 subcellular localization, which was published in 2007 (Expt. Cell Res.) The P.I. of the team was not the senior author in this work. Another recent paper of the group -re: the mitochondrial localization of hMSH5 and stimulation of mtDNA repair after oxidative stress- is quoted by one of the team member as under revision in HMG, but is not confirmed as accepted in the updated list of publications. The publication record on hMSH5, which should be the point of strength of the project, is therefore quite limited.

Finally, a technical report on the rapid identification of unknown heteroplasmic mutations across the entire human mitochondrial genome (Nature protocols 2006) could be of general interest for the field of mtDNA mutations but its potential does not seem to have been fully investigated. The remaining production of the whole team (including doctoral theses, scientific communications, etc.) is centered again on studies of patients with mitochondrial disorders or diseases associated with alterations of mitochondrial function (like Wolfram syndrome and type 2 diabetes). Eight additional papers represent collaborations initiated by other groups during the same 5 years period.

This team, which includes, among others, two researchers with teaching duties, 4 postdoctoral fellows and 1 Ph.D. student has received a significant support from the hospital (3 positions for an research engineer). A recent recruitment through a University appointment occurred recently.

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

The team and its leader are well established at the national level in different Consortia and Committees devoted to the development of protocols and collaborative studies for the diagnostics of mitochondrial disorders. They are clearly part of a good French network in the field of mitochondrial disease but have little international visibility. The team leader is the president of the one ARC (Association pour la recherche contre le Cancer) committee.

There is no apparent recruitment of investigators from abroad except a recent one, who identified Spiky, a new mitochondrial partner of Twinkle helicase, through a 2-hybrid screen while working in Sweden. Spiky might be an interactor of Twinkle. This work is still unpublished, and it is not clear how it could contribute to the proposed project, if this preliminary finding is developed further.

The participation of the group in a European network (EURO-WABB) brought a funding of 117 K Euro. Other fundings come from national agencies which have being providing a large financial support.

The team shows evidence that collaborations and partnerships go beyond national boundaries.

The numerous appointments of the principal investigator in national committees illustrate the contribution of the team to the development of diagnostics of mitochondrial disorders.

- Appreciation on the scientific strategy and the project

There is a significant problem in identifying the direction that the project will take towards cancer and/or ageing research during the next 4 years. None of the proposed lines of investigation has gathered a sufficient amount of data to make this point clear. Among these, the only published study of the group deals with the cell distribution of hMSH5 protein and there are significant doubts about its conclusions (which have not been verified for example by E.M.). Overall, there are several significant questions on the proposed project, including the use of overexpressed proteins in cells, lack of details on the proteomic studies, analyses of KO mice. Since the work in progress is almost entirely unpublished, it is difficult to judge its reliability.

The allocation of resources suffers from the uncertainty about the direction the project will take during the next 4 years.

The gap existing between the research performed at present by the group and that foreseen in the project does not contribute to the construction of a cutting edge strategy.

- Conclusion :

  - Summary:

The previous work done in the diagnostics of mitochondrial diseases is of good quality but the team does not have a clear strategy for research in the field of cancer and/or ageing. The cell biology aspects and the implications of the findings on MSH5 need to be strengthened. The few preliminary findings, which might lead to the development of an interesting line of research -re: the role of mitochondria dysfunctions in cancer- are at present not sufficiently strong.

  - Strengths and opportunities

The team has strong personnel support from hospital and can take advantage of the resources deriving from the clinical and molecular diagnostics services performed by the laboratory of genetics and by the Reference Center for Mitochondrial Diseases.

  - Weaknesses and threats

The different locations of IRCAN in the Tour Pasteur and of the Reference Center for Mitochondrial Diseases in the Archet 2 Hospital implies that the same personnel involved in the research activities in the former and in diagnostic activities in the latter will apparently have to move from one location to the other. This will seriously jeopardize the development of the proposed research project. In addition, several basic questions regarding aspects of fundamental biology of mitochondria remain unanswered like the mitochondrial localization of hMSH5 and the stimulation of mtDNA repair mechanisms after oxidative stress. Pursuing these objectives implies the involvement of highly trained permanent staff and this appears to be lacking.

  - Recommendations

The team should recruit staff scientists, focus on a defined topic and provide some clear-cut evidence on the importance of MSH5 to mitochondrial biology. The team might want also to take more advantage of the patients and families resources that are available through the laboratory of genetics and the Reference Center for Mitochondrial Diseases at Archet 2 Hospital. As an example, they could identify new nuclear genes involved in mitochondrial dysfunction by using the platform of Next Generation Sequencing available at IRCAN. However, it is not clear how the in depth study of the two available and interesting large pedigrees described in the application would integrate in the proposed project.

Team 4 : Carcinogenesis-related chronic active inflammation

Team Leader : Paul HOFMAN

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	6	5
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	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	/
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	/	
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	7	6

- Appreciation on the results

The main research interest of the group has been on the interactions through chronic inflammation, pathogens and carcinogenesis, mainly in the digestive tract, and more recently in the lung and the thyroid. From a morphological and physiological approach, with a degree of dispersion in the interests, the team has progressively moved to a more experimental and explicative approach and adopted a much more focused project. This was successful and led to important achievements, such as the recent demonstration that apparently silent polymorphisms may be clinically relevant through the alterations of the interactions with regulating miRNAs.

The group is highly productive, with a high number of ACL (more than 100) and 4 patents. However, many are related to the clinical activities of some members of the team, and are not directly relevant to the main research objectives. Nevertheless, the relevant publications represent a good production of about 30 papers, usually published until recently in journals with good or very good impact factors (Am J Physiol, PLOS family ...).More recently, the team reported important new results in an excellent journal (Nature Genet, 2011).

- 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 contracted local and national partnerships of excellent quality and relevance to their own projects.

The team leader shows numerous invitations and participations in national and european medical congresses (32 invitations).

The team has proven able to attract three active and productive full time researchers in the last 4 years. It includes a number of medical researchers coming from the main areas of interest of the team and testifying the strong clinical connections of the group.

It can be noted a good participation to international networks, however, mainly in the field of biobanking.

The team has a good capacity of fund raising (about 1000 k€ from local and national sources) and a recognized capacity to organize high quality technological platforms and biological resource centers, mainly oriented to support the own research interests of the team.

4 patents have been filed.

- Appreciation on the scientific strategy and the project

The research project is highly focused on the role that neutrophils may play a role in tumor progression and dissemination. The main hypothesis of the group is that neutrophils may influence the behavior of tumor cells, especially through the release of miRNA in their pericellular environment. This hypothesis will be explored by an integrated strategy combining experimental approaches (including animal models) and a translational approach based on well-characterized samples of human tumors, available through the local biobank. The general aim of the research is “cutting edge”, clearly original and highly innovative, with little competition at the national and international levels. The working hypothesis is based on recent results of the team and on preliminary observations; if verified, results will be very important and will open a new direction in the study of the interactions between tumor cells and their environment.

There is no problem of resource allocations and a good adequation between project and human resources.

The main research project has the potential to be of “cutting edge” format.

- Conclusion :

  – Summary

This is an attractive team, with an original and innovative research project and an excellent insertion in the local clinical environment, resulting in important recent achievements. This team is equally well devoted to basic and translational research and, with its strong clinical background, will be a very valuable asset to the future IRCAN.

  – Strengths and opportunities

Innovative and highly focused project, excellent opportunities of translational research, excellent connections with the clinical environment, high visibility of the team leader, important productivity.

  – Weaknesses and threats

The bases supporting the working hypothesis have to be strongly established and a number of alternative mechanisms and possible pitfalls must be carefully excluded.

  – Recommendations

It is important to maintain the highly focused character of the project, increase the level of participation to competitive international applications, increase the scientific visibility of the whole team at the national and especially, international levels and promote the young researchers of the team.

Team 5 : Ageing and Diabetes

Team Leader : Emmanuel VAN OBBERGHEN

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5	6
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3 (1SC incl.)	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	8	4

- Appreciation on the results

The research focus on metabolism and ageing is highly relevant for the new institute (IRCAN). The prevalence of diabetes and obesity is constantly increasing and therefore, it is of utmost importance to decipher molecular mechanisms that impair healthy ageing and lead to cancer formation under these conditions.

The group has a significant publication record of 58 publications in peer-reviewed journals, among those 43 as first and/or last author. Most of them are in many different specialty medical-oriented journals. Nevertheless, one may note one publication in Curr. Biol., two in J. Biol. Chem. and one in Oncogene.

However, the number of projects is impressive. In future work, the group should focus on a subset of most-relevant projects aiming to get more high-impact paper publications.

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

The team appears to be highly motivated. The planned new institute (IRCAN) has further stimulated the enthusiasm of the group. The inclusion of a junior group leader was a smart move to bring in expertise on mouse model and miRNAs. This could especially be relevant for the functional analysis of newly identified miRNAs that may be linked to the development of metabolic and cardiovascular disease. The combination of the experience of the team leader in metabolism and the expertise of newly arrived scientist in mouse models and functional analysis of miRNAs looks like a classical win-win situation. This combination could be very strong to analyze functionally the influence of miRNAs on metabolism, cancer, and possibly aging.

The team leader has a very good international standing. He has received several very prestigious research awards and he is constantly invited to speak at international conferences. He is involved in several EU projects indicating his international collaborations. In addition, the group has many national collaborations.

- Appreciation on the scientific strategy and the project

The research team focuses on a very important and highly competitive research area –the evolution of diabetes, specifically the influence of developmental factors and aging-related factors on the evolution of diabetes. The research program is well structured and highly innovative. The team should consider narrowing the focus. Some of the work plans on organ pathological changes in diabetes (endothelial-¤-cell interaction in pancreas, kidney) are not

supported by strong research results. Other topics appear to be more advanced, specifically the work on miRNAs that are associated with the development of diabetes. It would be of utmost importance to study the functional in vivo relevance of these miRNAs in mouse models. The involvement of a recently hired scientist and the link to cardiovascular research could be very beneficial for this research direction. Eventually, this could lead to the evolution of a suitable successor for the present team leader, who may consider retirement in 4-5 years.

- Conclusion

  - Summary

In summary, the research group (including the junior group) has a very good track record and works on a highly important research topic, which is relevant for both aging and cancer. The new mechanistic studies on miRNAs in diabetes development and cardiovascular disease appear highly attractive and if studied in appropriate in vivo models could be highly successful.

  - Strengths and opportunities

The visibility of the research group. The recent recruitment of a junior group leader who could play a major role in the future development of the research project of the team. The new focus on miRNAs in the epigenetic control of gene transcription, its role in diabetes development, and the consequences on cardiovascular disease that represent a very attractive research topic.

  - Weaknesses and threats

The possible retirement of the team leader in the next 4-5 years.

  - Recommendations

The group publishes well but should try to get more high impact papers. Given the importance for aging and cancer of this topic, it will be important to make plans for the continuation of the research program. If successful, the project of the junior group leader could provide a solid basis for a long term perspective of the team.

Team 6 : Epithelial homeostasis and tumorigenesis

Team leader : Chloé FERAL

- Staff members

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

- Appreciation on the results

During her post-doctoral training, the team leader has been interested in integrins and one protein interacting with them : CD98hc. She developed several original constitutive and conditional engineered mouse models. The main goal of the project is to evaluate the importance of CD98 in the skin using mouse molecular genetics and to investigate the consequences of CD98 deletion on skin homeostasis, and tumorigenesis. The project is solid and focused. The originality of this project will be residing in the characterization of the molecular mechanisms underlying the function of this protein, if indeed the deletion of this gene will show a phenotype. Also, since this protein has a potential dual functions (regulating integrin signaling and participate in the transport of aminoacids) this might be interesting to understand.

Eight articles were published in association with her post-doc (3 as first authors including a JCI and a JCB, 2 as second author in J Exp Med and JBC ; she was coauthor in MCB 2008, Nat Immunol 2009, and Curr Res 2010). The work was published in excellent and very good journals. The team as such did not produce any publication yet, but one paper has been submitted. Since 2006, she was invited in two conferences and performed one oral communication (2 out of 3 in France). The team was created in January 2009 with an AVENIR/INCa grant. The evaluation of the team as such is not feasible for the last 4 years period.

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

The team leader was invited once to an international conference.

The team will be composed of 3 permanents + 3 non-permanents (1 CR2, 2 ITA Inserm + 1 ITA CDD, 2 Post-docs). One of these postdocs was recruited from abroad as a post-doc in a well-known lab. This seems ideal to reinforce the team.

The team leader continues her collaboration with her former postdoc laboratory and started a collaboration with team 7 at IRCAN. Altogether, this is very promising.

The team leader obtained an Avenir grant and other fellowship grants. Thus, the team has funding for the running budget and non-permanents staffs until 2012.

It appears that the team leader is quite well networked at the local and international levels.

As mentioned, the team has i) a clear and focused question, ii) the appropriate fellows to perform the work, iii) the fundings, iv) the biological tools and v) the structure (lab space, animal colony, histology room, etc..). However, it is also important to note that up to now, all publications come from the very successful postdoctoral period of the team leader. The youth of the team makes its visibility per se not yet appreciable.

- Appreciation on the scientific strategy and the project

The proposed project aims to investigate wound healing and skin carcinogenesis in mice with temporal and/or spatial ablation of CD98hc in keratinocytes. It will address the physiological role of integrins and integrin-associated proteins in keratinocyte biology (adhesion proliferation and differentiation, as well as re-epitheliazation during wound healing on one side) but also the involvement of altered integrin signaling in skin disorders including cancer. In parallel, the team will perform functional studies on isolated CD98hc-deficient keratinocytes to assess the impact of CD98hc loss, and the roles of different CD98hc domains on integrin signaling. Finally, it is planned to decipher CD98hc-dependent integrin regulation and amino acid transport.

The strategy is straightforward and well thought. The chosen methodology is straightforward.

The project is well-planned regarding budget, number of persons and questions.

The project is not highly innovative at this point but is solid. According to the limited resources, the team will have time to generate original science with other CD98hc partners and their roles in skin biology.

- Conclusion :

– Summary

The team is working on a well-focused aspect of the regulation of integrin concentrating on one specific protein CD98hc. All the requirements to succeed are fulfilled. This protein has other partners, which can be very important in the understanding of the function of CD98hc. The proposal is well written.

– Strengths and opportunities

The project is well thought and feasible. With regard to the available scientific experience of the team and the experimental tools, the research plans are well feasible. In vivo model is of interest and it is quite simple to establish in vitro models to better evaluate other aspects of biology such as biochemistry. The team leader showed that she can raise money.

– Weaknesses and threats

Lacks PhD students (no HDR). As a young team leader, she will have to show her quality as a manager. She will have to hire PhD students once she will have her HDR. A high quality animal colony is essential for this team. The overall number of cages and know-how will need to be increased in the near future to allow this team (and the others) to develop their project without a gap of 1-2 years. A high impact publication will be required to allow the renewal of external funding that will run out in 2012.

– Recommendations

(i) Needs to obtain her HDR as soon as possible and to recruit PhD student urgently. (ii) Generates close interaction with pathologists who are present in the centre. (iii) Publish high quality papers.

Team 7 : Hypoxia signaling and Cancer Metabolism

Team leader : Jacques POUYSSEGUR

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	9	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	/
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	/	
N6: Number of Ph.D. students (Form 2.7 of the application file)	/	
N7: Number of staff members with a HDR or a similar grade	6	4

- Appreciation on the results

The team has a long-standing interest and track record in elucidating mechanisms of cellular growth control. In the field of hypoxia signaling and aberrant cell metabolism in cancer the team performs science of highest international caliber.

The team leader has published an exceptional number of papers in excellent and very good journals of biomedical research. Between 2006 and 2010 the team leader published 43 original and 24 review articles. Among those were several invited reviews in leading journals such as “Cancer Cell” and “Nature Reviews in Cancer” which reflects his international reputation. This is highlighted by an excellent number of 2200 citations of these articles from 2006 until today.

During the period under review, the team consisted of 10 staff scientists. None of the CR1 published as impressively as the team leader: one had 4 articles; another had 6 articles out of those 2 as a first or last author; one CR1 had 5 articles out of those 3 as first or last author. One CR1 only published review articles.

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

Extensive collaborations with local, national and international groups (Australia, Japan) are visible and the participation in EU-FP7 Metoxia and Gliomet programs reflects the international networking of the team.

The team leader has been elected for the French Academy of Science in 2007 and gave the Carl Cori award lecture in 2008 (The Roswell Park, USA). Within the period under review the team leader has given 152 lectures abroad, most of them in US, Europe and Asia. One CR1 has presented 11 lectures. 7 oral communications were given by two other team members (3+4).

The team recruited 6 post-docs, including foreigners (Canada) and had collaborators on sabbatical year from other countries.

The team raised 1250 keuros (2 ANR, 1 INCA, 1 Ligue label, 1 arc and EU-FP7 Metoxia and Gliomet programs).

The team has numerous local, national and international collaborations.

During the period under review one patent has been filed.

- Appreciation on the scientific strategy and the project

The proposed future research represents a logical continuation of the current interest and the successful ongoing research. The proposal is excellent both in its concept, quality of objectives and, thus, feasible.

The methodology and associated work plan are very well thought through and there is no concern and the appropriate allocation of resources.

The scientific strategy is directed towards the development of novel therapeutic strategies for cancer. The proposed project focuses on the role of hypoxia-inducible transcription factor HIF-1 in the activation of glycolysis and the regulation of the intracellular pH (pHi). Cancer cells are characterized by a very high metabolic rate and, thus, an increased glycolysis and also a powerful pHi regulating machinery. The metabolic alteration and adaptation of cancer cells has been initially described nearly a century ago by Otto H. Warburg in the 1920s but the subject received renewed attention within the last years. The team belongs to the leading research groups addressing this subject. The major breakthrough was the demonstration by his laboratory that the knockdown of carbonic anhydrase IX (CA IX) impairs tumor growth in vivo. CA IX is one of the most inducible genes upon hypoxia and has a role in pHi regulation as it enables CO2 hydration even at low pH levels typical for tumor cells.

- Conclusion :

– Summary

With Team 7, the IRCAN includes a team leader and a laboratory of highest international reputation that performs research at the forefront of biomedical science. The objectives of the project include knock down/out approaches for interesting candidate molecules/genes in tumor cells and subsequent xenograft studies on nude mice.

– Strengths and opportunities

The team leader is one of the very best biologists in France. Each of the proposed objectives has the potential for one or more publications in excellent journals and may contribute to the issuing of patents.

– Weaknesses and threats

The team leader's contribution to IRCAN during its founding phase appears to be of critical importance. However, his request for an " Emeritus Professorship" status (September 2011 to September 2016) is pending. This raises the question for how long the team leader will head the research group and what will happen at the latest after 2016. With the team leader's retirement within in the upcoming period, IRCAN will loose a highly respected and internationally visible researcher.

– Recommendations

The committee agrees with the team leader on the objectives to study the mechanisms of interest first in simple model systems such as cultured cells or xenograft mouse models. However due to the general concerns about the value of these models for predicting therapeutic efficacy in humans, it may be useful to validate initial findings on mouse models that reflect the type of spontaneous tumor development (for example the MMTV-PyMT mouse model of breast cancer) and to test those - at least for the most interesting candidate targets.

Analysis of such mouse models would significantly extend the scientific outcome of the work and may help answer the question whether these developed strategies, that target the metabolic shift or pH regulation of cancer cells, not only interfere with tumor growth but also with metastasis.

The panel also emphasizes the need for a clear plan for the future. Among others, the timely recruitment of a successor of the team leader, who is of a similar top international caliber or has the capabilities to step into the footprints of the team leader is crucial. This would allow the IRCAN to continue with the research theme of hypoxia signaling and cancer metabolism.

Team 8 : Genetics and physiopathology of eptihelial cancers

Team leaders : Thierry MAGNALDO and Guerrino MENEGUZZI

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	8	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6 (2SC incl.)	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4	
N6: Number of Ph.D. students (Form 2.7 of the application file)	6	
N7: Number of staff members with a HDR or a similar grade	6	4

- Appreciation on the results

This team results from merging of two previous collaborating teams. One of the group leader (Magnaldo) recently moved to Nice, masters great expertise in 3D skin cultures from patients with various genetic diseases, and has an interest in gene transfer. During the period 2006-2010, Magnaldo team published 18 publications. In the publication records, the team is leader in the vast majority (15 first/last authorship). The laboratory published in very good (eg Oncogene) or good journals. There are four senior author papers (including Oncogene and PLOS One) and all report work made in Villejuif. The group was associated to excellent (eg Gene&Dev) journals. Magnaldo was associated to a Gene&Dev (2006) and Cancer Research (2007) publications, which are highly cited (171 citations). The other team leader (Meneguzzi) is more senior and has a very good visibility in the dermatology field. He joined the center largely independently from his previous team, which was implicated in cell adhesion and extracellular matrix in the context of the skin. Menguzzi team published 22 publications. In the publication records, the team is leader in half of them (10 first/last authorship). The group published in very good (eg Oncogene, JCS, JCB) or good journals. They also published in the best journals of their specialties (eg J. Inv. Derm.), either as senior author papers (2), or in collaboration.

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

The first team leader has significant visibility in the dermatology field, as indicated by 10 conference invitations, 1 patent with licence and long lasting industrial support (L'Oreal, Galderma..). The second team leader also has a very good visibility in the field, with 20 invitations to conferences. Both have good international cooperations and have secured significant funding.

- Appreciation on the scientific strategy and the project

The group will be progressively directed by the first group leader. Those projects involving the second group leader were clearly delineated and appeared well-focused and important. A set of experiments linked to the previous observations made by the authors is proposed (characterization of the carcinoma associated fibroblasts (CAF) phenotype found in dermal fibroblasts of XP-C patients, role of epigenetic changes..). They suggest to explore the basis for the acquisition of the CAF phenotype by fibroblasts derived from several genodermatoses, including ROS production and epigenetic changes. The group has considerable know-how and reported some very interesting

findings. Yet, there was a feeling that too many goals were pursued and that some choice should be made. Interesting links with two other groups of the center are proposed, but should be further substantiated.

- Conclusion :

  - Summary

Two different groups merging forces, with no anticipated management issues. Very significant expertise in the dermatology field. Good industrial contacts. Some interesting and provocative preliminary findings.

  - Strengths and opportunities

Access and know-how for primary cultures of skin from patients ex vivo and in vivo. Unorthodox hypotheses. Solid know-how and contact in the dermatology field. Good models and international cooperations.

  - Weaknesses and threats

Relatively modest publication records, which can be improved with their current results. Some questions were raised on the strength of approaches using 3D culture of primary human cells, when compared to genetically defined mouse models. Each of these approaches its advantages and disadvantages. Depending on the genes of interest one or the other approach can be more appropriate.

  - Recommendations

Every effort should be made by the PIs to enhance their scientific visibility. This probably means focusing on fewer projects, in order to secure more visible publications.

Team 9 : Genetics of solid tumors

Team leader : Florence Pedeutour

- Staff members

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

- Appreciation on the results

This is a proposed new team at IRCAN led by a MCU-PH in Oncology. The research program of the team is mainly translational and is dedicated to the genetic characterization of soft tissue tumors. The laboratory is considered as a reference in the field of molecular cytogenetics of solid tumors.

Taken in account the clinical activity and the size of the team, the scientific production of the team is very good with more than 15 articles produced by the team itself (Int J cancer, Cancer genet Cytogenet, Virchow Arch, Genes Chromosomes Cancer, Cancer letters, Clinical Cancer Res) and about 30 articles as collaborative works.

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

The team leader as a good national visibility in the soft sarcoma field and has the capacity to raise sufficient fundings from competitive agencies (PHRC, NCI, ARC, Ligue)

- Appreciation on the scientific strategy and the project

Three projects are proposed:

- the main project is centered on the genomic and functional characterization of both adult and infant adipose tissue tumors. This project is relevant to the competence of the team and will benefit of the skill of IRCAN for the functional studies on HMGA2 and for the miRNA profiling project, but is not at this stage, highly innovative.

- a second project will characterize renal cell tumors both at the genomic and immunohistochemical levels. It comes from recent results obtained by the team in collaboration with the Pathology and Urology department.

- a third not yet initiated project will analyze a specific type of odontogenic tumor (KCOT). The aim is to evaluate in a cohort of KCOT patients the biological aggressiveness of this tumor in a retrospective immunohistochemical and genomic study.

- Conclusion :

  - Summary

The activity of the team in the cancer field is good concerning translational studies but unbalanced with fundamental research.

  - Strengths and opportunities

The recognized competence of the team in cytogenetic and its clinical applications.

  - Weaknesses and threats

The extension of the genetic studies to other tumors (renal and odontogenic) may weaken the efficiency of the team. The overall projects are not considered as very innovative.

  - Recommendations

Basic science should not be forgotten. To concentrate efforts on the expertise and strength of the team and develop more innovative questions applied to basic science on soft tissue tumors.

Team 10 : Cancer and normal neural stem cell plasticity

Team leader : Thierry VIROLLE

- Staff members

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

- Appreciation on the results

The group published 3 papers in the last 5 years in Cell Death and Differentiation (2X) and J Neuroscience. The group recently submitted 2 papers in the same type of journals. On the overall, working in very fashionable theme, the group needs to publish papers in journals with higher impact.

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

While the team has secured some funding, the PI has not obtained prestigious grants such as Avenir, ERC starting grant or Marie Curie grant of excellence. The PI has not been invited to speak to any prestigious meetings.

- Appreciation on the scientific strategy and the project

The group identified a clustered mIRs expressed upon in vitro differentiation of glioblastoma multiform (GBM). They now want to investigate the therapeutic impact of overexpression of these mIRs cluster in tumor cells. They observed that mIRs overexpression stimulates GBM differentiation through the secretion of soluble factor(s). They want now to test what are the(se) factor(s) secreted upon mIRs that promote GBM differentiation.

While these results may not be relevant to understand the biology of GBM, since these miRs are not expressed in primary human GBM and are only induced during in vitro differentiation, this project may lead to potential clinical applications.

- Conclusion :

  - Summary

While the PI has good research strength, the committee feels that the research project is a bit unfocused.

  - Strengths and opportunities

The group is well connected with the clinicians that allow the team to develop potentially clinically relevant applications.

– Weaknesses and threats

Too many risky and unrelated projects.

Strategies need to be reevaluated. For examples, they proposed to perform three different chip_seq analyses: epigenetic modifications linked to the expression of the mIRs cluster, beta-catenin and egr1. This approach is not trivial and required some expertise that the group does not necessarily have for the moment.

– Recommendations

To limit the number of projects and prioritize them. Effort should be concentrated on the more promizing subjects. Priority should be given to publish their research in high impact journal. Strengthen the composition of the team by recruiting high talented post docs.

Team 11 : Normal and pathological angiogenesis

Team leader : Gilles PAGES

- Staff members

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

- Appreciation on the results

The past research activities of the team leader have dealt with various aspects of intracellular signaling, with a special focus on the ERK pathway. There was a progressive shift from signaling to tumor angiogenesis. A first step was the demonstration of the involvement of ERK in VEGF signaling. More recently, the team has developed an original exploration of the biological consequences of the anti-angiogenic strategies used in clinical practice. The research has focused on renal cell carcinoma and several experimental models (cellular and animal) have been developed. The recent reorientation of research has resulted in original and somewhat provocative findings, which may have important clinical impact.

The production includes 32 ACL, with 9 in last author, in good or very good specialty journals (Cancer Res, Oncogene, J Biol Chem, Hepatology, Endocrinology ...). It is important to remind that the team leader had important teaching duties as MCU until 2008, before becoming full-time researcher at this date (while still maintaining a significant involvement in teaching).

The team leader has initially developed his research within the team 7, before developing autonomous projects. He contracted numerous partnerships at the national and international levels.

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

The PI shows a good number of invitations in national (mainly) and international conferences (13).

There are 4 post-docs in the team.

The PI has shown a good capacity of fund raising (about 1,000 k€), mainly through national applications

The team leader has a number of national and international partners, and a good network of collaborations. He is a board member of the recently founded French Society for the Study of Angiogenesis.

One patent has been filed and it exists interesting opportunities of socio-economic partnerships, as testified by two contracts with big pharmaceutical companies.

- Appreciation on the scientific strategy and the project

The scientific project is well focused but ambitious. Its most interesting part is on the consequences of the anti-angiogenic strategies now used in clinical practice and especially, on their somewhat unexpected effects on the expression profile of angiogenic molecules. The two major topics are: (1) the study of proangiogenic ELR+CXCL cytokines and (2) the role of "anti-angiogenic" VEGF isoforms that may interfere with anti-angiogenic therapy. The importance of the results obtained would be strengthened by the development of more relevant animal and cellular models and by the exploration of additional tumor models susceptible to be treated through anti-angiogenic strategies. It is also important to have a strong clinical connection in order to verify the relevance of the experimental findings to the clinical situation.

The small size of the group may be a handicap for the full development of the research project and of its opportunities.

The questions raised by the team are original. Even if, so far, the published results do not open very innovative fields for future research, they may be of potentially great relevance for clinical practice.

- Conclusion:

  - Summary

It is a small group, having performed an important effort to focus its scientific project on timely and clinically relevant issues

  - Strengths and opportunities

Project with a good strategy, important socio-economic opportunities and potentially important clinical relevance. Insertion in a relevant network of partnerships.

  - Weaknesses and threats

Small size of the team (1 full time researcher, 4 post docs), which may hamper the full development of the opportunities open by the research project.

  - Recommendations

To improve the attractiveness and visibility of the whole team. To develop a close management of the research project and to priorize its most innovative part. To implement more accurate models for the study of the biological questions addressed by the team. To set up an active policy for the recruitment of additional researchers.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
INSTITUTE FOR RESEARCH ON CANCER AND AGEING OF NICE	**A**	**A+**	**A+**	**A**	**A**
RETROTRANSPOSON AND GENOME PLASTICITY [GILSON-CRISTOFARI]	Non noté	A	Non noté	A+	A+
EPITHELIAL HOMEOSTASIS AND TUMORIGENESIS [GILSON-FERAL]	Non noté	B	Non noté	A	A
TELOMERE, SENESCENCE AND CANCER [GILSON-GILSON]	A+	A+	Non noté	A+	A+
CARCINOGENESIS-RELATED CHRONIC ACTIVE INFLAMMATION [GILSON-HOFMAN]	A+	A	Non noté	A+	A+
GENETICS AND PHYSIOPATHOLOGY OF EPITHELIAL CANCERS [GILSON-MAGNALDO-MENEGUZZI]	A	A	Non noté	A	A
NORMAL AND PATHOLOGICAL ANGIOGENESIS [GILSON-PAGES]	A	A	Non noté	A	A
MITOCHONDRIAL DISEASES AND MTDNA STABILITY [GILSON-PAQUIS]	B	B	Non noté	B	B
GENETICS OF SOLID TUMORS [GILSON-PEDEUTOUR]	A	B	Non noté	B	B
HYPOXIA SIGNALING AND CANCER METABOLISM [GILSON-POUYSSEGUR]	A+	A+	Non noté	A+	A+
AGEING AND DIABETES [GILSON-VAN OBBERGHEN]	A	A+	Non noté	A	A
CANCER AND NORMAL NEURAL STEM CELL PLASTICITY [GILSON-VIROLLE]	B	B	Non noté	B	B

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

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

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

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

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

Présidence et
Services Centraux

Université Nice SOPHIA ANTIPOLIS

Nice, le 11 avril 2011

Affaire suivie par :
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N/REF : 2011-1755

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

Ref : Rapport d'évaluation S2UR120001723 - Institute for Research on Cancer and Ageing of Nice - 0060931E

Monsieur le Directeur,

Faisant suite au travail effectué par le comité de visite de l'AERES et du rapport d'évaluation émis sur l'Unité de Recherche « Institute for Research on Cancer and Ageing of Nice » portée par l'Université Nice Sophia Antipolis, vous voudrez bien trouver ci-joint la réponse que nous désirons apporter à ce rapport.

Celle-ci ne comporte pas d'éléments correctifs factuels mais des observations de portée générale visant à marquer, au-delà des quelques précisions apportées, une forte adhésion aux recommandations très positives faites par le Comité de visite que nous remercions pour son travail constructif.

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

UNIVERSITE DE NICE - SOPHIA ANTIPOLIS
1.1.1996

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

Pierre COULLET

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Laboratory of Biology and Pathology of Genomes

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Tél : 04 93 37 77 86 - Fax : 04 93 37 70 33

Nice, April 6th 2011

Object : Evaluation of the project of creation of the Institute for Research on Cancer and Ageing, Nice (IRCAN)

To whom it may concern,

On behalf of the direction of the future IRCAN, and of all the members of the project, I want to express my sincere appreciation to the evaluation committee for the excellence of their analysis on the project of creation of IRCAN at the Pasteur/CAL campus of Nice. We are very grateful for the quality of the exchanges with the members of the Committee.

We thank the Committee for the very positive comments on the project, on its scientific originality and on our effort to structure an outstanding research on cancer and ageing.

We also appreciate the pertinent recommendations to the IRCAN direction and individual teams, which will be extremely helpful in our ongoing and future discussions with our funding institutions.

Regarding the specific comment on the recruitment of external teams, we would like to stress that we have preserved enough free laboratory space to accommodate four new teams. As noted by the Committee, we are close to install a team from Germany working on *C. elegans*. Moreover, in 2010 we launched an international call, which, as an indication of the attractiveness of the future IRCAN, resulted in the establishment of a short list of 10 strong candidate teams. These teams will be auditioned by the IRCAN SAB in May 2011. Another indication of the dynamics of research within the Pasteur/CAL campus is attested by the recruitment outside of Nice of four IRCAN teams during the last three years : two of them from ENS Lyon (teams 1 and 2), one from IGR, Villejuif (team 8), and one from San Diego (team 6).

In line with the strong advice regarding the extension of the animal house, we are pleased to inform AERES that the Pasteur/IRCAN project Steering Committee, which is commissioned by the University of Nice Sophia Antipolis, has officially allocated three floors of the Pasteur Tower (roughly 1000 m^2) to the future animal house. Construction of the novel facility, which is scheduled to start in 2012, is programmed by an international expert in design of animal houses.

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Overall, the report reinforces our determination to create IRCAN. We are confident that our supervising bodies will follow the Committee's recommendation by allocating the human and financial resources necessary to hire new outstanding teams, complete the equipment of the technical platforms, make functional the extended animal house, and thus provide the best conditions required to optimize the start of IRCAN.

Team 5 "Ageing and Diabetes"
The statement that "*The research program is well structured and highly innovative*" is truly rewarding. We just would like to draw the attention on the fact that the medical-oriented publications appeared in high-impact factor journals (e.g. the IF of Diabetes is 9,02) and that the junior group published in Dev. Cell (2008), Genes Dev (2005) and in Curr Biol (2006).

Team 3 "Mitochondrial diseases and mtDNA stability".
We fully agree with the committee that we have to «*take more advantage of the patients and families ressources that are available through the reference center for mitochondrial diseases*». In fact, one of our approach does concern the identification of new genes involved in mtDNA instability by using patient families. As an example, the study of a large family presenting with mtDNA instability and optic atrophy «plus» phenotype led us to identify *MFN2* (mitofusin 2) as a new gene involved in mtDNA instability, and to make a link between mitochondrial fusion and mtDNA repair (manuscript in preparation). We also agree that it will be interesting to use the future platform of Next Generation Sequencing planned at IRCAN. In a second family, we performed a genome-wide scan of SNPs and identified a candidate region of 30 Mb in length, including about 100 genes. A step of exome sequencing is currently in progress. Finally, we would like to emphasize that the topic of this team is directly related to the IRCAN scientific project since mitochondrial instability is linked to ageing.

Team 11 : "Normal and pathological angiogenesis"
The committee raised the problem of the smallness of the team. Although the team currently comprises seven members, we will follow the recommendation of the committee by setting up an active policy for the recruitment of additional top-quality researchers.

Pr Eric Gilson