MEDyC - Matrice extra-cellulaire et dynamique cellulaire

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

EXTRACELLULAR MATRIX AND CELL DYNAMICS (MEDyC)

From the

University of REIMS

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From the

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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: EXTRACELLULAR MATRIX AND CELL DYNAMICS (MEDyC)

Requested label: UMR

N° in the case of renewal: UMR 6237

Name of the director: FX MAQUART

Members of the review committee

Committee chairman

Mrs Corinne ALBIGES-RIZO, Institut Albert Bonniot, Grenoble, France

Other committee members

Mrs Gillian MURPHY, Cancer Research UK, Cambridge, UK

Mr Arnoud SONNENBERG, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Mr Emmanuel BEAUREPAIRE, Ecole Polytecnique, Palaiseau, France

Mrs Paola DEFILIPPI, University of Torino, Italy

Mr Eric GOORMAGHTIGH, Université Libre de Bruxelles, Belgique

Mr Norbert LATRUFFE, Université de Bourgogne, Dijon, France (CNU)

Mr Pierre GILLET, Faculté de medicine de Nancy, France (CoCNRS)

Observers

AERES scientific advisor

Mrs Catherine DARGEMONT

University, School and Research Organization representatives

Mrs Florence NOBLE

Report

1 • Introduction

- Date and execution of the visit

The site visit started on February 7th afternoon and was completed on February 8th evening. This visit was facilitated by a detailed, clear and extensive document provided in advance. Even though the schedule was tight, the evaluation took place in excellent conditions with presentations and discussions with the director, group leaders, scientific staff, technical and administrative staff, students. A debriefing time was organized by the committee after each team's oral presentation or staff meeting. A short visit of the laboratory was organized.

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

The current unit (UMR 6237) is the result of the fusion of 2 former UMR located in Reims in 2008 (UMR 6198 "Extracellular Matrix and Cellular Regulation" associated with Life Sciences department and UMR 6142 "Drug, Intracellular Dynamic and Nuclear Architecture" associated with Science and Technology department). This fusion allows the development of interface between biology, medecine, physics, applied mthematics and engineering through spectral imaging to study cell-extracellular matrix interactions in normal and pathological conditions (tumor invasion and inflammatory disease). The unit is located in a new building adjacent to the hospital allowing supply of human samples, library set up and development of translational research. The Unit is also part of IFR 53. The unit has a real position in the training program at the University of Reims Champagne Ardennes. According to the university delegate, this unit represents one of the best teams in the University. Regional and industrial partnerships have been established. So far the unit is recognized as 70% INSB and 30% INSIS.

- Management team

François-Xavier Maquart (affiliated to INSB) is the director of the Center, assisted by a Vice-director (affiliated to INSIS), a Deputy-Director (from Faculty of Sciences), and an Administrative Assistant. There is no indication of a financial assistant and about overheads. However institutional funding for the unit is shared between teams according to their needs (typically more goes to team 3 who runs more equipment; some funding is kept to start new projects, which is discussed by the direction committee). Contracts are managed by individual teams. Once a month the strategy is discussed during an executive committee between members forming "the directive committee" consisting of the director, vice director, the deputy director and team leaders. A supplementary committee named the "laboratory Council" including the directive committee and one representative from each electoral college, meets three or four times a year to discuss issues of general interest. The director is assisted by a health and safety committee.

- 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)	50	51
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1 CCA 1 AHU 3 ATER 6 POST-DOCS	2 CCA 1 AHU 3 ATER 8 POST-DOCS
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	15,4	16,4
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	2,75
N6: Number of Ph.D. students (Form 2.7 of the application file)	27	27
N7: Number of staff members with a HDR or a similar grade	33	35

2 • Overall appreciation on the research unit

• Summary

The overall scientific level, facilities, social and scientific atmosphere are good. The fusion of 2 former UMR CNRS has played an important role in establishment and development of scientific potential in the field of skin and extracellular matrix biology and imaging pathological tissues fostering intensive internal collaborations. It seems that there is a functional and effective communication between Team 1, carrying out more fundamental research, Team 2, involved in more translational research and Team 3 devoted to applied and biotechnological research for health technology. The unit plays an important role in the local environment but should try to increase its international visibility (foreign post-docs, more international seminars,…). The Centre has produced an impressive number of papers in peer-reviewed journals, despite heavy teaching duties. Although the absolute number of publications has probably increased globally in the three teams in the past four years, this has not been accompanied by a general increase in the quality, as indicated by the average impact factor of the journals. This is partly due to a lack of work in depth on molecular mechanisms, to heavy teaching duties and also to a self underestimation of the quality of the work. The recent recruitment of some high-profile and dynamic young scientists in teams 1 and 3 should be very beneficial to the unit. The unit should be congratulated for having developed original, relevant and very demanding imaging approaches in the field of cancer diagnostics/classification through industrial partnership and to couple these skills to the extracellular matrix expertise. The director stressed the urgent need for full time scientific staff without teaching duties for reinforcing team and reaching competitive research, with which the committee concurs.

• Strengths and opportunities

Clear strengths of the research center are (i) expertise in vibrational spectroscopic imaging and (ii) expertise in skin, extracellular matrix and matrikine biology. Major efforts to interprete biology in biomedecine have been done. Most of the groups have an extensive network of national or in some cases international collaboration, as well as with industrial partners. The fusion between the two original labs took place in 2008 and has been already fruitful. A real support from University and local agencies was noted.

• Weaknesses and threats

The coherence of research projects in the laboratory and within the teams could be improved. Emphasis should be on the most successful and promising projects and given that a variety of models such as skin, cardio-vascular system, digestive tracts and diabete pathology have been presented, the number of model should be restricted accordingly. Absence of cutting-edge technologies, except for team 3, and lack of molecular mechanisms were noted. It will be important to ensure that clinically trained researchers have adequate laboratory based science colleagues to support their research.

The critical mass of full-time researchers is too low since only 5 CNRS scientists have been recruited and most of the staff is medical/biological staff with over heavy teaching duties hindering competitive in research. The ratio between postdocs and Staff is low. Attractivity for people from abroad should be improved. The research unit has limited international visibility at prestigious academic conferences (Gordon, EMBO…). The website of the laboratory has to be completed, made more visible and attractive for potential recruitment and communication purposes, especially if the unit follows a policy of recruitment of full time researchers, settting up new teams (AVENIR ATIP program), establishment of Chair of Excellence (University/ INSIS CNRS).

- Recommendations to the head of the research unit

Studies on the molecular mechanisms should be encouraged in order to improve the impact of the findings. The committee encourages the setting up of programs to discharge teaching duties such as “CNRS délégation” or “Institut Universitaire de France” .The committee also recommends the active pursuit of efforts towards a more international profile by creating more international collaborations through international funding, allowing the recruitment of foreign postdocs and PhD. It would be important to strengthen the PhD program by allowing students to invite international speakers (e.g. 1-2 per year), or to organize one-day international workshop and to attend a PhD student lunch with all external speakers which would increase their participation and exposure. The PIs need to develop more hypothesis-driven projects and should make efforts to focus more on their main research topics. Emphasis should be done on the most successful and promising projects and on publishing in higher impact factor journals in order to favour quality over quantity of papers. The unit has to make efforts to identify the individuals who will be the best positioned to be the future heads of the different work packages. The committee comments that the gender ratio amongst project leaders is unbalanced.

- Production results

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

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	51/51
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	5/5
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	100%
A4: Number of HDR granted during the past 4 years	5
A5: Number of PhD granted during the past 4 years	34
A6: Other relevant item in the field *(i.e. number of first and/or last authors original publications in peer review journals)*	First author : 145 Last author : 137

3. Specific comments

- Appreciation on the results

  - Relevance and originality of the research, quality and impact of the results

Experience in skin/extracellular matrix/matrikines biology, expertise on skin pathology (melanoma invasion, skin aging and bullous emphigoid pathology) and the development of vibrational spectroscopy and imaging in the unit have had a significant impact on the scientific community. Involvement in the development and fostering of translational research is impressive. It is important to note that some senior scientists and team leaders are very well known in their respective fields of expertise and are very often invited to international meetings. This situation generated an impression of heterogeneity in the performance and the quality of the research of the different teams. Detailed mechanistic studies are sometimes missing, which explains the low impact factor of many publications.

Although the absolute number of publications is impressive during the past four years (270), this has not been accompanied by a general increase in the quality, as revealed by the average impact factor of the journals (average impact factor around 5, a lot of publications below 3). However results from team 3 have been published in the best journals in their area of research.

Collaborations are well chosen. The quality and stability of industrial partnerships are impressive (Loreal, Galderma and Horiba)

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

All the group leaders have been trained in France and the absence of foreign leaders is noticed. However the committee has noticed the presence of a few foreign scientists. The committee felt however that the representation/presence of the most successful groups at the most prestigious international conferences did not necessarily match the quality of their publications which is clearly detrimental to the visibility and attractiveness of the research unit. Both PIs and staff scientists/post-docs are encouraged to attend more international academic meetings (Gordon, EMBO, Keystone…).
In general the number and reputation of prizes and distinction awarded to the members of the Centre is not very high. Many invited lectures in national and less in international meetings are noticed. A few prestigious invitations mostly concern a few senior scientists. Some are prestigious like FECTS meeting (Davos) in the field of extracellular matrix biology and RSNA (Chicago) in the field of imaging .
The unit has difficulties to recruit foreign students and post-docs, probably due to the lack of its visibility at the international level. The committee encourages the implementation of an open advertisement policy for open PI positions in the future.

The research unit has successful funding records on competitive national and international grants and networks (ANR, INCA, CNRS program, PHRC…). However it remains difficult to evaluate if the financial support is appropriate for each scientific project and for the human resources as the value of some grants can be low. The committee recommends either to select calls or to pay attention to the suitability or accuracy of the grant. The unit research has good financial support by Région Champagne Ardennes. One obvious strength is their ability to raise funds from industrial partners (Horiba, Loréal, Galderma).
The unit has taken advantage of excellent local opportunities for translational research, for collaboration with the local hospital and to obtain relevant biological samples and information from hospital services of the Reims University Hospital (dermatology, gastroenterology, digestive oncology, metabolic disorders, cardio-thoracic surgery) but also with Institut Jean Godinot , Centre regional de lutte contre le cancer. Some international collaborations with joint publications are noticed (Belgium, UK, Poland, Italy, Norway, India, Germany, Finland).
It is important to note that the unit has achieved the creation of a company (Regentis) originating from the translational research and 6 patents are issued from the unit.

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

As it was not clear to the committee how the strategic scientific decisions are made, these need to be better defined. The committee understood that institutional funding (CNRS, University) is shared amongst the 3 teams, and can be used to start yet-unfounded exploratory project, after discussion between the team leaders. Then, teams find and run their own contracts (ANR etc). Internal and external communication strategies and tools like website of the unit have to be considerably improved. The number of staff with teaching positions seems above average since out of the 55 permanent members of the institute 51 are professors or associate professors.

Teams 1 and 2 are each led by a senior and well-respected scientist together with a younger scientist. Team 3 has one renowned head. Within each team, staff members, doctoral students and technicians work under the direct supervison of a project leader on specific research projects. The number of staff scientists in teams 1 and 2 is relatively high as compared to that of team 3, while there are more PhD students working in team 3 than in teams 1 and 2.

The committee noticed a clear satisfaction of the PIs, staff scientists, pos-docs, PhD students and technicians about the unit. However the centre needs a more clearly defined Management Team, including a financial manager. The ways that strategic decisions are taken should be better defined, with the input of scientific coordinators other than the director, the vice-director and deputy director.

Scientific interaction is composed of weekly workshops for students, of a monthly plenary meeting and of only monthly seminar from external speakers. The international nature of the scientific animation is missing. It should be improved by increasing the frequency of external and foreigh speakers. Emergence of cutting edge projects has been noticed in each team.

There is no doubt about the involvement in research training since most of the scientific staff are from university giving regular course (up to 250h/year which is more than the official time of 192h/year) or managing Master such as “Biology/chemistry/Health” and graduate school “Sciences, Technologies and Health”.

- Appreciation on the project

The force of the unit is the combination of academic, translational and technological research in the field of skin biology in physiological and pathological conditions. The unit will be divided in three teams. Team 1 is involved in the basic research on matrix receptors, signalling and regulation of proteolysis. Team 2 is involved in translational research focusing on extracellular matrix in inflammatory and tumoral pathologies. Team 3 is running the “cell and tissue imaging” technological platform and involved in the development and analysis of spectroscopic imaging and technologies for health. Some of the teams’ projects were judged as excellent. Even though the structure of the unit is well thought because of the combination of academic, translational and technological research, some projects are either too heterogeneous or too ambitious but they could be rapidly adjusted. While some work packages included in each teams’ plans are clearly of an international standard, others experience some difficulties to reach a high level of visibility and originality. This is clearly detrimental to the visibility and long-term reputation of the team leaders. Team 1 and 2 are well established in the field. The big concern for team 1 and 2 is that this is a huge body of work is planned and much could only reach a superficial level of understanding in four years. The difficulty of team 1 and 2 may be in prioritising the research efforts since some observations are still at an early stage and the underlying mechanisms are not known. The scientific long-term project of team 3 is of very high quality and very relevant in the field of oncology.

The committee believed that the unit has a strong scientific potential and targets relevant scientific questions. However the committee noted that the development of many projects could disperse the focus of study and the possibility for the team leader to strengthen her international visibility and publish in first ranked journals with broader readership.

The policy for the allocation of resources is the raising of grants by each individual team and most of the teams seem to have sufficient grants. Recurrent funds from INSERM, CNRS and the University seem to be allocated to the platforms, which can be used freely by the members of the Institute and the remaining funds are shared between the three teams. In addition to recurrent funds, the University is providing space and is taking care of the overheads which constitutes a substantial financial support for the unit. The director has a very important local role by coordinating local efforts (region Champagne-Ardennes) aimed at providing coherence and structure of the project. In term of human resources, most professors appear to have heavy teaching duties, which may be seen as an obstacle to the development of their research. Professors should be more encouraged to apply to the Institut Universitaire de France or CNRS delegation, allowing them to gain higher visibility and devote a larger fraction of their time to research.

The unit brings together fundamental research areas (ranging from molecular biology to cell biology) and applied research devoted to skin biology and pathology. The unit has developed strong links with the University Hospital Resources. They also carry out several biotechnological cutting edge project.

4 • Appreciation team by team and/or project by project projet

- Title of the team and name of the team or project leader

Team 1 : Matrix receptors, signaling and regulation of proteolysis

Team leaders : Laurent MARTINY and Hervé EMONARD

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	19	20
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)	2 ATER 2 post-docs	2 ATER 3 post-docs
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	7,9	8,1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	10	10 ? (estimation)
N7: Number of staff members with a HDR or a similar grade	9	10

- Appreciation on the results

Team 1 studies the role of matrikines derived from matrix macromolecules in the regulation of matrix proteinase activity arranged into 4 programmes 1.1 – 1.4; they also study the interaction between metalloproteinases and TIMPS, the regulation of proteolysis through MMPs endocytosis by the LRP-1 receptor and the pharmacological regulation of matrix metalloproteinases and physiopathological approaches. As outlined in a recent review, degradation of elastin by elastases leads to the generation of elastin fragments, designated as elastokines in keeping with their cytokine-like properties. Generation of elastokines from one of the longest lived protein in human might represent a strong tissue repair signal.

Programme 1.1 Matrix proteases regulation by matrix macromolecules modules

This project was a strongly collaborative venture between teams 1 and 3, as well as some external collaborators. The team obtained interesting results with the synthetic peptide VGVAPG and other natural peptides from elastin on human skin fibroblasts and on tumor cells. In general these peptides promote survival, and sustain invasion and proliferation. They can also play a protective role in the contractile function of the mycardium during ischemia reperfusion (see also Programme 1.4). However, as reported in the literature, continuous exposure of cells to these matrikines, through increased elastase(s) expression with age, can contribute to the formation of a chronic inflammatory state and ancillary consequences. Importantly, binding of elastokines to S-Gal, their cognate receptor, stimulated matrix metalloproteinase expression in normal and cancer cells.

The structures of selected matrikines associated with the elastin receptor and receptor antagonists have also been addressed. The team, in collaboration with Team 3, have identified the structure of peptide agonists showing that the active peptides may have a turn structure and are not structurally constrained.

The work to date is generating interesting data, but many projects are still at the early stages of development and require biological validation. The effects of elastin peptides on cell survival and invasive properties are particularly exciting. The opportunity to elucidate the signalling mechanism of the elastin receptor should eventually have substantial impact. Work on elastin peptides will move into an important phase of biological evaluation. The value of such work extends to the interest in EPs for drug delivery etc.

Programme 1.2 Matrix metallo proteinase regulation by their natural inhibitor

Another research field is represented by the characterisation of the role of TIMP1 in myeloid cell differentiation, in which a TIMP1 receptor has been identified as well as the downstream signalling pathways associated with cell survival and differentiation in leukemic cells. In this context the group has developed a model of TIMP-1/proMMP-9 interaction. The work on leukemic cells has been pursued studying the role of TIMP-1 interaction with the proMMP-9/CD44. This project also considers the role of cell-ECM interaction in leukemic cell migration and consisted of several different studies in which the role of the uPA and MMP proteolytic systems was addressed.

Programme 1.3 Regulation of matrix proteinases by endocytosis

The team has conducted a programme of research concerned initially with the endocytic regulation of matrix proteinases in relation to both physiological and pathological remodelling. This exciting area of work has produced seminal data on the signalling linked to LRP-1 ligation and the consequent effects on cell behaviour This has led to a wider interest in the general endocytic receptor LRP-1.and its role in mediating the clearance of ECM molecules involved in the dissemination of cancer cells. LRP-1 may facilitate the development and growth of cancer metastases in vivo. However the precise contribution of the receptor during cancer progression remains to be elucidated, due to the lack of mechanistic insights into the intracellular signaling networks downstream of LRP-1. Interestingly Team 1 has studied LRP-1 in human endometrium and in tumor cells, for its ability to protect the secretory endometrium and to prevent cancer proliferation. In thyroid carcinoma cells they characterized the molecular signaling relays involved in the LRP-1-mediated stimulation of cancer cell invasion and identified the LRP-1 beta-chain as a main docking site for focal adhesion components and mitogen-activated protein kinase (MAPK)-containing complexes. They highlight that LRP-1 maintains malignant cells in an adhesive state favorable for invasion by controlling ERK and JNK-dependent pathways. Consistently its silencing prevented malignant cell invasion. Links to groups with interests in cancer and Alzheimer's disease are of the utmost importance for this team.

Programme 1.4 Pharmacological regulation of matrix proteinases and pathophysiological approaches

This project is rather applied and is based on the influence of elastokines on migration, proliferation and differentiation of keratinocyte. Most of the results have not yet been published due to confidentiality issues and have been undertaken as part of grants from pharmaceutical and cosmetic companies. This is potentially an added value, indicating good relations with socio-economic partners, but it is disappointing that the results cannot be published to elevate the profile of this work . Studies on EP effects on cell (keratinocyte) behaviour, including production of MMPs and members of the uPA system, are in this category. They are currently largely descriptive and somewhat preliminary. Some aspects fit with the proposed studies of WP1 in the next period. Novel exciting work on the role of EPs in aspects of myocardial ischaemia have been carried out. Of particular relevance is the analysis of their mechanism of action on endothelial cells and cardiomyocytes. The role of NO in this is of particular interest. The cardioprotective effects of EP in an ex vivo model is still at an early stage. The implication of lactosylceramide involvement is significant and hopefully will be pursued in the next period. Therefore, although these data are not completely original, the work may lead to some new insight and most of all should constitute a platform for further functional assays based on in vivo models. Collaborative work (UMR6229) on the development of MMP inhibitors is well established and resulted in the production of a good MMP9 inhibitor. However this also has significant activity against MMP2. This is a challenging field of research and it is not clear if it should continue in the same vein. Other studies cover peptide fractionation techniques and the study of alfalfa extracts for MMP inhibitory activity have made some progress but not sufficient for peer review publication.

This Team works on overlapping but distinct topics. The scientific level of Team 1's activities is good as judged by the impact of its publications (average of 20 publications per year ,with about 3 publications with IF of 5-6 and the remaining with mean IF below 5). 10 PhD theses have been produced. Collaborations have been established with national and international groups (Luxemburg, Italy and USA) but it is not obvious whether this has yet resulted in joint publications.

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

The team's work is likely to have impact since their work is rather unique and not being substantially addressed elsewhere. Their interactions with the other teams locally are good and they have important industrial links. Links to groups with interests in cancer and Alzheimer's disease are of the utmost importance for this team. International and national collaborations have contributed significantly to the output of the group. However,the team should work further on this aspect. Work with labs interested in Elastin peptide for drug delivery etc. could be very fruitful. Recruitment of high level visiting scientists (or full time researchers) could be improved. It has been noticed that there is no staff members issued from foreign countries. The recruitment of creative, high-level scientists from abroad is encouraged. Members have been invited to speak at 4 national and 5 international conferences over the evaluated period. Funding seem to be sufficient, are essentially coming from national agencies with a balanced repartition between ANR, INCA agencies, national institutions (CNRS, University) and regional agency. The participation with international or national networks is good but could be improved. The international network is essentially european. The group has obtained 2 patents and has participated to the creation of a company (Regentis).

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

The management made by a tandem of a senior and well reputated scientist with a younger scientist. Staff members, doctoral students and technicians work under the direct supervison of a project leader on specific research projects. The progress of the work is discussed weekly in research meetings and once a month at a plenary meeting of the entire unit. There is no mentioning of editorial work for international journals, or participiation in international reviewing committees. Contribution to teaching and structuration of the research is excellent and well-coordinated.

- Appreciation on the project

The research plan proposed by Team 1 aims at identifying the role of extracellular matrix molecules or its specific domains in cell invasion and dissemination and to study the mechanisms of action of active molecules at different levels. The major goal is to identify new therapeutic targets and alternative treatments. The proposal consists of four WPs:
WP1 Physiopathological approaches of elastolysis. Receptors, signalling and therapeutical aspects
WP2 TIMP-1 receptor and matrix proteolysis
WP3 LRP receptors in physiopathology: proteolysis and signalling
WP4 Structure/Function/Dynamic relationship of matrix proteins

Due to the restricted number of full time researchers involved it would be better to focus on less WPs or, better, to reduce the number of Tasks in the WP1, WP2 and WP3.
For example, in WP1 **Physiopathological approaches of elastolysis. Receptors, signalling and therapeutical aspects** Task 1.3 on identification of the murine receptor that will allow the generation of an in vivo animal model is rather demanding, would require a substantial amount of preliminary work to assess the level of expression of EBP in mouse and should be sustained by an appropriate number of researchers. In WP1 two other interesting Tasks are the 2.1 (Elastase-derived elastin peptides) and the 3.2 (Elastin peptides and tissue repair/generation). These two Tasks could already represent an adequate amount of work for the WP1. An outstanding question relates to the role of different EP receptors in aging human tissue where the EBP becomes uncoupled. Expression of this receptor with age, tumour development and in wound healing needs to be clearly defined. It appears that not all activities are mediated by the identified elastin receptor complex, e.g. the effect on telomerases, and this needs to be clarified at the earliest possible juncture. Overall this is a substantial and ambitious programme. 4 years funding should allow significant advances to be made. All the studies are feasible, although it may be difficult to achieve significant progress on all aspects in the time given the personnel available and their heavy teaching commitments. Many of the studies will produce fundamental new data and others will have a more 'translational' goal with potential for future IP and wealth creation.

WP2 on **TIMP-1 receptor and matrix proteolysis** reproduces the dual aspect of working on TIMP-1 receptor dynamics and associated signalling pathway and on leukemic cells. The importance of MMP9/CD44 as a TIMP1 receptor relative to MMP9/LRP-1 could be addressed with the WP3 team members. As already discussed above the study of leukemic cell invasiveness is rather broad and impractical, e.g. genetic manipulations in mice, and needs to be revised.

WP3 on **LRP receptors in physiopathology: proteolysis and signalling** deals with study of LRP-1 interactome in collaboration with mass spec facilities, UMR6184/6149 and biotech, and its structural and functional interactions in cancer and neurodegenerative disorders. This project has three main aspects, the interactome, the signalosome and the post-translational modifications that are all three relevant for the biology of LRPs. The rationale for continuing to focus on MMPs/TIMPs, and not other LRP-1 ligands is not clear as this group and others have established that this may not be of the greatest biological significance. However, it is appreciated that they may act as a useful model as many of the tools, e.g. fusion proteins, have already been prepared. The proposal to identify LRP-1 interaction sites with other membrane partners/ligands and the development of 'mini receptors' is particularly exciting, ground breaking research, e.g. in the context of designing agents for delivery across the blood-brain barrier. Structural analyses of LRP-1 in silico are proposed, but there are few details to judge the value of this. The structure of the LRP-ICD is to be investigated, but it should be borne in mind that this may only assume a structure when interacting with signalling partners. Such a study should be withheld until information from Task2 informs on this topic. Task2, looking at the intracellular signalling mechanisms downstream of LRP-1 ligand binding, is a most promising and interesting project. It is also proposed to further validate some of the 2000 genes apparently modulated by LRP-1 ablation in cells. The danger of this is that such changes are the result of the modulation of the many LRP partners rather than a direct effect and this is clearly too big a task to unravel. A more focussed transcriptome analysis needs to be considered. The team plan to identify LRP-1 shedding activities and the dynamics of their cellular association with LRP-1. This is a substantial topic if it is to move beyond phenomenology, as is the role of the soluble extracellular domain of LRP-1. It is also proposed to study the LRP-1 ICD that is generated by proteolysis. The case of Notch, where the ICD is enormously important but was very difficult to detect in the nucleus without the use of reporter techniques, could be studied before embarking on such a venture. It may be necessary to address this question using senstive reporters as GFP etc labelling may not be informative. However, if LRP-ICD is identified in the nucleus this could guide the approach to the transcriptome analysis, which could be done by overexpression of the ICD alone.

The WP4 on the **Structure/Function/Dynamic relationship of matrix proteins** originates from a new group recently established in Reims. This will provide structural bioinformatic and molecular modelling that will offer new molecular targets and tools andhas been developed with interactions with all the other WP in Team1 in mind. It involves the interface of physics and biology and biochemistry and aims to inform the research of all the groups. This is a very novel and innovative approach, albeit unproven in terms of overall contribution to the research effort.

New computing methods and graphics to study ECM macromolecules by IR and Raman spectroscopy will be established. Various bioinformatic data bases will also be set up to allow a new look at secondary structures and the virtual screening and docking of proteins and pepetides relevant to the Team, e.g. EP receptor, various matrikines including the EPs, etc. Docking algorithms will be explored. The proposal could have been clearer in terms of the anticipated outcomes in the first 4 years and the timing relative to the lab work of the other WPs. The idea to use the data to design small molecules mimicking natural peptides seems an exciting prospect, but it is not clear how viable this concept will be. Clearly cutting edge research, however.

As a general comment the committee would have been helped by a more structured presentation of the results and of the research program. A GANTT chart with the schedule of the different WPs and the contribution of the different researchers would have been very helpful.. The policy for the allocation of resources is the raising of grants by each individual workpackage and most of the workpackages seem to have sufficient grants. Moreover cutting edge projects must be defined

- Conclusion :

  - Summary

WP1 is a substantial collection of projects focussing on aspects of elastin peptide actions on cells. Several of the basic studies are cutting edge and, given the right investment of research effort could be interesting and rewarding. The strengths lie in the previous experience of the team amd the planned interactions with other teams/expertise. The difficulty may be in prioritising the research efforts since some observations are still at an early stage and the underlying mechanisms are not known. It would be useful to construct a timetable of the plans to appreciate the amount of investment of effort on each goal and their relative importance. The expected outcomes within the 4 year time frame and the final goals of the studies are not clear.

WP2 is a small team and their project portfolio is rather broad and impractical. The work on TIMP receptors (MMP9/CD44) may be best carried out in conjunction with the CD44/LRP-1 work of WP3. Research questions pertaining to matrix proteolysis by cells is not well defined and there are too many tasks for the size of the team. The WP2 should focus on a single novel activity that would allow them to gain recognition in the field.

WP3 : The work proposed is based on a sound foundation of previous studies and is both exciting and cutting edge. It could also have long term implications for translational approaches. The big concern is that this is a huge body of work and much could only reach a superficial level of understanding in four years. A prioritisation of the studies, starting with some of the generic identifications of interacting partners of LRP-1 upon which to base further focussed effort would be the most appropriate procedure. The precise timelines of each part of the proposal need to be drawn up.

WP4 : This is highly novel, albeit high risk, work that could give the teams an innovative approach to their future work. How it will fit into the timescale available is not apparent. Importantly, the work involves good external collaborations. It should also attract bioinformaticians wishing to develop new tecniques for the analysis of protein interactions.

  - Strengths and opportunities

Some efforts are done to link academic research with biomedical research through CHU interactions and to synergyze with teams 2 and 3. There are a real established expertise in the field and a strong involvement in teaching (ranked number 1 in the biomedical units in Reims). WP1 and WP2 present previous experience of the subteam and the planned interactions with other team of the lab with complementary expertise. WP3 presents a productive programm, it is a dynamic subteam wit good international partners. Composition, expertise and funding of the group are adapted to the project. Enthusiasm and ability to interact with biologists have been noted for WP4.

  - Weaknesses and threats

The overall impression is that all the subteams belonging to Team 1 share common research themes, but have scattered their work in too many aspects to be highly productive. A major concern is that although a large amount of data has been obtained, the originality and interest of the research can be further improved. For example in depth examination of specific pathways would help to strengthen the relevance of specific mechanisms. Moreover, the generation of in vivo models to support further research, would be important. Overall there was too much disparity between the different WP and inability to adress the future potential of outcomes of their research. More precisely:

WP1: there is a lack of sufficient evidences for the nature of the receptor for the elastin fragment in aging. The proposed generation of in vivo animal model requires additional data on the nature and existence of this receptor.

WP2: Research questions are not well defined. There are too many tasks for the size of the team. Insufficient details are supplied. The team is not well recognized in the field

WP3 : The project portfolio has become too dispersed, and has to be prioritized

WP4 : It was perceived that there was a failure to convey the applicability of the technologies to translational biomedecine

- Recommendations

Output must be improved to increase the visibility and attractivity of the team. Synergy between the WP should be improved. The team need to prioritize their research to adress outstanding issues about functional elastin peptide receptors in aging humans. WP2 should fuse with WP3. WP3 Should stay focused. WP4: Need to validate the simulation studies

- Title of the team and name of the team or project leader

Team 2 : Extracellular matrix in infllammatory and tumoral pathologies

Team leaders : Philippe GILLERY and François-Xavier MAQUART

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	12	14
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 CCA 1 AHU 1 PH 2 post-docs	2 CCA 1 AHU 1 PH 3 post-docs
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3,8	4
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1,75	1,75
N6: Number of Ph.D. students (Form 2.7 of the application file)	10	11 (estimation)
N7: Number of staff members with a HDR or a similar grade	10	11

- Appreciation on the results

WP1: Late post-tranlational modifications of extracellular matrix and cell functions

The members of team 2 study collagen carbamylation and its effect on interaction with cells. Carbamylation is a late, post-translational modification that has been observed in several diseases. It involves covalent binding of isocyanic acid, a decomposition product of urea, to the free ε-amino group of lysine. Carbamylated proteins have been found *in situ* in neutrophils, monocytes and erythrocytes. Furthermore, carbamylated proteins have been detected in renal tissue of uremic patients. The members of team 2 have shown that carbamylation of type I collagen *in vitro* changes its biological properties, leading to an altered neutrophil interaction with and response to the modified collagen. A lysine residue at position 1047 of the proα1(I) chain, critical for binding to LFA-1, was identified as a potential site of carbamylation. Furthermore, it was shown that advanced glycation products (AGE) formed by glycoxidation of collagen, alter its structure and function, and lead to a dysregulation of the inflammatory functions of PMNs via interaction with the receptor for AGE. The work on carbamylation and glycoxidation has been described in a series of articles published in journals with impact factors ranging from 3.4 to 6.1. Direct evidence for collagen carbamylation *in vivo* is lacking and hence in order to reveal the physiological relevance of this work further study is needed .

WP2: Tumor progression and the role of basement membrane collagens

The research in this program is focused on the identification of small fragments of various extracellular matrix components, matrikines, with anti-tumor activity. Previous studies from various laboratories have shown that proteolytic fragments of ECM proteins can have anti-tumor activity by inhibiting endothelial cell proliferation and promoting apoptosis or by preventing endothelial cell migration. The work of team 2 focuses on the anti-tumor and anti-angiogenic activities of the NC1 domain of the α3 chain of collagen IV, also called tumstatin. They identified a short peptide sequence within the NC1 domain that has the same anti-tumor properties as the complete NC1 domain and showed that the biological activity of this peptide depends on a ▫-turn conformation. A cyclopeptide derived from tumstatin and designed to constrain the ▫-turn conformation, displayed improved bioavailability. It affects ▫1 clustering, ▫1-dependant cell migration, FAK phosphorylation and actin cytoskeleton organization.

In a search for novel proteolytic ECM fragments with anti-tumor activity, the team members identified the NC1 domain of collagen XIX and the α4 chain of collagen IV endowed with such activity. The anti-tumor and anti-angiogenic properties of these fragments was shown in various *in vitro* and *in vivo* models and the minimal sequence for the activity of the type XIX collagen NC1 domain was determined. Clinical studies with endostatin, a C-terminal fragment of type XVIII collagen, have thus far been disappointing. Nevertheless, the proposed studies presented in task 4 (p337), aimed at increasing the inhibitory activity of these fragments by grafting anti-tumor drugs onto them, might be important. However, the choice to graft long chain fatty acids has not been substantiated, nor has it been explained how the grafting approach will be carried out. The quality of the past research is good (average impact factor of the 4 papers is 4.5) and the studies proposed under task 1 and 3 are a logical sequence of the research that is already being carried out.

WP3: Glycosaminoglycans and proteoglycans in tumor invasion

In this program, the anti-tumor activity of lumican, a member of a family of small leucine-rich proteoglycans (SLRP), is being studied. This family of proteoglycans, which additionally comprises decorin, biglycan and fibromodulin bind via their protein moiety to collagens, and may regulate interfibrillar spacing. The studies presented show that the expression of lumican in the peri-tumoral stroma is inversely correlated with melanoma progression, and that there are two distinct active sites on lumican. One sequence (LLR1-6) promotes cell adhesion, while another sequence corresponding to LLR9 inhibits the migration of melanoma cells. Lumican regulates cell migration via integrin α2β1. Additionally, it was shown that lumican reduces the development of lung metastases by inducing apoptosis and inhibiting angiogenesis. It has been reported that decorin has similar anti-tumor activities through inhibition of tumor cell proliferation and suppression of tumor-cell mediated angiogenesis. A major weakness of the research on lumican is that no studies have been undertaken to understand the mechanisms responsible for its anti-tumor activity. Just identifying sequences with anti-tumor activities is not considered to be original research. This lack of originality in research is probably best demonstrated by the fact that the results of this work have been published in relatively low impact factor journals (ranging from 1.3 to 3.6).

WP4: Extracellular matrix, inflammation skin disease associated signalling

The studies in this program concentrate on defining a role for inflammation in melanoma progression as well as in the autoimmune diseases Bullous Pemphigoid (BP) and Cicatricial Pemphigoid (CP). A proteomic approach was undertaken to identify proteins whose expression is associated with different steps of melanoma progression in order to develop new diagnostic strategies. Axl receptor appears to be an interesting candidate because it is overexpressed in uveal melanomas. Furthermore, it has been shown that CXCL10 (IP-10) from peripheral blood mononuclear cells (PBMCs) has an inhibitory effect on melanoma invasion. The concentration of CXCL10 was also significantly higher in supernatants of cultured PBMCs from patients in remission compared to those from patients with progressed disease. CXCL10 is produced in response to IFN-□ in monocytes, endothelial cells, keratinocytes and fibroblasts. A correlation between CXCL10 inhibition of tumor progression by the recruitment of mononuclear cells and an antagonistic role on angiogenic factors has been previously established in patients with hepatocellular and renal cell carcinomas. Moreover, others have shown that retroviral gene transfer of CXCL10 inhibited the growth of human melanoma xenografts. Thus, the novel aspects of the work presented here are limited. However, because novel insights may be obtained, we feel that to continue the research on the role of inflammation in melanoma progression is important.

In the studies on BP and CP and inflammation, members of team 2 developed an ELISA assay for the rapid detection of auto-antibodies against laminin-332. Previous studies have shown that the main auto-antigen in patients with Bullous Pemphigoid (BP) is the NC16A domain of BP180 and that pathogenicity of anti-BP180 auto-antibodies is dependent on activation, recruitment of neutrophils and release of inflammatory factors (IL-1, IL-6 and IL-8), leading to secretion of metalloproteases such as MMP-9 and elastase and loss of epidermal-dermal cohesion. The members of team 2 have focused their studies on the involvement of CXCL10 and PGP peptides, derived from the breakdown of BP180, in the inflammatory reaction leading to the disruption of hemidesmosomes. Data presented show that the levels of CXCL10 are elevated in BP patients and that treatment with CXCL10 increased the secretion of MMP-9 and human leukocyte elastase, which can cleave BP180 and laminin-332, resulting in the rupture of hemidesmosomes and cleavage of the epidermal-dermal junction. One of the goals is to study the effect of CXCL10 (measured by ELISA) on MMP9 secretion and BP180 cleavage.

A fair number of papers have been published by the team over the last few years, but they all appeared in low to moderate impact journals. Not a single paper has been published in a journal with impact factor higher than 6. Additionally, six PhD theses have been produced. The objective should be to perform more mechanistic studies to increase the impact of the research. 1 patent has also been produced.

The team maintains a strong interest in health-related research with emphasis on cancer and bullous diseases of the skin. The overall quality of the work is good, but there is clearly room for improvement in terms of impact, originality and attractivness of the research. Collaborations have been established with other research groups both nationally and internationally (Belgium, Germany, Poland, Finland, USA), but it was not obvious whether this has yet resulted in the publication of joint papers.

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

The two heads but also several group leaders have been invited to speak at national and international conferences. No invitations have been received for prestigious meetings such as the Gordon Research Conference, Keystone meeting, EMBO meeting, etc. The number of foreign scientists is two low.and the recruitment of creative, high-level scientists from abroad that bring in new ideas and methodological expertise is encouraged.

The team has received funding from several agencies, including ANR, INCa, CNRS, regional cluster (CPER), private organizations and charities, as well as from industrial partners. Additionally, four grants from international cooperative programs were obtained.

The participation with international or national networks could be improved. Collaborations with members of the other projects and teams, as well as with national and international research groups have been established for all three work-packages. However, these collaborations have as yet not led to joint publications.

The group has obtained important results concerning the therapeutic application of the YSNSG cyclopeptide, which has led to a patent in 2007 and established several industrial partnerships.

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

The management made by a tandem of a senior and well reputated scientist with a younger scientist. staff members, doctoral students and technicians work under the direct supervison of a project leader on specific research projects. The progress of the work is discussed weekly in research meetings and once a month at a plenary meeting of the entire unit.

The team's involvement in international activities could be improved. They have organized several international and national scientific meetings, but do not appear to have other international responsibilities, i.e. there is no mentioning of editorial work for international journals, or participiation in international reviewing committees.

The interaction between the team members is very good and their contribution to teaching and structuration of the research is excellent and well-coordinated.

- Appreciation on the project

WP1: Non-enzymatic post-translational modifications of extracellular matrix proteins and inflamm'aging
The experiments outlined in the work-package deal with the analysis of the structural-functional consequences of the late-posttranslational processes, the effect of deglycated proteins on cell functions and the search for mechanisms to repair carbamylated proteins. Additionally, the pathophysiological consequences of the late-posttranslational modifications will be investigated in mouse models for renal insufficiency. These experiments also involve the implementation of innovative techniques to determine and characterize the modified proteins. In summary, this is a potentially interesting research line, provided that the researchers can demonstrate that collagen carbamylation occurs *in vivo*. If they cannot do this, the team members may reconsider whether this project is worthwhile and pursue other objectives. Collaborations have been established with national and international groups and new collaborations are under consideration.

WP2: cell-tumor microenvironment interactions and inhibition of melanoma progression.
The objective of this work is to study the effects of various matrikines and lumican on angiogenesis and lymphangiogenesis through regulating the expression and activation of MMPs (MMP-2, MMP-9 and MMP-14). Additonally, the effects of matrikines and lumican on the differentiation of mesenchymal stem cells (MSCs) into endothelial progenitor cells (EPCs) will be investigated. Preliminary data indicate that lumican induces a strong expression of TIMP-3 in MSCs and EPCs while decreasing the expression of TIMP-1 and TIMP-2. It is hypothesized that altered TIMP expression may explain the angiogenic effect of lumican, but apart from some correlations there are no additional data to support this assumption. In fact, the reported large variability in TIMP-3 expression between donors will make it difficult to show that a general mechanism of the action of TIMPs is responsible in lumican regulated functions. This will decrease the impact of the proposed research. Another objective is to identify signalling pathways responsible for the anti-tumor and anti-angiogenic properties of matrikines (minimum active sequence, receptor identification, adhesion force measurements, cell cycle studies, effects on transcriptome). Furthermore, more structural analogs will be designed and synthesized from the YSNS sequence in collaboration with chemists. It will be investigated whether the anti-tumor activity of the cyclic peptide (YSNSG) can be increased by replacing glycine with lysine and grafting long chain fatty acids on it. Additional studies will be conducted to test the hypothesis that a decreased expression of collagen IV and thus of matrikes is associated with aging and skin cancer. Finally, the role of CXCR3A/B and their ligand CXCL10 chemokines will be evaluated in melanoma progression. WP2 is an ambitious project and managed in 6 subdivisions corresponding to 6 tasks. A critical element for future success is increased integration between these 6 sub-groups to further address mechanistic endpoints.

WP3: skin remodelling and tissue repair in bullous diseases

The proposed experiments to study the role of CXCL10, PGP peptides and GXXPG peptides and MMP-9 expression in the aetiology of BP and CP are important and will probably contribute to a better understanding of the mechanism by which the epidermis is separated from the dermis in BP and CP. The group is relatively small for the amount of work proposed and will need to be extended for sufficient progress and being competitive.

More detailed information should have been given on the way the resources are distributed and used. However, it seems that members of the team can use grants for projects, which are given to them on an individual basis. Most of the work-packages seem to have sufficient resources.

The studies proposed in WP1 are irrelevant, unless evidence can be provided that collagen carbamylation occurs *in vivo*. Some of the projects concerning WP2 are strong but others are weak. Project 2 is not very well thought-out and also project 5 does not appear to be strong. It should therefore be reconsidered whether these projects should remain part of the work-package. The other projects involve interesting and important studies. However, the research concerned is not original. WP3 appears to be a well-defined and relevant project.

- Conclusion :

The amount of work described in this work-package is too large for the capacity of the team. Therefore, a selection of topics must be made. Anyway, some of the aspects of the proposed research seem to be more interesting than others. Furthermore, the expertise for some aspects of the research appears to be insufficient. Finally, if, as has been mentioned above, it cannot be shown that carbamylation of collagen occurs *in vivo*, part of the proposed project becomes superfluous.

- Summary

The proposal deals with the study of cell interactions with extracellular matrix and the importance of alterations in these interactions in pathological processes such as aging, inflammation and cancer. A course of actions will provide information related to topics indicated in the following 4 programs:

- Late post-tranlational modifications of extracellular matrix and cell functions
- Tumor progression and the role of basement membrane collagens
- Glycosaminoglycans and proteoglycans in tumor invasion
- Extracellular matrix, inflammation bullous autoimmune skin disease associated
- signalling.

- Strengths and opportunities

The proposed research addresses important areas of (cell) biology that are highly relevant to human health and disease. The team has a strong involvement in the clinical network in skin pathology. They also have access to an excellent source of human material and they are beginning to exploit state of the art animal models. The team was successful in obtaining several national and international (European) grants. In general the proposed methods are adequate and the team has all the appropriate knowledge to carry out the project. Where experience is lacking, the members have established collaborations to carry out these studies. WP1 is potentially interesting but rather speculative project WP2 is presented by a research group with good reputation in the field of cancer biology and matrikines with good resources and international partners for translational research. For WP3, the head has a proven track record and is well-respected in the field of skin biology and skin autoimmune diseases. The proposal offers a well-prepared set of activities focussed on the study of ECM-cytokine interactions in Bullous Pemphigoid diseases of the skin, and appropriate and productive collaborations have been established.

- Weaknesses and threats

The main weakness is the relative lack of mechanistic studies, which is stressed by the lack of publications on this subject in high impact journals. Their participation as invited speakers at major international conferences in the field is modest. The number of PhD students is low whereas the number of HDR is high. Scientific strategy must be well thought. For example, in WP1, There is no evidence that collagen type I is modified by carbamylation *in vivo*. Thus, proof for this concept is lacking. In WP2, No attention is given to a possible impact of the results on the treatment of the disease and the strategy of designing new drugs is not well developed.Finally, the size of the research group in WP3 is too small for conducting such a large study and the extent of investigations should either be limited or more participating researchers should be recruited.

- Recommendations

The team has to focus on the most promising projects and may consider giving up some aspects of the non-competitive projects. Closer collaborations with pharmacologists should be encouraged to conduct pharmacokinetic and -dynamic studies of matrikines in animals. In particular, WP1 should develop adapted tools and approaches to identify and quantify carbamylation. Expertise of the team is not suficiently experienced to solve this potentially interesting issue. For WP2 tasks should be prioritized and they should concentrate on studying mechanisms instead of identifying new matrikines and also reinforce collaboration with team 3. Finally, it is recommended that they test matrikines in more accurate and relevant mouse models. Future considerations of CXCL10 chemokine on neutrophile functions in BP disease including the role of other proteases in WP3.

- Title of the team and name of the team or project leader

Team 3 : Biophotonics and technologies for health .

Team leaders : Pierre Jeannesson and Olivier Piot

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	15	18
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1 ATER 2 post-docs	1 ATER 2 post-docs
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2,7	3,7
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	12	14 ? (estimation)
N7: Number of staff members with a HDR or a similar grade	16	14

- Appreciation on the results

The team has developed over the years an original and highly relevant expertise on Raman and infrared spectroscopy of cells and tissues. One specific aspect of the work is that they developed effective data analysis and algorithmic strategies to extract spectral signatures from normal and pathological tissues. Spectral signatures were thoroughly validated in several practical contexts. This is important and necessary methodological work which had and will continue to have impact.

The area of research of Team 3 is very relevant in the field of cancer research. The focus on extracellular matrix and its effect on cell behavior and drug action is very novel. The imaging approaches, based on vibrational spectroscopy as well as the innovative correlative cryo-light scanning and transmission electron microscopy (CLI-STEM) are original. The latter method has been created by team 3 and collaborators in physics.
In particular, team 3 has developed a very original research in the field of imaging pathological tissues with vibrational spectroscopy, either Raman or FTIR. Without any staining of the histopathological samples team 3 is providing molecular characterization at a resolution close to cell dimension. This characterization is based on the vibrational spectrum of the sample, i.e. not only on proteins or nucleic acids but more generally on the molecular composition including lipids, sugar, small metabolites, etc… opening a new field for the establishment of diagnostics in cancer research. The research that has been developed is

- original: in France, the group is number 1 in this domain. A search on PubMed with the key words “FTIR imaging tissue France” reveals that only Bordeaux is doing some significant research in this field. Yet, the group in Reims is more advanced in this new area of research. In Europe, the number of groups starting investigations in this direction is yet very small and, worldwide, Europe is leading in this domain.
- unmatched in France or Europe in general as far as the use of techniques such as polarized Raman spectroscopy is concerned. The results obtained are very promising. The interdisciplinary project of multimodal imaging is another very original approach which combines data obtained at about the same resolution by different techniques.
- new: the technology allowing the recording of FTIR images with MCT detector arrays is recent and generates thousands of spectra at each shot. Application to biological problems has remained quite limited so far but is expected to become a major area of research in a near future.

- very demanding: handling hundreds of thousands of spectra is an enormous task and everything needs to be created: processing algorithms, multivariate statistic analyses, golden standard for reference,… Processing only needs to take into account corrections for water vapour, for paraffin present in tissue slices, scaling, and further processing such as second derivatives … The research has been performed with much rigor and overall is of very high quality.
- relevant to the field of cancer diagnostics/classification. The vibrational spectrum signature is a unique signature of a physiological state of a tissue. While microarrays shed some light on specific features of a disease, cost, spatial resolution (mixing response from different tissue area) and reproducibility remain a major problem for their introduction in the clinic. Vibrational imaging provides cheap, fast, and cell-dimension resolution signatures of the disease. Results accumulated by team 3 indicate that introduction into the clinic could be considered in a near future.

The research output is of high quality and is very good in terms of publications and communications in scientific meeting. Some publications have high impact factors, for instance for the pharmacology aspect of team 3 work. Yet, other publications have lower impact factors but in general results have been published in the best technical journals in this area of research. In this recent field of research, impact factors cannot generally be compared with the best journals published in more mature area of biology or medicine. In conclusion, publications are overall excellent.

An obvious strength of team 3 is the establishment of strong links with several medical teams. This is usually a limiting factor for the development of this type of research as medical doctors and spectroscopists do not necessarily speak the same language. The interest of the medical team and the continuity in their collaborative research are very promising factors for the future of team 3.

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

Team 3 is present in all international meetings on vibrational imaging. Different members of the team usually present invited conferences and participate to scientific discussions. Team 3 is usually among the international leaders and organizers of high level meetings. They also organized themselves international conference.

Recruitment of foreign scientist is present but could be improved at the level of the permanent positions.

Funding is sufficient; equipment of high quality has been acquired. Fundings from national program (ANR, INCA) and charities (ARC, Ligue) have been raised and European money has been attracted through different program (FP6, FEDER, Egide), demonstrating European integration of team 3. Funding are also coming from industry (Galderma, PFM, L'Oréal, Hariba)

The level of participation of team 3 in international network is good. Participation to different European networks is only one example demonstrating collaborations with foreign partners.

Concrete results are a series of proves of concept. This is a real achievement as the research is very innovative and tools as well as concepts have to be built simultaneously. A large number of collaborations in complementary areas have been established, which is another achievement of team 3. Collaboration with industry is also a major feature of team 3. Both new instrumentation and new applications are being developed with strong industrials partners in a very collaborative spirit.

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

Team organization seems well thought, with an intelligent management of the director change.

It is the responsibility of team leaders to introduce new innovative projects and they have perfectly fulfilled their role. Many different projects of team 3 are cutting edge. Furthermore, team 3 members appear to have a collective responsibility in the emergence of innovative projects.

Members of team 3 have strongly contributed to structure research at the local level. Indeed, they bring tools that are necessary for the thematic of the ANR in general. A high number of collaborations have been settled either within team 3 or with the other teams. Furthermore, there are many collaborative projects with local researchers not involved in the ANR, in particular in the field of physics or oncology.

- Appreciation on the project

The scientific long-term project is very relevant in the field of oncology. It is based on innovative imaging approaches designed at identifying different classes of tumor tissues for both diagnostic of the disease and prediction of the sensitivity to antitumoral treatment. This project is of very high quality and could bring an important contribution in the field of oncology. Work packages 1 and 2 consider both tissues from biopsies and cancer model grown in 3D cultures.

The approach is particularly promising because it is sensitive not only to RNA/DNA but also to all metabolites present in the cells, including sugars, lipids, small metabolites and even to protein secondary structure,… From that point of view is very complementary to existing genomics or proteomics approaches. It is also promising because it does not require specific reagents such as antibodies neither does it require staining of any kind. In turn, the method is particularly cheap to use once the equipment is available and fast (a few minutes at most).

Fusion of data from different origins (vibrational, MALDI, clinic,…) is of course a of interest for fundamental research and for a better understanding of the molecular differences existing between the different cells or tissues.

Development of new Raman probes for in vivo measurement is highly relevant to clinical oncology.

Handling the huge amount of data, designing the best statistical approaches, analyzing together data obtained by different techniques at different spatial resolution and integrating results from TERS/nano-FCS/SNOM will be a real challenge. Fortunately, European collaboration (Norway in particular) will bring the necessary skills and work force in this part of the project.

The second work package dedicated to cell microenvironment and anticancer agents is particularly appealing. It is only recently that the importance of the microenvironment has been fully considered. In particular, the poor relevance of 2D cultures has been pointed out but little has been done to address the problem. Team 3, WP2, shall bring the missing attention to the relevance of cancer cells in culture and will integrate the spectroscopic approaches in a series of biological/biophysical observation, helping fill the gap between vibrational spectroscopy and molecular data.

The policy for the allocation of resources seems well designed, and Team 3 has enough money through scientific end industrial contracts.

Most of the projects of team 3 are cutting edge. The only concern is the potential to carry out all these projects simultaneously

- Conclusion :

  - Summary

Team 3 has a well established expertise in Raman and Infra Red microspectroscopy/imaging on cells and tissues. It achieved important and successful ground work (e.g. spectral library and methodology). Team 3 successfully interfaced works between optics, biology and mathematics. This success is largely due to complementarity of expertises within the team. The success of team 3 is reflected in effective collaborations with various companies (development, patents on instrumentation and their applications) as well as with national and international research teams. Prospective management is clearly defined for coming years. Importantly, team 3 appears to be particularly motivated and dynamic.

  - Strengths and opportunities

Strengths include (i) the well-established team expertise in Raman/IR microspectroscopy and analysis of cells and tissues (2) the thematic (oncology, cell culture), (3) a set of collaborations highly necessary with medical teams, physicists, statisticians as well as with industries.

  - Weaknesses and threats

The only treat that can be identified so far is of possible scattering of the efforts in different directions, (for instance different pathologies, different technical approaches) without going beyond the proof-of-concept. The real leaders in the future will be those who will bring the technique to the clinic. Fundamental cell biology aspects should be improved and should better integrate current knowledge.

- Recommendations

The recommendation is to continue this excellent work and identify one key pathology/technique/collaborator which could draw the interest of the medical world in general. CLI-STEM approach is very innovative technically speaking but the potential outcome of this research in term of biological information should be better defined. The team should try to target high-ranking journals to give more visibility to the methodological work.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
MATRICE EXTRA-CELLULAIRE ET DYNAMIQUE CELLULAIRE (MEDYC)	**A**	**A**	**A**	**B**	**A**
MATRICE EXTRACELLULAIRE EN PATHOLOGIES INFLAMMATOIRE ET TUMORALE [MAQUART-GILLERY-MAQUART]	A	A	Non noté	B	B
BIOPHOTONIQUE ET TECHNOLOGIES POUR LA SANTÉ [MAQUART-JANNESSON-PIOT]	A	A+	Non noté	A	A
RÉCEPTEURS MATRICIELS, SIGNALISATION ET RÉGULATION DE LA PROTÉOLYSE [MAQUART-MARTINY-EMONARD]	A	A	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**

UNIVERSITÉ
DE REIMS
CHAMPAGNE-ARDENNE

Reims, le 12 AVR. 2011

Le Président de l'Université de Reims
Champagne-Ardenne

à

Mesdames, Messieurs les Membres du Comité de l'AERES

Référence à rappeler
Secrétariat de la Présidence
presidence@univ-reims.fr
N/Réf. : 73 /11/PRES/RV/MG

Objet : **S2UR120001889 - Matrice Extra-cellulaire et Dynamique Cellulaire (MEDyC) - 0511296G**

Dear Colleagues,

First of all, we would like to thank the expert visitors for the helpful advices and recommendations they provided. We would like, however, to correct some points of the report concerning team 2 :

- About WP1 (pages 15,16 and 17)

We acknowledge the fact that the study of collagen carbamylation constitutes an unexplored topic, and then could be a risky project. However, the occurrence of protein carbamylation *in vivo* has been clearly demonstrated by other groups (see, for instance : Wang, Z. et al. Nat. Med., 2007, 13:1176-1184 ; Apostolov, E.O. et al., J. Am. Soc. Nephrol., 2010, 21:1852-1857). The mechanisms of accumulation of carbamylated proteins, and especially matrix proteins, are still unknown, and constitute precisely the originality of our study. Contrarily to what is written in the report, we have the sufficient expertise to solve this issue. Especially, we routinely perform LC-MS/MS assays of CDPs (homocitrulline) and AGEs, using ISO15189 certified methods. Moreover, our visibility in the field at the international level is demonstrated by two recent reviews published or under revision in "Clinical Chemistry" (Impact Factor = 6.3).

- About international collaborations (page 17, 1st §, last sentence) :

It is written : "*Collaborations have been established with other research groups, both nationally and internationally (Belgium, Germany, Poland, Finland, USA) but it was not obvious whether this has yet resulted in the publication of joint papers*".

Actually, these international collaborations have resulted in 6 joint publications, all in the heart of our topics :

-with Germany and Finland : Prof J.A. Eble (University of Frankfurt), Dr C. Franz (University of Karlsruhe), Prof J. Heino and Dr S. Käpylä (University of Turku) :

- Zeltz, C., Brézillon, S., **Käpylä, J., Eble**, J.A., Bobichon, H., Terryn, C., Perreau, C., **Franz, C.M., Heino, J.,** Maquart, F.X., Wegrowski, Y. Lumican inhibits cell migration through α2β1 integrin. Exp. Cell Res., 316:2922-2931. (doi:10.1016/j.yexcr.2010.08.002)
-

-with Poland : Prof A. Malicka-Blaskiewicz, Dr A. Radwanska (University of Wroclaw) :

- Brezillon, S., **Radwanska, A.**, Zeltz, C., Malkowski, A., Ploton, D., Bobichon, H., Perreau, C., **Malicka-Blaszkievicz, M.**, Maquart, F.X., Wegrowski, Y. Lumican core protein inhibits melanoma cell migration via alterations of focal adhesion complexes. Cancer Lett., 283:92-100, 2009

- Brezillon, S., Zeltz, C., Schneider, L., Terryn, C., Vuillermoz, B., Ramont, L., Perreau, C., Pluot, M., Diebold, M.D., **Radwanska, A., Malicka-Blaszkiewicz, M.**, Maquart, F.X., Wegrowski, Y. Lumican inhibits B16F1 melanoma cell lung metastasis. J. Physiol., Pharmacol., 60(S4):15-22, 2009
- **Radwanska, A.**, Baczynska, D., Brezillon, S., Popow, A., Maquart, F.X., Wegrowski, Y., **Malicka-Blaszkiewicz,M**, Lumican affects actin cytoskeleton organization in human melanoma A375 cells. Life Sci., 83:651-660, 2008

-with USA :

- Prof P.J. Roughley (Shriners Hospital, Montreal, Quebec) :
  - D'Onofrio, M.F.*, Brezillon, S.*, Baranek, T., Perreau, C., **Roughley, P.J.,** Maquart, F.X., Wegrowski, Y. Identification of β1 integrin as mediator of melanoma cell adhesion to lumican. Biochem. Biophys. Res. Commun., 365:266-272, 2008. (* : co-premiers auteurs)

-Pr A.M. Schmidt (Columbia University, New York, NY).

- Touré, F., Zahm, J.M., Garnotel R., Lambert, E., Bonnet, N., **Schmidt, A.M.**, Vitry, F., Chanard, J., Gillery, P. Rieu, P. Receptor for Advanced Glycation End Products (RAGE) modulates neutrophil adhesion and migration on Glycoxidated extracellular matrix, Biochem. J., 416:255-261, 2008

- About the paragraph entitled : « Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners" (page 17):

It is written : "*collaborations with members of the other projects and teams, as well as with national and international research groups have been established for all three work-packages. However, these collaborations have as yet not led to joint publications*".

This last affirmation does not correspond to the reality. Actually, many publications have been done in collaboration with national and international research groups : in addition to the 6 publications resulting from international cooperation, mentionned upper, we also published many papers in collaboration with national or other international research groups. See for instance :
Corbe-Guillard, E. et al., Clin. Chem., 2010 ; Bastuji-Garin, S. et al., J. Invest. Dermatol., 2010 ; Antonicelli, F. et al., Br. J. Dermatol., 2010 ; Joly, P. et al., J. Invest. Dermatol., 2009 ; Maneix, L., et al., Rheumatology, 2008 ; Joly , P. et al., N. Engl. J. Med., 2007 ; Kypriotou, M. et al., J. Biol. Chem., 2007 ; Marot, D. et al., Endocr. Rel. Canc. 2007 ; Jaisson, S. et al., Matrix Biol., 2007 ; Jaisson, S., et al., Chem. Biol., 2006 ; Marot, D. et al., Gene Ther., 2006 ; Debret, R., et al., J. Invest. Dermatol., 2006 (**and many others**)

Publications with the other projects and teams of our unit have also been done, particularly with team 3. See, for instance :
Zeltz, C. et al., Exp. Cell. Res., 2010 ; Tfaily, A. et al., Anal Bioanal. Chem., 2010 ; Ly, E. et al., Exp. Dermatol., 2010 ; Mainreck, N. et al, J. Pharm. Sci., 2010 ; Millerot-Serrurot, E. et al., Canc. Cell. Int., 2010 ; Ly, E. et al., Analyst., 2009 ; Ly, E. et al., Analyst., 2008 ; Fourre, N. et al., Canc. Sci., 2008 ; Ly, E. et al., Appl. Spectrosc., 2008.

Yours faithfully.

François-Xavier MAQUART
Porteur du Projet

Richard VISTELLE
Président de l'Université