ICT - Immunopathologie et chimie thérapeutique

Rapport Hcéres

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

Research Units Department

AERES report on unit:

Immunopathologie et Chimie Thérapeutique

Under the supervision of the following institutions and research bodies:

Université de Strasbourg

CNRS

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

Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head

Pierre Glaudes

Unit

Name of unit:	Immunopathologie et Chimie Thérapeutique
Acronym of unit:	ICT
Label requested:	UPR
Present no.:	UPR 9021
Name of Director (2009-2012):	Ms Sylviane MULLER
Name of project leader (2013-2017):	Ms Sylviane MULLER

Members of the committee of experts

Chair:	Ms Florence APPARAILLY, Montpellier
Experts:	Mr Jagadeesh BAYRY, Paris, France
	Ms Chantal DAMAIS, Villejuif, France (representative of CoNRS)
	Mr Gilbert FAURE, Nancy, France (representative of CNU)
	Mr Ralf KÜPPERS Essen, Germany
	Mr William OLLIER, Manchester, United Kingdom
	Mr Pierre VIERLING, Nice, France

Representatives present during the visit

Scientific Delegate representing AERES:

Mr David DOMBROWICZ

Representatives of the unit's supervising institutions and bodies:

Ms Florence NOBLE, CNRS

Mr Eric WESTHOF, Strasbourg University

Report

1• Introduction

Date and conduct of visit:

The visit began on Thursday 8th December 2011 at 9.00 am and continued till 5.00 pm. After a general presentation by the Director of the unit, oral presentations were given by each of the four team leaders for the 2013-2017 period. Separate discussions were held with the unit's director, permanent research staff, post-doctoral fellows and PhD students, technicians and engineers respectively. University and CNRS representatives were then met and finally discussions with the unit Director on the report were held.

History and geographical location of the unit, and overall description of its field and activities:

The unit was created in 1993 and it has been directed by Ms Sylviane MULLER since 2001. The unit's funding by CNRS has been renewed twice (2005 and 2009). The UPR 9021 "Immunologie et Chimie Thérapeutiques " is one of the three CNRS units forming the Fédération de recherche "Institut de Biologie Moléculaire et Cellulaire" (IBMC) headed by E. Westhof and is located on the "Campus Central" of Strasbourg University. At present, the unit is located on two floors of the IBMC building and one floor (hosting Team 1) of the adjoining Institut de Physiologie et Chimie Biologique. Its total space is 755 m2.

The UPR 9021 is named "Immunologie et Chimie Thérapeutiques " and has consisted of the 6 following teams during the 2007-2011 period.

1. B cell tolerance and autoimmunity (leader: Mr T. MARTIN who joined the lab in January 2009)

2. Immunobiology and therapy of lupus (leader: Ms S. MULLER)

3. RANK and cutaneous immunology (leader: Mr G. MUELLER)

4. Immunomodulation & membrane receptors (the leader will be leaving the lab at the end of 2012 for the Faculté de Pharmacie)

5. Organic nanomaterials and delivery (leader: Mr A. BIANCO)

6. Biomimetic chemistry (the leader left the lab in September 2009).

The proposed future organisation for UPR 9021 (now entitled "Immunologie et Chimie Thérapeutiques") will be composed of teams 1, 2, 3 and 5 and there is a clear research focus on systemic lupus erythematosus (SLE).

Team 1 has largely worked on B cell biology and identifying of B cell genetic defects that could explain impaired immunological tolerance in SLE patients.

Team 2 has worked on understanding the molecular and cellular mechanisms responsible for the breakdown of tolerance in SLE by examining autoantigens and B cell epitopes and suppressive properties of Tregs. The team also investigated targeted strategies for immuno-intervention in SLE.

Team 3 worked on the biology of cutaneous immunology, with a specific research focus on dermal CD14+ cells and the role of the RANK molecule in epithelial stem cell biology and skin lymph node homeostasis.

Team 5 (team 4 for the new planned period and referred as such in the present document) has been working on vectorisation of treatment delivery through using carbon nanotubes.

Management team:

The unit Director since 2001 has been Sylviane MULLER who is DRCE1 at CNRS.

The management team named "club des 4" (all team leaders) takes decisions that are discussed within the "club des 13" (all permanent staff scientists) and "club des 10" (for engineers and technicians).

Unit's direction is very active in terms of intellectual property: 2 companies were launched (NeoMPS and ImmuPharma), 38 patents obtained during the previous period, of which 10 are already licensed.

The unit is essentially organised like a small research pharmaceutical company with a top-bottom and bottom-up research strategy, ranging from fundamental research through to drug development and clinical trials with excellent interactions with clinicians.

The entire unit shares all the resources, with the exception of salaries, obtained from grant applications.

Unit workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	6	5	5
N2: EPST or EPIC researchers	8	8	8
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *on a permanent position	8,1 [6.6 / 2.3]	9,4 [7.4 / 1]	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1.5 [1.5 / 0]		
N6: Postdoctoral students having spent at least 12 months in the unit	12		
N7: Doctoral students	16		
N8: PhD defended	15		
N9: Number of Habilitations to Direct Research (HDR) defended	2		
N10: People habilitated to direct research or similar	11	10	
TOTAL N1 to N7	**51,6**	**22,4**	**13**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.
Definition and downloading of criteria:
http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

2 • Assessment of the unit

Overall opinion on the unit:

This is a productive unit largely focused on dissecting the aetio-pathogenesis of SLE using sophisticated molecular immunology, functional assays and mouse models, to explore disease pathways, going from the gene to the biological/pathological function. There are also excellent examples of therapeutic innovations and opportunities for intellectual property protection. The senior scientists are both nationally and internationally recognised for their research contributions to the field of functionalized carbon nanotubes, SLE and autoimmunity. They are also active and successful in generating research grant income for their projects.

Strengths and opportunities:

The unit works on global issues related to SLE and autoimmunity that are and will continue to be highly relevant. The work has both basic science knowledge and therapeutic impacts and will be potentially applicable to other autoimmune conditions.

Obvious potential exists for the identification of new drug targets for modulation of immune and inflammatory pathways. The unit is able to produce drugs for phase II and III trials.

Publication and patent records are excellent: some important highly cited publications were published in high impact factor journals.

The unit has an excellent visibility (CNRS silver and bronze medal). The director of the unit is coordinator of Labex Medalis.

The unit is attractive to PhD, post-docs and CR with respect to recruitment and it has five permanent ITA.

The unit has a good ability to raise funds through competitive grant applications (national and EU FP) and is very well inserted into translational networks (almost entirely due to team 2).

The unit takes opportunities for protection of intellectual property: it launched a large number of licenced patents and 2 companies (NeoMPS, ImmunoPharma). There is a fruitful collaboration with industry for teams 2 and 3. The experts underline its capacity to generate revenues by licensing the products (5th largest revenue to CNRS in biological science).

Its Reference centers are national and European (co-organisation of international symposia).

Very good overall collegiate atmosphere can be find in the unit.

2 junior scientists have been recruited (1 MCU + 1 CR at CNRS). All the junior scientists are doing very well, PIs are 32 and dedicated to their research project.

Weaknesses and risks:

Scientists lack clear ideas regarding the development of the next potential leaders and the need to encourage junior staff to take on more responsibility.

The unit is heavily dependent on senior lab members for international visibility and for raising the funds. The international positioning of young research scientists is weak and they present a lower number of publications. Some final year PhD students reported no publications.

The overall research organisation of the unit appears less than optimal in terms of synergy as three teams work on immunology and autoimmunity research questions and one team is focused on nanomaterials and vectorisation with limited translational activity on biology. Except teams 1 and 2, other teams are less than optimally interconnected. One scientist working on the role of IL-21 in SLE has been moved from team 2, where her work was well integrated in their proposed project, to team 4 with the apparent aim of reinforcing the biological expertise in team 4.

Although the science of the unit is excellent, no collaboration has been developped with some key international groups working on SLE genetics. The 5 year publication record of some of the scientists at a more intermediate level is currently less than optimal.

There are too many chemical platforms developed by team 4 in the light of strong international competition in the field of drug delivery. A good chemistry research group left the unit for Bordeaux and thus the remaining chemistry support has shrinked.

Only 3 permanent scientific staff are under 40. Teams 1 and 3 are missing 1 full-time researcher to strenghten their future activities.

Team 4 does not demonstrate a clear scientific integration with the rest of the activity of the unit. This team's project is more technology- than hypothesis-driven work and therapeutic based applications should be planed in the near future.

Recommendations:

The unit should start to develop and implement a clear management strategy for the future, and to increase involvement and responsibility of more junior staff in the global and strategic management of the unit .

The unit should reinforce interactions and collaborations between the four research teams and thus foster further synergy. In particular, team 4 should make more efforts to build interaction with the rest of the unit. Optimal structure might have been to merge teams 2 and 4 to take advantage of the past successful experience of team 2 in bringing chemistry to true therapeutic drugs. It should not weaken a team for reinforcing another one with the move of a well-integrated reseracher.

The unit should attempt to investigate regulatory issues and in vivo proof-of-concept regarding the carbon nanotubes-containing drugs.

Researchers who devoted significant efforts to generate new mouse models should be strongly encouraged to published their results. Junior staff should more be encouraged to write and submit papers. PhD students should be strongly encouraged to write more than 1 paper (a review on the literature for example) with the help of more experienced researchers, and to participate in international training schools and meetings . The number of seminars by external fellows should be Increased.

The unit has to explore ways of increasing collaboration with international groups working on SLE genetic studies as such groups have limited functional / molecular immunology capacity and expertise.

3 • Detailed assessments

Assessment of scientific quality and production:

Objectives are related to autoimmunity (SLE) and drug delivery devices. Broadly, many scientific objectives are very original and their research questions are pertinent. The senior lab members are nationally and internationally well known and their scientific production is good. Projects are clearly focused to create further knowledge and translate their research from the bench to the bedside.

Overall the level of scientific publication of the unit is good (approximately 2 publications per person per year) with 143 international peer-reviewed publications since 2007 (including 7 review articles and 16 inter-team publications), and 12 book chapters.

However, the publication output is not uniform among the teams. Teams 2 and 4 are highly productive. Of the 14 lab members (6 professors/assistant-professors and 8 researchers + 1 who retired before 2007), 12 are first, first or last author at least once.

Most of the papers have been published in good or leading journals in their specific research fields : Immunology/Virology/Chemistry/Nanotechnology/multidisciplinary sciences (*Ann Rheum Dis*, *PLoS Pathog*, *Arthritis Rheum*, *JI*, *JAI*, *J Virol*, *Cancer Res*, *Angew Chem*, *Diabetes and Cell Death Diff*). A smaller number of publications however appear in more noteworthy journals including *Nature Nanotechnology* (IF >20), *Chem Soc Rev* (IF=20.1), *Acc Chem Res* (IF=12.2), *PNAS* (IF=9.7), *Angew Chem* (IF=12.7) and *Blood* (IF=10,5), *ACS Nano* (9.9). 25 and 7 % of the publications have appeared in reviews with an IF ≥ 8 and 10, respectively.

Collaborations are active and productive as demonstrated by many papers based on collaborative work.

Assessment of the unit's integration into its environment:

The unit has successful track record in identifying novel targets and therapeutic products and working with industry. Some of these molecules/agents have gone into the translational pathway and are the basis of clinical trials. The unit has attracted significant external research funding and some studentships/fellowships.

The lab members have also filed 7 (6 french and 1 US) new patents during 2007-2011 (and 26 active patents from the past period). One patent has been licenced to ImmuPharma giving rise to subsequent royalties (5th largest revenue to CNRS in biological science). Two companies have been launched. Two molecules are included in phase I and III clinical trials for cancer and SLE, respectively.

Since 2007, the past and present teams have obtained 11 ANR grants, 4 fundings from the FP6 and FP7 EU programmes, 2 from INCA, 4 from CNRS, 2 from ANRS, 1 from INSERM, 1 from Région Alsace, and 6 from Fondations or Associations (SIDACTION, Arthritis Courtin), 1 from a collaborative Indian-French research programme. The unit has also signed 7 contracts with industrial partners (ImmuPharma, BioDelivery Systems, Roche, BASF Beauty Care Solutions, SERB, Transgene, Cephalon).

The unit hosts PhD, Post-doc and CDD receiving support from national and international government agencies (CNRS, Ministère de la Recherche, Univ de Strasbourg, Ministère des Affaires Etrangères, ERASMUS, INCA, Région Alsace, EU : 37); Foundations (FRM, Fondation Arthritis Courtin, Fondation Fundayacucho, Ligue contre le cancer : 10); Associations (ARC, ARP : 2), and private/Industry (CIFRE/Transgene, CIFRE/ImmuPharma : 4).

The Director of the unit is coordinating the Labex Medalis that involves teams 1, 2, 3. The unit is also a member of national and international networks including (i) Pôle de compétitivité "Innovations thérapeutiques" (team 2) (ii) RTRA Chimie Strasbourg "International Center for the Frontier Research in Chemistry" (teams 2 and 4), (iii) Labex CSC – Centre de Chimie des Systèms Complexes (team 4), (iv) Centre de Référence National pour les Maladies Autoimmunes Systémiques Rares (coordination team 1), and (v) of the French-German network dedicated to the Lupus Biobank (coordination team 1).

Assessment of the research unit's reputation and drawing power:

Senior members of the unit have high national and international visibility for their research and are obviously highly regarded by their academic peers. This is also supported by their ability to initiate excellent international collaborations and attract students that is translated into the award of 11 ANR and 4 European grants. Prizes reported are the followings: CNRS silver and bronze Medals in 2009; Immunotherapy Prize of LFB ; Dina Surdin Prize of Socité Française de chimie, Journals Grant for International Authors from Royal Society of Chemistry, International award of excellence by the Endocrine Society and Pfizer, Thesis prize by Alsace BioValley; and Apollo-B prize by Roche.

Since 2007, the unit has recruited 3 research CNRS (2 by competitive entry examination and 1 mutation), 1 assistant-professor (université de Strasbourg). Team 1, formely an INSERM unit, which is composed of 2 professors and 2 assistant-professors, has joined the UPR 9021 in 2009. The unit has integrated 3 technical staff.

Two HDR were obtained in the last five years.

12 postdoctoral fellows coming from abroad (Russia, Spain, Canada, China, Italy, India, Netherlands, and Argentina) have been trained in the lab over the past 4 years.

16 PhD students are presently in the lab and 50% have been trained outside from UdS, and 33% abroad. 23 PhD students have obtained their PhD degree; all these PhD students were fully supported by grants/fundings for the 3-4 year thesis period from the CNRS, université de Strasbourg, French "Ministère de l'Enseignement et de la Recherche" and "Ministère des Affaires Etrangères", ANR, EU, ANRT (CIFRE), Région Alsace, Ligue contre le Cancer, ARC, and other associations.

Members of the unit participated in the co-organisation of several international symposiums, in the organisation of regional and national congresses and scientific meetings or are editors of journals (*Carbon*), special issue of *Journal of Peptide Science*. Some are also editorial board members of journals: *Journal of Peptide Science*, *Journal of Nanomedicine*, *Nanotechnology Reviews*; *Open Autoimmunity Reviews*; *Arthritis Res and Therapy*, *Int J Immunopathol & Pharmacol*, *Current Protein and Peptide Science*, *The Open Biochemistry Journal*, *The Open Rheumatology Journal*, *Genetics & Epigenetics*, or members of professional associations (SFI, AAI…)

They were also invited to present seminars (49) and to present at congresses (61).

The teams have extensive collaborations with local and national laboratories (Rennes, Lille, Nantes, Lyon, Bordeaux, Nancy, Paris, Reims, Marseille, Villejuif, CEA Saclay), as well as foreign institutions (USA, UK, Germany, India, Austria, Norway, Sweden, Switzerland, Netherlands, Italy, South Korea, Singapore, Japan).

As mentioned above, the unit is also coordinating the Labex Medalis and is involved, as a member, in national and international networks including (i) the pôle de compétitivité (ii) RTRA Chimie Strasbourg "International Center for the Frontier Research in Chemistry", and, as coordinator, in (iii) Centre de Référence National pour les Maladies Autoimmunes Systémiques Rares, and (iv) of the French-Germany network dedicated to the Lupus Biobank.

Assessment of the unit's governance and life:

The unit is a member of the federation of research units IBMC whose other members are UPR 9002 and 9022, member of GDR -I GNT.

The quality of governance is also good and appropriate. Indeed, the research unit organises weekly lab meetings and journal clubs, a monthly "Immunology circle", and 3 annual meetings to follow the progress of the PhD student's research. An annual meeting with all the staff is also organised. For this meeting, the team leaders present their research results and their programmes for the next coming year. Moreover, every month, the head of the lab organises two meetings, one with all the researchers, the other one with all technical staff. These strategic meetings are mainly intended to foster in-house communication, to take decisions concerning the organisation and life of the lab, and to build interactions between the teams. They also focus on strategy, developments and decision making.

They are 3 internal technical platforms (imaging, plasmon resonance, animal facilities) Staff members are responsible for Safety and Hygiene, radioprotection, animal facilities.

The PUPH, MCUPH and MCU staff are active in teaching. Also 4 of CNRS scientists contribute to bachelor and master teaching. The staff are responsible for input into biochemistry and cellular biology master programs of université de Strasbourg ; responsible for Immunology within the Life Science Faculty, université de Strasbourg ; responsible for teaching programs on cancer and immunology in the Pharmacy Faculty of Strasbourg.

Staff members are also involved in the (co)-organisation of various scientific meetings and programs (INSERM Atelier, member of GDR programs, formation of candidates (CNRS, Hospital) ; 6th, 7th and 8th Int. Congress on Autoimmunity, 7th Eur. Lupus meeting, Symposium on Carbon Nanotubes, etc.).

The researchers are expert members and council members of many regional and national organisations including the CNU, the Conseil scientifique de l'INSERM, the Conseil scientifique de l'université de Strasbourg , and the CoNRS.

Assessment of the strategy and 5-year project:

Overall the strategy and 5-year project plan appears sensible and largely built on the unit's previous and successful track record. A proportion of their strategy represents the natural progression and translation of this previous work whilst some is new.

From a strategic point of view, the main goals of the unit will be dedicated to the lupus disease which is its core of expertise both at the scientific and clinical level.

Teams 1, 2 and 3 are heavily focused on SLE and to some extent can be seen as being an integrated area giving good critical mass. Proposals are original and will undoubtedly lead to greater understanding and appreciation of normal and aberrant immune/inflammatory pathways both in SLE and other conditions. It is important for the future strategy to be able to eventually discriminate whether the molecules identified are either “cause” or “effect” in SLE development. Regardless these findings will represent important pieces of information.

Team 1 should consider the information provided by the international SLE Genome wide association study consortia and possibly working in collaboration with such consortia. Projects of team 3 would benefit from a link with the clinic.

In spite of the unique capacities of the unit, which puts together chemists, biologists and clinicians, these multi-disciplinary expertises are still spread over too many projects (mainly those of the chemistry team 4), which are not focused on lupus. Indeed, team 4 is missing proof-of-concept and should focus its projects and grant applications more on the unit’s interests in SLE. Lack of synergy of team 4 with other teams of the unit is obvious.

In summary, this unit is working very successfully in a highly competitive research area at an international level.

Overall, numerous hypotheses and objectives are original. Intellectual properties have been already protected. Licencing of patents appears to be a major source of financial generation. Less original is the project exploring the role of infectious agents in triggering autoimmunity.

Risks are the following: international competition on SLE in general ; uncertainty of generating results (high risk projects : teams 1 and 4) ; question on biodegradibility of carbon nanotubes (team 4).

Assessment of the unit’s involvement in training:

In addition to the PUPH, PCUPH and MC université de Strasbourg staff, whose duty is statutorily devoted to part-time teaching, 4 of the 8 CNRS researchers contribute to teaching at the university at the licence and master levels. Nearly 35 licence and master students (18 at the M2R level) or students from biotech school have also been hosted for one to twelve months in the unit during the 2007-11 period.

The unit has played an active role in hosting and training bachelor, master and doctoral fellows: it trained 23 masters, 3 bachelor, 10 trainee fellows; 23 PhD theses were defended and 13 are ongoing; it hosted 11 post-doctoral fellows. PhD and post docs had/have allocation from Government (national or international), foundations or private organisations. Three annual meetings where the progress of the PhD student's research is examined are organized.

Involvement in Doctoral School activities is relatively less important : the unit organised a summer school of Doctoral School of Health and Science (2011).

The unit has followed the future developments of PhD fellows : majority of them are persuing post-doctoral studies either in France or abroad. A good proportion are employed in companies. Two are unemployed.

Good financial support for students who are highly enthusiastic and happy. Two of them are going to apply CR1 and CR2 at CNRS. PhD students however seem to have little concern about having more than one first author publication that is the minimum required by the University.

4 • Team-by-team analysis

Team 1: B cell tolerance and autoimmunity

Team leader: Mr Thierry MARTIN

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	4	4	4
N2: EPST or EPIC researchers	0	0	0
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff * on a permanent position	3	3	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	0		
N7: Doctoral students	6		
N8: PhD defended	3		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	4	4	
TOTAL N1 to N7	**14**	**7**	**4**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:
http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

Team 1 is studying environmental and genetic factors implicated in the breakdown of B cell tolerance in autoimmune diseases, in particular lupus. In one approach, they identified genes with dysregulated expression in B cells of lupus patients. For three upregulated and three downregulated genes, functional studies to be performed in a cell line and mouse models either already generated or are being generated. The first results indeed show influence of the genes under study on B cell activation and BCR signalling. This is an original approach, very promising initial results were obtained, technically demanding methods were applied (e.g. generation of mouse lines), and the results have potentially a high impact on our understanding of immune dysregulation in lupus. In a second approach, a novel "knock-in" mouse model for autoreactive B cells was created to study the interplay between infections and autoimmunity development. The mouse line will be crossed with several autoimmune prone lines. The impact of infections on the development of autoimmunity has long been discussed. Therefore, this is an important study with an original approach. The initial results with the "knock-in" mouse line and a Borrelia infection are very promising. Additional studies revealed novel abnormalities in the peripheral blood of patients with systemic lupus and CVID.

The major research results from this team over the last five years are the followings:

- Identification of B cell defects in patients with lupus during quiescent phase: decreased memory B cells and their membrane CD19 expression
- Identification of a novel gene that regulates B cell functions. Carabin as a negative regulator of B cell activation in preventing BCR-TLR9 costimulation-induced autoimmunity
- Identification of a novel mechanism involving thrombosis in antiphospholipid syndrome during pregnancy
- Uncovering quiescent lupus patients' heterogeneity based on B cell transcriptome analysis
- Identification of role of MyD88 in controlling hypergammaglobulinemia and autoantibody production during bacterial infection
- Correlation of autoimmunity in common variable immunodeficiency with an increased CD21low CD38- B cell subset.

These data have clear basic science knowledge generation and therapeutic impacts, allowing a better understanding of the pathogenesis of lupus as well as the identification of potential diagnosis/prognosis biomarkers and therapeutic candidates.

Team 1 is composed of 4 Professors or Assistant Professors, 3 ITA and no full-time scientist from either CNRS or INSERM. All four of them are active in research, clinic and teaching, and all professors and assistant professors are producers.

Overall, the results obtained during last five years are of excellent quality. These results provide novel mechanisms of pathogenesis of autoimmune diseases. While their results on role of B cell genetics in lupus are original and are platform for next five years, their results on role of infectious diseases as triggering factor for autoimmunity is not so original as the axis of 'autoimmunity-infection' has long been known. An additional strong point is the largest European cohort of common variable immunodeficiency patients and the team is a participating member of the national referral center of immunodeficiency. The next five years strategy is largely based on taking some of these results/findings forward around the area of genetics of B cell biology in SLE and they should link genes to phenotype. Their work on environmental/infectious triggers for SLE is less advanced and mature.

The quantity and quality of publications for this team over the last 5 years is perhaps a little less than normally expected for active groups like the present one with 13 members. It is likely to be due to deviation of major efforts during last couple of years towards uncovering the genetic defects in T and B cells in patients with lupus and CVID. However, it has to be considered that extensive amount of time and effort have been needed to generate the new mouse models and to built a relevant cohort of patients, now being used, both which are time consuming and cause delays in publication output. The team is now devoting its energy for the next period of time to generate and publish their findings and thus their publication output is likely to increase significantly over the next two years.

Over the 2007-2011 period, several articles were published, including three studies in the top autoimmunity journal (*J Autoimmunity*), and in the *Eur J Immunol*. The team has published 13 articles in good international journals (among which 2 reviews): 6 articles in journals with IF>8 (*Blood* and *J Autoimmun*), 4 with IF >5 (*J Virol*, *J Thromb Haemost*, *Eur J Immunol*) and 2 with IF>4 (Infect Immun and PLoS ONE). Among 13 articles, the team members have major authorship positions (first or last authorship) in 10 articles. The highest IF is 10.5 (*Blood*) but it is not a major article from the team and where only one team member is co-authors of this article. Of note during this period, one of the team members has published 5 articles from her previous lab. Noteworthy are one publication each in *J Exp Med* (IF 15), *Blood* (IF 10.5), *Oncogene* (IF >7) and *Mol Ther* (IF>7). Also, the share of PhD fellows in the publications of Team 1 is low (4 out of 13 publications), it corresponds to around 30%.

Two PhD theses were defended during this period, one is leaving for a post-doc in Yale. Two out of the 4 PhD students are in their 3rd and 4th year without publication. One will most likely publish within next year and the other one is a dentist only part-time dedicated to her PhD. Two abstracts have been selected for oral presentations in International congresses and one of the team members is last author on these abstracts. However, first authors in these oral presentations are from another institute in Illkirch. Therefore, these two oral presentations indicate success of a local collaboration but not exposure of PhD fellows of the team for international conferences. On the other hand, two of three abstracts communicated as poster in national/international congresses have PhD fellows of the lab as first author.

Assessment of the research team's integration into its environment:

The team is the least active of the research teams in terms of valorization of research and contract research with Industries.

Four national grants have been obtained over the past period (projet GIS maladies rare ; Fondation Arthritis Courtin, 2 PHRC interregional and API project of University Hospitals of Strasbourg, 180 K€) and one Europrean (European Inter-regional Franco-German: total: 2.8 M €; team: 1.85 M€).

The team is a national reference center for rare systemic autoimmune diseases (since 2006).

Assessment of the research team's reputation and drawing power:

The two senior researchers are nationally and internationally recognized for their research contributions to the field of autoimmunity hence their high activity in delivering national and international presentations at meetings. In particular, one of the team members was invited for 10 national/international meetings on Autoimmunity/Rheumatology. However, other members have not received any invitation during this period. The apparent lack of invitations for the team leader is surprising given the high quality of his work. On team member has received Immunotherapy Prize from LFB.

Four PhD students have worked in the group over the past period. The team has not attracted PhD/Post-docs from abroad. They have successfully attracted one technician at the Strasbourg University (previously in Lyon University). No full-time researcher has been recruited.

Several international collaborations have been developed. The team is active in national and international research/clinical networks. The lab is a national reference center for rare systemic autoimmune diseases (since 2006) and a participating member for the referral center of immunodeficiency (A. Fischer, coordinator). One team member is a coordinator of a Lupus Biobank (2011-14) that involves 14 centers in France and Germany and since 2010 and another one is a member of 'Autoimmune Disease Working Party' of 'European Group for Blood and Bone Marrrow Transplantation'. In addition, the team has collaborations with the Garvan Institute of Medical Research (Australia) and the University of Florida (USA).

Team members are active in raising funds for research : four national in total (project GIS maladies rare ; Fondation Arthritis Courtin, PHRC interregional and API project of University Hospitals of Strasbourg) and one European (European Inter-regional Franco-German).

Assessment of the strategy and 5-year project:

The project aimed at identifying the genetic defects in B cells of lupus patients and to define the role of viral and bacterial infections as triggers of autoimmunity in genetically susceptible mice. Thus, there is continuity from their previous work and in synergy with other teams in particularly Team 2. The team has devoted a lot of efforts over the last few years towards delivering these objectives. Using microarray studies of B cells from lupus patients, the group has identified 6 genes of unknown functions dysregulated in peripheral blood B cells of lupus patients and potentially implicated in the disease process. They have already identified that one of these genes, Carabin, is a negative regulator of B cell functions and its down-regulation facilitates autoimmune response. By using genetically

modified mice, they now intend to study the role of these genes in the pathogenesis of autoimmune disease and the role of infectious agents in triggering autoimmune process. These studies are expected to provide insight into new biological pathways implicated in autoimmune process and eventually novel therapeutic targets and diagnostic tools. The study of six genes by generation of mouse models to analyze the impact of infections on the development of autoimmune diseases is well under way and exciting initial results have been obtained. The further evaluation of these models will take several years but the team is experienced in this field. This is a very important and promising medium- to long-term research project.

A grant application for one part of the project is currently submitted to ANR.

Plan for recruitment of full-time scientists (post-doc or CR) is not clear.

The global approach of the research team is novel as it tries to identify B cell defects in lupus (autoimmune disease in general) and aims to provide the role of these selected genes of unknown functions in the pathogenesis of disease. These projects are highly original. This is largely based on previous findings and the new ideas they have come up with. The major focus revolves around genetic defects in B cells and the role of infectious triggers including bacteria and viruses. There is some risk in that not all models will lead to major novel insights into autoimmunity, but the potential returns are high enough so that it is highly recommended to take this (minor) risk. Also, the group is working on a disease (SLE), which is highly heterogeneous in its pathogenesis. Therefore, results may apply to only a subgroup of patients. An important point is that the team is aware of these complications.

By looking at the specific objectives and the preliminary data available, it looks like the project will require more than 5 years to achieve all the goals, especially when planning all the mouse studies. However, the reputation of the team members in delivering constant high quality results in the domain of autoimmunity and primary immunodeficiencies is a positive point and gives reassurance for the realization of research goals. The team has raised considerable financial resources and has the competence to generate transgenic mice models. The group could benefit from more technical/scientific support for animal experimentation to achieve this plan. Furthermore, these types of studies usually raise more interesting questions than answers and therefore it would be sensible to have a very clear plan for prioritization for the genes to be investigated. Thus before undertaking this study, it would also be advisable to devote some time to carefully assess recent GWAS and replication studies on SLE. These could give some insight about whether the genes already selected relate more to “effect” than “cause”. Similarly, more thoughts into the environment-based studies could be beneficial.

The possible therapeutic targets of B cells are questionable due to the latest negative results on B cell depletion therapies in SLE patients.

Conclusion:

Overall opinion on the team:

The team should be complimented for its skills and expertise in the area of functional and molecular immunology and much of its proposed project is original and will deliver important findings. The scientists leading this research theme have an excellent and justified international reputation. Indeed, the group is well known both nationally and internationally for its research activities at the leading edge of the field of SLE/autoimmunity related to the characterisation of normal and aberrant immune pathways, especially for B cell function.

The team is performing highly original and important work to better understand the role and mechanisms of B cell tolerance breakdown in the pathogenesis of autoimmune diseases. They have the reputation of delivering constant high quality results in this area. This has resulted in some good publications in high impact journals. It would be useful to consider the genes selected for study in the context of what is know from international genome wide association studies and give some consideration to the issue of “cause” or “effect” for the genes they are studying. It would also probably be useful to establish some formal collaboration with these groups. Now, the team should quickly maximize the return of their preliminary results obtained with transcriptomic analysis of B cells from lupus patients and should identify the role of the newly identified six genes in the pathogenesis of autoimmune disease.

Strengths and opportunities:

The team has generated attractive mouse models and is well experienced in the analysis of such models.

Three members of the team are medical doctors and have a good clinical infrastructure.

The team has already gathered good preliminary data and methodologies and identified six relevant genes required for future research.

The team is active in national and international research/clinical networks and in raising funds for research. Team has the developed relevant international collaborations for future work.

Team members have a track record of raising research funding (national and European).

Team mebers have high international reputation and will have no problem working with leading international groups also working in the area.

Weaknesses and risks:

The publication output has been reasonable but not high over the last few years in the light of the 13 team members. However, this is largely due to the preparative work to generate the mouse models and building the cohort of lupus patients and still represents a good production when considering teaching and clinical duties than research that all the scientific staff supports.

There is no permanent CNRS/INSERM scientist. This might be a reason for the low share of PhD fellows in the publications (4 out of 13 publications, which corresponds to around 30%).

The comittee points out a weakness in attracting international PhD/post-doc fellows and in valorization of results and industrial collaborations.

The comittee notices uncertainty for generation of results in experimental models for the proposed projects.

The group is working on a disease (lupus), which is highly heterogeneous in pathogenesis. Therefore, results may apply to only a subgroup of patients.

On this subject, there is a strong international competition. The group does not appear to collaborate with groups working on SLE GWAS. The proposed research plans for environmental risk factors is less mature and is thus more risky.

Recommendations:

The team should:

- Quickly relate the findings in the mouse models to the human situation (e.g the six genes in the first part of the project were originally found to be dysregulated in B cells of human lupus patients) as this might indicate future research directions.
- Prioritize the work plan and first concentrate on the two or three most promising genes in the light of human data.
- Design an alternative strategy in case of impossibility to get expected results proposed in the project.
- Explore collaborations with other groups working on SLE genetics and autoimmunity in general.
- Further elaborate the investigation of environmental factors.
- Make all effort for increasing the research critical mass of the group by a.) attracting international PhD/post-doctororal fellow; b.) recruiting at least a post-doctoral fellow in order to have one full-time scientist in the team. c.) as a medium-term aim, attract/recruit a full time permanent scientist.
- Increase the quantity (while maintaining the quality) of publications with more visibility of PhD/post-doc fellows - especially when students with some years PhD still do not have paper yet as 1st author.
- Elaborate a valorization strategy for results on transcriptome analysis of B cells from the lupus patients and with relevant animal models, especially exploring possibilities for collaboration with industry.

Team 2: Immunobiology and therapy of lupus

Team leader: Ms Sylviane MULLER

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	1	1	1
N2: EPST or EPIC researchers	4	3	3
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff * on a permanent position	1	1	
N5: Engineers, technicians and administrative staff * on a non-permanent position	2		
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	10		
N8: PhD defended	7		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	3	3	
TOTAL N1 to N7	**21**	**5**	**4**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

The team is studying basic mechanisms of SLE pathogenesis, including the role of posttranslational modifications of autoantigens in apoptotic cells, specific features of plasma cells in lupus-prone mice, and the role of regulatory T cells. Also studies about the role of IL-21 in SLE have been initiated. In another part of the project, a translational approach is being followed, studying the role of a modified peptide derived from a nuclear protein as an immunmodulatory factor in SLE. Clinical studies are currently underway, and the first results show a positive effect. In a further project, not directly related to SLE, the suitability of specific pseudopeptides for cancer therapy are being tested.

These are all original projects, and important novel insights into disease mechanisms of SLE have been obtained, such as the recognition of abnormal Treg functions in SLE mice and altered plasma cell functions in kidneys of lupus-prone mice. The first promising data from clinical studies with the P140 peptide are also a major result.

The team has been successful in publishing their work, with many publications (43) in good to excellent journals, including *Nat Nanotech*, *NAR*, *JAI*, *J. Immunol.*, *Ann. Rheum. Dis.*, *Arth. Rheum.*, *Cancer Res.*, *PLoSOne*, *Diabetes*, *J Virol* and *Cell Death Diff*. All scientists are producers, but only the team leader and 2 scientists are reported as invited speakers.

Several PhD projects were finalized during the report period. 36 patents are reported.

Assessment of the research team's integration into its environment:

The development of P140 into clinical trials in patients with lupus, as well as the N6L in cancer therapy program, represents successful translational developments in collaborations with companies.

The team is highly active in valorization with 36 patents, among which 10 are licensed and is very successful in launching biotech companies and bringing molecules into clinical trials.

The team has financial support from pharmaceutical companies. It was very successful in recruiting extramural funding with 7 major funds listed: 2 ANR, 2 Arthritis fondation Courtin, 1 Sidaction, 2 "contrats région", 1 ANRS. They benefit from royalties on their licensed patents and are able to support several non-permanent staff thanks to their link with industry.

Team 2 is a partner team of 1 "Pole compétitivité" (Innovative therapeutics), of 2 GDR CNRS.

The team leader is the coordinator of the "initiative d'excellence" Labex Medalis.

The unit is « centre de référence national des maladies autoimmunes systémiques rares ».

Assessment of the research team's reputation and drawing power:

The team leader received several prizes including silver medal of CNRS in 2009 and had numerous invitations to conferences. Another team member also received the bronze medal of CNRS.

The team leader was a member of the organising committees for several conferences. She has several national and international collaborations.

The team recruited a number of students and postdoctoral scientists from France and abroad, but no researcher has been recruited over the last period.

Assessment of the strategy and 5-year project:

The team presents a comprehensive program for the next few years. The work on IL-21 will be intensified. With the new project on the relationship between autophagy and disease development in SLE, an original field of research will be opened. The combination of basic research on SLE pathogenesis and translational studies is being continued and highly relevant. Also the combination of mouse-based studies with human focused investigations is positive. Because of the experience and previous success of the team, the planned experiments have a high chance to be successfully carried out.

The team is very efficient in establishing translational research from bench to bedside.

The team appears to be well supported by funding from both agencies and companies.

The IL-21 project is very original. IL-21 is certainly an important molecule to study in SLE. However, the transfer of one of the team members to team 4 weakens the potential development of this research theme.

Although the group has no expertise on autophagy, the autophagy-SLE project is very novel and might lead to highly interesting results.

Conclusion:

Overall opinion on the team:

This is a very successful team, which is also evident from the multiple publications and the generation of considerable fundings. Important and original studies on SLE are performed, with a fruitful combination of basic and translational research projects.

Strengths and opportunities:

The team is highly experienced in the field and has developed most promising ideas and work plans.

Translational approaches, which have already reached the status of clinical studies, are a further strength.

The team future direction is obvious and the dynamics of this group is positive.

The team leader has an excellent national and international visibility.

Weaknesses and risks:

The IL-21 project of team is weakened with the move of one scientist to team 4.

There is no obvious team leader able to take over the projects on the long run.

Recommendations:

The IL-21 project has very high priority.

Team 3: RANK and cutaneous immunology

Team leader: Mr Christopher MUELLER

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	2	2	2
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff * on a permanent position	1	1	
N5: Engineers, technicians and administrative staff * on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	0		
N7: Doctoral students	3		
N8: PhD defended	2		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	2	2	
TOTAL N1 to N7	**6**	**3**	**2**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

The team specialises on dermal immunology, studying the link between cutaneous tissue and the immune system and more specifically on dermal CD14+ cells and how they may interact to regulate the balance between immunity and tolerance. To this aim, the team focuses on the role of the protein RANK in epithelial stem cell biology and skin lymph node homeostasis.

An important role of RANK in hair follicles and epidermal homeostasis has been demonstrated. The team has experience with *in vivo* mouse models of hair renewal and is focusing on the role of RANK by using mice deficient for RANKL and transgenic for RANK. In absence of RANK, the hair cycle is arrested and the role of this molecule intervenes on stem cell activation with diverse effects on hair follicles and cutaneous proliferation.

Another application of this RANK approach relates to lymph node homeostasis because RANK transgenic mice have post natal growth of skin draining lymph nodes with an increase of B cell follicles.

To better understand how the cutaneous immune response is collectively shaped by its immune cells, the group is studying dermal CD14+ cells. These cells display phenotypic and functional similarities with anti-inflammatory macrophages but convert into alternatively-activated macrophages. For dermal macrophages, which do not survive in culture when on their own, the group developed an organo-tropic human skin model, where dermal-type macrophages are co-cultured with dermal fibroblasts. This co-culture system will be used to study tissue – immune cell interactions.

Considering that the team is rather small, important contributions have been made regarding immune cells in the skin and the functions of RANK. The work is original. The future project of the team has been focused on two areas: the role of RANK in skin and lymph node biology, that strengthened the link with the project's unit.

The publication volume of the team (2 full-time researchers) is rather low with no reviews and 5 publications coming from direct work of the team (and 4 from collaborations). The IF of the team production is fair, with 1 article published in a high profile journal (*PNAS*), and then journals of IF between 4 and 6 (*PLoS NTD*, *J Immunol* and *J Leukocyte Biol*). This production is largely due to the team leader.

A concern is the lack of publication for a PhD student who defended his thesis in 2011.

Assessment of the research team's integration into its environment:

The project was supported by BASF Beauty Care Solutions, and two patents have been submitted. Three patents applications have been submitted. One other grant over 100 k€ is listed in the team summary.

All the team's projects are funded, either through private (BASF Beauty Care Solutions, French Society of Dermatology research) or institutional entities (ANR, CNRS). For 2012, more than 250K€ have been obtained. Two smaller extramural grants were also obtained. In the project plan, an EU grant funded for 2011-2014.

Assessment of the research team's reputation and drawing power:

No prize has been reported.

Four invitations were reported for presentations to foundations and courses, but no prestigious invitation to meetings or institutes, which suggests a lower international visibility.

The team is rather small: 2 CNRS researchers, 1 ITA and 1 PhD student at beginning of report time; now still 2 CNRS researchers and 1 technician but 2.5 PhD students.

The team is collaborating with several other groups in France and abroad and reports 4 publications from this collaborative work.

Assessment of the strategy and 5-year project:

The new projects are built on the prior studies but now form a more focused approach. One main aim is to further characterise the role of RANK in the skin and the lymph node stroma. To dissect the role of RANK in distinct cell types, a number of murine transfer experiments are planned. The team will now also study the role of RANK in SLE. Indeed, the role of RANK and CD14+ cells in cutaneous lupus will be studied. This is a medium- to long-term project, which builds on the experience of the team, *in vitro* and *in vivo* models developed over the past period. It also focuses on aspects of autoimmunity, bringing this team closer to the teams 1 and 2. The work plan has a very good chance of leading to important novel insights.

Two grants to support the projects are already available.

One of the 2 scientist contributing to this team worked on viral aspects on the previous team 3 skin projects but her project is now no longer in the focus of the new team 3 project.

The project regarding cutaneous lupus (CLE) is more related to the macrophages approach because CLE skin releases very little RANKL, however the idea is to explain this discrepancy with psoriasis. The study will be carried out with the Dermatology department of Pr. Dan Lipsker (Hôpital Civil de Strasbourg).

The project is original. It is presently unclear whether RANK indeed has a significant role in lupus, so there is a risk that no major findings will be made for this part.

Conclusion:

Overall opinion on the team:

The team is small, however the publication output is good. The team has much experience with RANK and dermal antigen presenting cells, so that the new projects have good chances for success.

Strengths and opportunities:

The novel inclusion of aspects of autoimmunity brings this team closer to the main topic of the unit.

Their inclusion into a new EU collaborative grant gives new opportunities for collaborations and a better international recognition. The formation of the EU-funded stromal network will create a great opportunity to establish the team as expert in RANK and secondary lymphoid organ stroma homeostasis.

The recruitment of German students is a positive step and close ties with a German University are planned in the form of a bilaterally-funded Doctoral College. This initiative is further encouraged by crediting the University of Strasbourg as IDEX University, joining the excellence label of the Universities of Karlsruhe and Freiburg. Their success in collaborating with a cosmetic firm as well as with two chemistry labs will create novel applications, funding sources and therapeutic possibilities.

Building on their experience with RANK and lymph node stroma, adoptive bone marrow transfers and the knowledge of the UPR 9021 unit on lupus (teams 1 and 2), team 3 will address this issue by studying the link between RANK, stroma and SLE autoimmunity. The recently accepted formation of an EU-STROMA network, where their team is participating with 1½ funded PhD position, is a reflection that research on stroma of secondary lymphoid organs is a key theme for the international research community.

The participation to the Labex Medalis will help translation of data to the clinic.

Weaknesses and risks:

The team was previously more scientifically distant from the main theme of the unit, as it did not address autoimmunity in its research, and dermatology is quite distant from the topics of the other teams.

The clinical input in the project for translation to human pathology is weaker than other themes.

It is not completely clear how they will analyse primarily the effects at the level of the tissue and cell in the skin, or in the blood, and whether molecular approaches or cellular approaches will be used.

Recommendations:

This team would definitely benefit from having a closer working collaborative relationship with an academically / research-minded clinical dermatologist.

Efforts being put into clinical trials will definitely be improved by putting much more emphasis on stratifying the SLE patient groups being tested. This could be done by careful assessment and analysis of clinical phenotypes and/ or underlying genetic profiles. This does not necessarily need to be done by the team itself but could be done in collaboration with other groups.

There shall be many more interactions between team 3 and teams 1 and 2 in the near future to strenghten the focus around lupus of the unit's projects.

Team 4: Organic nanomaterials and delivery

Team leader: Mr Alberto BIANCO

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	2	3	3
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff * on a permanent position	0	0	
N5: Engineers, technicians and administrative staff * on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	5		
N7: Doctoral students	5		
N8: PhD defended	3		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	1	1	
TOTAL N1 to N7	**12**	**3**	**3**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:
http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

The team (2 permanent CNRS researchers) is largely exploring the chemical functionalisation of carbon nanotubes (CNT) and the CNT-based delivery of oligonucleotides and analogues (plasmid DNA, siRNA), peptides and other therapeutic molecules (doxorubicin, amphotericin) for therapeutic, vaccine or diagnostic applications and for use in biocatalysis. This group is one of the numerous groups world-wide exploring such a nanocarrier-based drug delivery strategy and one of the several groups exploring a CNT-based strategy. This CNT-based strategy constitutes an alternative, though much less versatile and more challenging, to the innumerable lipid or polymer-based nanocarrier delivery systems that have been described and investigated in literature since 1970. One should further underline that the nanocarrier-based strategy for therapeutic purposes had met limited successes since, up to now, as approximately only ten nanocarrier drug formulations are used in clinics, highlighting the numerous parameters that have to be considered/controlled, and numerous barriers (biocompatibility/toxicity, biodistribution, blood circulation, specific tissue/cell tropism, drug release, metabolism/excretion, etc.) that such systems have to overcome to find real applications in human therapy and diagnostics. Although the research is of excellent quality, its originality lies mainly in the use of CNT as nanocarriers. It is however not completely innovative as it relies on well-known and well-documented recipes (which have shown their limitations) used for the development of nanocarriers for the drug/probe delivery. It thus appears that the team has relied more on applying known recipes for exploring several applications at a more superficial level, and has as not yet explored new strategies for improving the efficiency, specificity of drug delivery systems based on nanocarriers.

The team has also explored the design and biological activity of nucleopeptides as analogues of oligonucleotides with the aim at improving the biological stability of the latter ones while retaining their affinity and specificity for complementary DNA/RNA strands. This strategy is very close to the widely explored "Peptide Nucleic Acid" (PNA) approach and it seems that the team has given up this project which had limited success.

Over the 2007-2011 period, the quantity and quality of productions for such a small team is excellent. Indeed, the team has published 53 papers (47 research articles, 6 reviews – *Acc Chem Res* (2008 ; IF=12.2) *Nat Nanotech* (2009 ; IF=26.3), *Chem Soc Rev* (2009 ; IF=20.1) and 8 book chapters) among which 23 peer-reviewed first or last author publications : 1 *Nat Nanotech* (2007 IF=14.9); 3 *ACS Nano* (IF= 9.9); 2 *PNAS* (IF=9.7); 4 *Adv Mat* (IF=8.2); 1 *FASEB J* (IF=6.5); 4 *SmalI* (IF=6.2); 1 *Nanomedecine* (IF=6.1); 1 *Nano Today* (IF=5.9), 1 *Chem Biol* (IF=5.8), 7 *Chem Commun*, 2 *JACS*, 3 *ChemEurJ* (IF=5.5). Of the 53 papers, 46 papers have an IF ≥ 4 and all are > 1.

2 Ph-D theses have also been defended and 22 conferences as invited speaker have been given.

The large quantity of productions of the team is partly due to very long lasting and strong collaborations with 2 academic international partners (in Trieste and London), which resulted in 41 joint peer-reviewed papers. The team has also 8 publications in common with former Teams 2, 4 and 6.

Assessment of the research team's integration into its environment:

The team applied with success for competitive ANR (2) and CNRS PEPS and PICS fundings. It is also participating in projects funded by the 6th and 7th PCRD (Total fundings : 1234 k€).

The team leader is also coordinating an indo-french collaborative research program on CNT-based constructs as biomimetic catalysts.The research of the team has featured in several press articles and interviews. Although team reported 2 patents, no partnership with a pharmaceutical group has yet been established.

Assessment of the research research team's reputation and drawing power:

The team is well-recognised in its domain of expertise, eg in CNT as drug carrier and delivery systems, as attested by the numerous invited conferences (22) that have been given by the team leader, who received a 2011 CNRS award for scientifc excellence. It is also attracting good scientists to work in the laboratory as 6 post-docs from abroad were hosted.

The team participates to national (RTRA Chimie Strasbourg, Labex CSC) and three international programmes (GDR-I- GNT (GraphenenanoTubes), 6th FP EU- NEURONANO and 7th FP EU- ANTICARB.

The team has long lasting and strong collaborations with 2 academic international partners - in Trieste (Italy) and in London (UK) -, which resulted in 41 joint peer-reviewed papers.

Assessment of the strategy and 5-year project:

The team has a comprehensive work plan, based on the previous results and fully based on the expertise of the group. The team leader has already received several major grants that secure the research funding for the next years.

Over the next five years, the chemistry team will be reinforced by one biologist CNRS researcher coming from team 2 and will focus on the following issues, most of which are in line or in continuation with its research during the last 2007-2011 period:

- investigation of the biodegradability of functionalised CNTs;

- pursue efforts aimed at the the multi-functionalisation of CNTs for targeted drug delivery with a special attention to (i) the selective destruction of harmful autoreactive B cells in lupus; (ii) the delivery of radiopharmaceuticals sealed in their interior and assessment of their toxicological and pharmacological properties; (iii) the development of magnetic CNTs by filling their empty internal cavity or by coating of their outer surface with iron magnetic iron oxide nanoparticles for MRI or for hyperthermia-induced therapy (either by IR irradiation or by magnetic field).

It will also explore the design of new nanomaterials based on adamantane-dendrimers.

Overall, the program is a very academic basic research dealing with highly sophisticated molecular constructs. Given the limited number of researchers based in the team some of the aims of the group may be too ambitious. Some of the potential pitfalls and problems expected with this work plan have not been explored in detail and this should be developed.

The objectives of the research plan appear currently somewhat theoretical. Moreover, for the development of future nano-therapeutic delivery systems, the numerous in vivo barriers to overcome for a nanocarrier to be used in therapy and/or diagnosis (and biocompatibility/biodegradability of the CNTs) have not been taken into account.

It was not clear what the team expects from generating new cationic CNTs or adamantane-based dendrimers and what the team wants to improve with respect to siRNA delivery or more generally with respect to drug/probe/contrast agent delivery for therapy and/or diagnosis.

Some approaches can be considered as risky (biodegradation, new project with adamantane).

Applications of the CNT as tools for diagnostic and for use in biocatalysis seem to be more realistic objectives to achieve in a near future.

Conclusion:

Overall opinion on the team :

The team has a very good expertise in nanotechnology and more particularly in the field of chemistry of CNTs and in CNT-based drug delivery which is well recognised. The team was very successful in its research and has an impressive high-level production which results from a very fruitful collaboration with 2 european partners. The team was also successful for raising national and european fundings.

Strengths and opportunities:

The team strengths and opportunities lie in its expertise in the chemistry of CNTs and in nanotechnology, in its excellent scientific production and invitations to conferences and its ability to develop successful collaborations with foreign academic partners, and to raise funds from coordinated research programs.

Weaknesses and threats:

The next 5-year project is currently not closely linked to the autoimmunity groups. It is further composed of too many and too ambitious (if not unrealistic) and consequently risky subprojects which are not commensurate to the team's workforce.

The research programm does not take enough into consideration the numerous requirements or specifications for the development of nanoscale materials for *in vivo* purposes. It is lacking applied or translational issues for preclinical development. Team 4 tries to refine devices but is not driven by innovative therapeutic issues.

As for most other drug nanocarriers, the low biodegradability and biocompatibility of CNT raises several issues potentially precluding therapeutical applications. It thus remains uncertain whether CNTs will find real applications in the highly-competitive and challenging field of drug (small molecules, DNA, siRNA, peptide, ...) delivery.

Recommendations :

Team 4 needs to focus more on selected valuable and realistic issues sized to the team's workforce and with the main focus of the unit.

Team 4 also needs more clinical and basic biology input. It would be better if it had closer working relationships with the other research themes and teams.

Team 4 should now devote more efforts on specific delivery (cell targeting) and mostly on *in vivo* and regulatory issues in order to definitively validate the CNTs as useful *in vivo* nanocarrier-based drug delivery systems for therapy (ADME assessment, comparative pharmocokinetic studies on the free versus encapsulated/associated drug).

The group needs to develop a longer term vision or where other clinical delivery systems may come from in the future.

Team 4 should dedicate part of its money, human resources, in the therapeutic direction.

5 • Grading

Once the visits for the 2011-2012 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the four criteria defined by the AERES and was given along with an overall assessment.

With respect to this score, the research unit concerned by this report (and, when necessary, its in-house teams) received the overall assessment and the following grades:

Overall assessment of the unit [Immunopathologie et Chimie Thérapeutique]:

Unité dont la production, l'organisation et l'animation sont très bonnes. Le rayonnement et le projet sont excellents.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	**A+**	**A**	**A+**

Overall assessment of the team [B cell tolerance and autoimmunity]:

Équipe dont la production et le rayonnement sont très bons. Le projet est excellent.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	**A**	**-**	**A+**

Overall assessment of the team [Immunobiology and therapy of lupus]:

Équipe dont la production est très bonne. Le rayonnement et le projet sont excellents.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	**A+**	**-**	**A+**

Overall assessment of the team [RANK and cutaneous immunology]:

Équipe dont la production est bonne, le rayonnement est bon mais pourrait être amélioré et le projet est excellent.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	**B**	**-**	**A+**

Overall assessment of the team [Organic nanomaterials and delivery]:

Équipe dont la production et le rayonnement sont très bons. Le projet est bon mais pourrait être amélioré.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	**A**	**-**	**B**

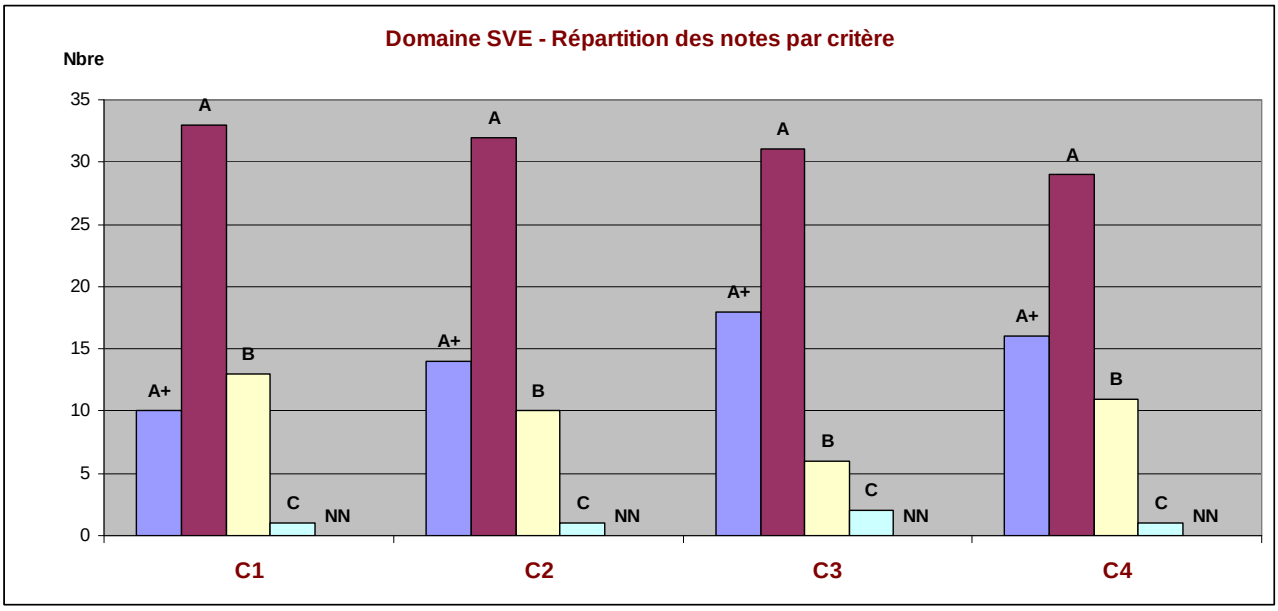
6 • Statistics per field: SVE au 10/05/2012

Notes

Critères	C1	C2	C3	C4
	Scientific quality and production	Reputation and drawing power, integration into the environment	Laboratory life and governance	Strategy and scientific project
A+	10	14	18	16
A	33	32	31	29
B	13	10	6	11
C	1	1	2	1
Non noté	-	-	-	-

Pourcentages

Critères	C1	C2	C3	C4
	Scientific quality and production	Reputation and drawing power, integration into the environment	Laboratory life and governance	Strategy and scientific project
A+	18%	25%	32%	28%
A	58%	56%	54%	51%
B	23%	18%	11%	19%
C	2%	2%	4%	2%
Non noté	-	-	-	-



7 • Supervising bodies' general comments

UNIVERSITÉ DE STRASBOURG

Monsieur Pierre GLORIEUX
Directeur de la Section des Unités de recherche
Agence d'évaluation de la recherche et de l'enseignement supérieur (AERES)
20 rue Vivienne
75002 PARIS

Alain BERETZ
Président

Strasbourg, le 6 mars 2012

Objet : Rapport d'évaluation de l'UPR 9021 Immunopathologie et chimie thérapeutique (réf. S2PUR13000-RT)
Réf. : AB/EW/N° 2012-100

Affaire suivie par
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Direction de la recherche

Cher collègue,

Je vous remercie pour l'évaluation de l'unité propre de recherche « Immunopathologie et chimie thérapeutique » (CNRS UPR 9021) dirigée par Madame Sylviane Muller.

Vous trouverez ci-joint les réponses du directeur d'unité de recherche à ce rapport d'expertise. Cette réponse comporte :

- les demandes de corrections d'erreurs factuelles, auxquelles il conviendra d'apporter la plus grande attention. Je vous recommande de donner suite à toutes les demandes de retrait d'informations mentionnées par Madame Muller ;

- les précisions et commentaires de Madame Muller sur le rapport d'évaluation, pour lesquels je n'ai pas de remarque particulière à ajouter au nom de l'Université.

Je vous prie d'agréer, Cher Collègue, l'expression de mes sentiments distingués.

Par délégation du Président
de l'Université de Strasbourg
Michel DENEKEN
Premier Vice-Président

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P.J. :

- **Une première partie corrigeant les erreurs factuelles**
- **Une seconde partie comprenant les observations de portée générale**

UPR 9021 Immunologie et Chimie Thérapeutiques
Institut de Biologie Moléculaire et Cellulaire -Strasbourg-

Observations portées sur le rapport d'évaluation de l'AERES
(activité 2007-2011/ projet 2013-2017)

Observations de portée générale

General strategy

At several occasions in their report, some of the committee members criticize our decision to have one of our immunologists moving from the team 2 to the team 4 (p.4, 2nd paragraph from the bottom). This decision was taken by the "club des 13" for at least three major reasons:

1. Most of the publications by Hélène Dumortier (team 2) during the period 2007-2011 are co-authored with Alberto Bianco (team 4). It is a matter of fact.
2. We can read in page 8 line 17, the "lack of synergy of team 4 with other teams of the unit is obvious". The committee should recognize that the presence of Hélène Dumortier in team 4 was strategic to change this situation and allows Hélène and Alberto to more closely collaborate on the Nanolupus program (engineering of multi-functionalized carbon nanotubes for selective destruction of harmful B cells in SLE) presented by Hélène to ANR and the Labex Medalis funding, for example.
3. Today, there is even not a single publication on IL-21 by H. Dumortier and F. Monneaux. The IL-21 project is effectively promising (presented during the visit of committee) but totally emergent in our Unit. It is therefore extremely risky.

The committee proposes to fuse teams 2 and 4 (p.3, repeated in p.5): this idea is not reasonable and would weaken the visibility of each team.

TEAM 1

- Several times the committee states that our group does not appear to collaborate with groups working on SLE genetics and particularly GWAS (p.4 last paragraph, p.5 last paragraph, p.8 4th paragraph, p.13 13th paragraph): team 1 has collaborations with groups working on mouse SLE genetics (Laurence Morel, Florida, US). Collaborations with groups working on human SLE genetics are in underway. This may have not appeared during the presentation/discussion but obviously Team 1 carefully and regularly assesses GWAS and replication studies on SLE and compares them with their transcriptoma data.

- The committee points out a weakness in attracting international PhD/post-doc fellows and in valorization of results and industrial collaborations (p.13, lines 17-18). If Team 1 succeeds in obtaining an ANR funding this issue should not be a problem any longer. Also, valorization of their transcriptoma results will depend on the analyses performed in their larger cohorts (PHRC and LBBR)

- The committee writes: "The possible therapeutic targets of B cells are questionable due to the latest negative results on B cell depletion therapies in SLE patients" (p.12, 6th paragraph). The committee is perhaps not informed that there is a general agreement among the scientific/MDs community that the negative results raised in the two main controlled studies on B cell depletion in SLE were mainly due to significant flaws in the design of clinical trials.

- There are contradictory messages by the members of the committee regarding the axis of "autoimmunity-infection" developed in Team 1: the project is said "less original" (page 8), "an original approach" (page 10, line 13), "not an original approach" (page 10, line 36). This axis is still highly controversial in the community of clinicians and although some experimental animal models have been characterized, the mechanisms relevant to human autoimmune diseases remain largely unknown.

- Page 11: The team leader has effectively been invited to give presentations in national/international meetings on autoimmunity/rheumatology. This has been omitted in the report book, it is our mistake and we apologize.

-Symposium on "Advances in Studies of Innate Defenses, Diseases Models and Development". Weizmann Institute of Science. Rehovot (Israel 2010): new mechanisms for the antiphospholipid syndrome.

-1ères Rencontres en Immunologie et Immunopathologie pratiques (RIIP). (Paris 2011). Circonstances diagnostiques du syndrome des antiphospholipides.

-Congrès National de la Société Française de Médecine Interne (Ajaccio 2009). Les cryoglobulinémies.

-Congrès National de la Société Française de Médecine Interne (Paris 2011). Les marqueurs pronostiques du lupus.

TEAM 2

No comment

TEAM 3

- Page 19, 14 lines from the bottom ("The team was previously more scientifically distant from the main theme of the unit….other teams"). This sentence is unclear and should be rephrased. If we correctly understand the sense, it is rather a positive evolution since the last evaluation of Team 3 and therefore should be inserted in the section "Strengths and opportunities" rather than in "Weaknesses and risks".

TEAM 4

We agree that carbon nanotubes can be considered one of the numerous drug delivery systems, however the chemistry on carbon nanotubes is not trivial and it is not performed just by simply applying known recipes. Since ten years team 4 is developing new approaches to functionalize carbon nanotubes towards their applications in biomedicine. Team 4 was a pioneer in this field by conducting the first studies on the use of carbon nanotubes as new drug delivery system (Pantarotto et al. Chem Commun. 2004 has received more than 450 citations). Team 4 is one of the national and world leaders on carbon nanotubes and not simply "one of the several groups exploring a CNT-based strategy" (page 21). The papers published by team 4 are highly cited and represent milestones in the development of this new technology for biomedical applications. Just to cite a few examples: the works on the double functionalization of CNTs have received more than 330 citations (Wu et al. Angew. Chem. Int. Ed. 2005; Pastorin et al. Chem. Commun. 2006). Overall, the work on nanotubes of team 4 has received more than 7000 citations since 2002 (Source Web of Science: 27 February 2012).

The preparation of functionalized carbon nanotubes is not simply a pharmaceutical recipe by mixing the different components. It requires a thorough understanding and characterization of the final products, fundamental to test them in vitro and in vivo. Moreover, the development of multi-functionalization strategies is crucial to allow conjugation of carbon nanotubes with a wide variety of molecules with therapeutic, targeting and/or imaging capability.

Concerning the integration with the other teams, it is clear that grant applications on use of carbon nanotubes on SLE are continuously submitted (e.g. Nanolupus project). The team has been working on this subject for the last few years, with the limitations related to a lack of financial support.

Team 4 is already working on the in vivo proof-of-concept using carbon nanotubes. In particular, team 4 is analyzing the impact of chemical functionalization, the potential degradation and the pharmacokinetics of administered nanotubes. These aspects are clearly pursued in the future plan of the team. Team 4 is also focusing on the multi-functionalization of carbon nanotubes for targeted drug delivery to improve specificity and efficiency of drugs.

Recently team 4 has started to investigate dendron structures based on adamantane because this rigid molecule with a well-defined three dimensional conformation can bring further advantages to the dendritic structure for studies of multivalent ligand/receptor interactions and design of novel carriers for the delivery of therapeutic molecules. Dendrimer-based carriers can be considered a possible

alternative to functionalized carbon nanotubes as they combine biocompatibility to intrinsic biodegradability.

Many of the projects are financed (EU grants, ANR); therefore personnel will be recruited to reinforce the team.

Finally, the project on the nucleopeptides has been stopped because of a strategic decision, rather than because of a “limited success” (page 21). Indeed, this project was developed by a PhD student in co-direction between team 4 and the University of Padova (Italy). Three publications already appeared and a fourth is in preparation. Team 4 has decided to stop this project as there was not the possibility to continue the collaboration, and because the team wishes to focus the future projects mainly on carbon-based materials.