Département de biologie structurale et chimie

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Département de Biologie Structurale de l'Institut Pasteur (URA 2185, URA 2128)

From the

Institut Pasteur

CNRS

December 2010

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

Section des Unités de recherche

AERES report on the research unit

Département de Biologie Structurale de l'Institut Pasteur (URA 2185, URA 2128)

From the

Institut Pasteur

CNRS

Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

December 2010

Research Unit

Name of the research unit :

Département de Biologie Structurale de l'Institut Pasteur

URA 2128 : Chimie Organique

URA 2185 : Biologie Structurale et Maladies Infectieuses

Requested labels : Two URAs

N° in the case of renewal: URA 2185 and URA 2128

Name of the director:

Département de Biologie Structurale : M. Michael NILGES.

URA 2185 : M. Marc DELARUE.

URA 2128 : Ms Sylvie POCHET.

Members of the review committee

Committee chairman :

M. Rob RUIGROK, Université Joseph Fourier, Grenoble, France

Other committee members :

M. Chistoph W. MÜLLER, EMBL, Heidelberg, Germany

M. Johannis P. KAMERLING, Utrecht University, Holland

M. Christian GRIESINGER, Max Planck Institute, Göttingen, Germany

M. Yinon Ben NERIAH, Hebrew-University-Hadassah Medical School, Jerusalem, Israel

M. Emmanuele PACI, University of Leeds, England

Ms Françoise COLOBERT, Université de Strasbourg, France (CoNRS)

M. Philippe WALTER, CNRS, Strasbourg, France (CoNRS)

M. Per BRANDTZAEG, University of Oslo. Norway (Pasteur Scientific Council)

M. David SIBLEY, Washington University Sch. of Med., USA, (Pasteur Scientific Council)

Observers

AERES scientific advisor

M. Yves GAUDIN

University, School and Research Organization representatives

M. Thierry MEINNEL (INSB, CNRS)

M. Tony PUGSLEY (Institut Pasteur)

Report

1 • Introduction

• Date and execution of the visit

The visit took place on December 6 and 7, 2010. This AERES visit coincided with the evaluation of the department by the Pasteur Institute. This was the reason why the review committee included two members of the scientific council of the Pasteur Institute (IP). The members of the review committee had two roles; first to review the scientific groups for AERES and second to provide additional reviews to the scientific council of IP on the groups that will close and that did not present a scientific project as a group plus on the technical platforms that do not have an independent scientific program. Because the Pasteur Institute wanted to have answers to several questions, the committee met with the scientific director and the director of scientific evaluations on the evening of December 5th. On the 6th and the morning of the 7th the committee met with the directors of the two URAs and the director of the department and with all the leaders of the scientific groups. The afternoon of the 7th was used for deliberations and on the morning of the 8th December the committee met with the scientific council of IP to report on the groups evaluated for AERES and on the non-evaluated groups and the platforms.

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

The department of structural biology and chemistry (DBSC) was created in 2001 by unifying structural biology groups that were associated with other departments. The organic chemistry unit was completely reorganised in 2005 and consists now of two groups and a laboratory of one person. The committee did not have the time to visit all the laboratories but the directors of the URAs told that the laboratories are scattered throughout the institute and that the organic chemistry groups are far away from the structural biology groups.

The department is principally concerned with the determination and computational analysis of the 3D structures of proteins, nucleic acids and oligosaccharides, which is essential for understanding their function at molecular or atomic level. The specificity of structural biology is that it attempts to explain the processes in a healthy cell, or the processes that are involved in disease, by the fundamental laws of chemistry and physics. Therefore, there is a very strong activity on methods development in structural biology and modelling of structures and structural changes based on physics laws. Further, there is a very strong activity on identifying drug targets for infectious diseases and on drug and vaccine development.

• Management team

The head of the Department is Michael NILGES with Daniel LADANT as deputy head. The director of the organic chemistry unit (URA 2128) is Sylvie POCHET, who also heads a group and the director of the Structural biology and infectious diseases unit (URA 2185) was Muriel DELEPIERRE but this will be taken over by Marc DELARUE for the next 4 years. The members of the structural biology unit identify very strongly with the department and did not even show an independent organigram. The members of the chemistry unit identify much less with the department and form a homogeneous group of people that are located away from the structural biology groups. Although the roles of the heads of CNRS URAs are clear because similar to that of other CNRS unit heads, the role and power of the head of the Department appeared less clearly defined to the AERES committee.

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

Département BSC	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	16,8	14,8
N2A : Number of full time researchers Pasteuriens	27	25
N3: Number of postdoctoral fellows	21	20
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	2
N5: Number of engineers, technicians and administrative staff (Form 2.6 of the application file)	58,25	52,25
N6: Number of Ph.D. students (Form 2.7 of the application file)	20	22
N7: Number of staff members with a HDR or a similar grade	31	33

URA 2185	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	13,2	11,2
N2A : Number of full time researchers Pasteuriens	21	19
N3: Number of postdoctoral fellows	17	18
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	1
N5: Number of technicians and administrative staff (Form 2.6 of the application file)	38,45	33,45
N6: Number of Ph.D. students (Form 2.7 of the application file)	19	21
N7: Number of staff members with a HDR or a similar grade	26	28

URA 2128	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3,6	3,6
N2A : Number of full time researchers Pasteuriens	4	4
N3: Number of postdoctoral fellows	4	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of technicians and administrative staff (Form 2.6 of the application file)	8,8	7,8
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	1
N7: Number of staff members with a HDR or a similar grade	5	5

2 • Overall appreciation on the research unit

- **Summary**

URA 2185 is a very good structural biology unit with some excellent groups and excellent visibility.

URA 2128 is a good organic chemistry unit but has to work on being more visible.

The added value of having a Department structure on top of both URAs is not obvious, mainly because only the members of URA 2185 identify with the Department and not those of URA 2128.

- **Strengths and opportunities**

The strength of this department is the fact that it is part of the Pasteur Institute making valuable in house collaborations possible. The combination of different structural biology, biochemistry and computational biology approaches for the determination of structures of complexes is very promising. The combination of structural biology and organic chemistry is an opportunity that should be transformed into a strength. The fact that two research groups from URA 2185 will retire should allow reinforcement and focus of research projects and the development of world class electron microscopy.

- **Weaknesses and threats**

At the moment there is no focused research theme in the department and the departure of two groups should not lead to a further dispersion in themes but rather to refocusing. Although most structural biology groups are widely recognized and visible, the visibility of the chemistry groups is limited. At the moment, the medicinal chemistry activity is far below its critical mass.

- **Recommendations**

The department should make an effort to integrate the structural biology and organic chemistry units and make better use of their complementarities. For URA 2128, the department should make a decision whether in-house

medicinal chemistry is a necessity and act accordingly. For URA 2185, the department should reinforce electron microscopy with hiring a senior group leader and use the possibility of the retiring groups for bringing focus in the research projects. In this respect a senior group in electron microscopy could be an integrating force for the department.

- **Production results**

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

Department BSC	
A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2 and N2a) who are active in research	44,8
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	19
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2 + N2a)]	0,977
A4: Number of HDR granted during the past 4 years	6
A5: Number of PhD granted during the past 4 years	20

URA 2185	
A1: Number of permanent researchers with or without teaching duties (recorded in N1, N2, N2a) who are active in research	37,2
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	17
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2 + N2a)]	0,975
A4: Number of HDR granted during the past 4 years	6
A5: Number of PhD granted during the past 4 years	18

URA 2128	
A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2, N2a) who are active in research	7,6
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	2
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2 + N2a)]	1,0
A4: Number of HDR granted during the past 4 years	0
A5: Number of PhD granted during the past 4 years	2

3 • Specific comments

- **Appreciation on the results**

The research in the department is related to infectious diseases (*M. Tuberculosis, Listeria monocytogenes, B. Pertussis, S. Aureus, S. pneumonia, Plasmodium falciparum*) and, thus, of strong relevance to all of us. The computational biology groups are of very strong importance to the structural biology community worldwide, in particular for groups that use NMR since some of the most used NMR analysis methods come from this department.

The members of the department published 482 papers. The average level of publications of the department is good, many publications in journals like Mol. microbiol., J. Biol. Chem., J. Mol. Biol. with a few papers in journals like JACS and PNAS and some exceptional papers like in Science (2 in 2005) and Nature (2006, 2009). However, many papers from the department, in particular from some chemistry groups, are from collaborations with other Pasteur or outside groups and do not describe the research subjects of the department. Some groups have had many students but other groups, in particular the chemistry groups did not have many students and, thus, only very few theses. Many groups have impressive lists of patents but only very few of these are licensed.

Most of the groups collaborate with the other groups in the department and most groups have collaborations with Pasteur groups outside the department. All but two groups are coordinators or collaborators of international grants (EU, HFSP).

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

With the exception of two groups, the level of international recognition through invitations to international conferences is very high. All but two of the group leaders have received French national awards (prizes from the Fondation de France, Académie des Sciences and bronze medals of the CNRS).

Due to the high international visibility of the Pasteur Institute it is absolutely no problem to attract people from abroad even though the majority of students is French.

All groups but one are collaborators or coordinators of multiple ANR grants, all but two are part of EU networks and others have extensive funding from industry. All groups have major sources of funding from outside.

Because the IP is such a large and excellent institution, many collaborations are necessarily with the other IP departments and such collaborations are stable. However, almost all groups have collaborations with foreign partners and have co-published with them. Many groups have research partnerships with private industry (pharmaceutical, chemical, computational industries) and are financed through these partnerships. Most groups have published patents since 2005 although only very few of these patents are licensed.

- **Appreciation on the management and life of the research unit**

The relevance of the organisation of a Department containing two CNRS research units (URAs) is not obvious. In particular the organic chemistry unit does not feel part of the department and students from this unit do not often meet the other students of the department even though there are two-weekly department seminars. The students asked for more student activities and were apparently not aware that IP has a very active student organisation that organises many events and seminars for the PhD students. The Department does not organise journal clubs, student seminars etc that would put the students forward and that would force them to present their work.

Apart from the two-weekly Department seminars there was no mention of other scientific animation. However, among the structural biology groups there is communication on the development of techniques that are presently absent in the department such as electron microscopy. For this reason a 5 year group started in 2009. An additional senior electron microscopy group could be an additional integrating element of the department that would further

strengthen the interactions of the two computational biology groups with the other structural biology groups. In some respects, the department seems to be more an organisation of infrastructure for the structural biology groups rather than a breeding ground for cutting edge initiatives.

There is only one university professor associated with the department although all groups are active in teaching at a local level, in particular in the courses organised by IP. Only a few groups are involved in international courses. The department is responsible for organising the local and Ibisa platforms for structural biology that will be brought together in a single structure called the Proteopole.

- **Appreciation on the scientific strategy and the project**

There is neither a single project for the department nor for the two URAs. Every group has its own scientific project that was only little developed in the written report and not really addressed in the oral presentations. Most groups announced that they would further develop the research that they were doing already. The committee noticed the absence of reflections on where the field would be in 5 years time, which, in a way was surprising since all groups have external financing for which such projections are necessary. The department could benefit from a joint ambitious project.

The committee did not receive much information on resources other than personnel paid by IP. It appears that the allocation of resources is decided directly by the scientific direction of IP and depends on past results, without much implication from the department.

The committee was very impressed with the sugar chemistry that is of a very high level and that aims to make antimicrobial vaccines. The computational biology groups develop new approaches for structural biology and, in particular, the method developments to determine structures from sparse data from various sources (hybrid approaches) are cutting edge and of great interest for the world-wide structural biology community. The recent results on membrane proteins from the malaria parasite will be of very high importance to the community.

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

URA 2128 E1 Chemistry of Biomolecules (Laurence MULARD)

- **Staff members**

URA 2128 E1	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N2A : Number of full time researchers Pasteuriens	4	4
N3: Number of postdoctoral fellows	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of technicians and administrative staff (Form 2.6 of the application file)	4,3	3,3
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	0
N7: Number of staff members with a HDR or a similar grade	1	1

- **Appreciation on the results**

In the context of the continuous battle against diseases, the research projects of the group are highly relevant. The chemical biology approaches of the group have their basis in the chemical synthesis of carbohydrates, peptides, and glycopeptides.

In the framework of developing carbohydrate-based conjugate vaccines against pathogenic bacteria, the choice for *Shigella flexneri* serotypes is timely and excellent. Due to the inherent immunological problems with polysaccharide-based vaccines, the development of synthetic, structurally well-characterized oligosaccharide-protein conjugate vaccines, based on the use of fragments of the related capsel and lipopolysaccharides (LPS), gets more and more attention, also from the vaccine industry. The choices for how to synthesize multiple repeating units of the LPSs of different serotypes of *S. flexneri* are original, including the recently developed enzymatic approaches for attaching glucosyl side chains. The deep focus on the serotypes 2a and 3a in terms of synthesis and immunological evaluation of the prepared fragments (induction of the right antibodies in mice) has led to definite choices for optimal epitopes, and a SF2a-TT15 neoglycoprotein candidate vaccine, built up from three reperating units of Rhaα2Rhaα3(Glcα4)Rhaα3GlcNAcβ2 (in total 15 monosaccharides) coupled to tetanus toxoid, is in place for phase I clinical trials. Besides the synthesis of the oligosaccharides, also attention is paid to understanding the induction in terms of mAb recognition and conformational behaviour (NMR, X-ray, modelling, antigenicity data). All the planned activities, i.e. focus on additional related *S. flexneri* serotypes, the introduction and evaluation of O-acetylation patterns, the continuation of the physico-chemical studies, the shortening of organic chemical routes by incorporation of enzymatic steps) are very well chosen, and of high importance for a further exploration of this difficult field.

The chosen strategies for the research line on synthesizing glycopeptides for anti-cancer immunotherapy making use of glycotripeptides (αGalNAcSer-αGalNAcThr-αGalNAcThr) in a multivalent synthetic concept (thereby presenting the Tn-epitope GalNAc in a multiple way) are original, and turned out to be successful. Note that the Tn antigens in mucins are masked in normal tissues, but they are expressed by several adenocarcinomas (e.g. breast, ovarian, colon, lung, prostate), and the focus is to induce therapeutic immunity against cancer cells through the induction of an anti-Tn antibody response. The generated synthetic immunogen, called MAG-Tn3 (universal CD4+ T cell epitope is a component of MAG), gave successful results in mice and primates, and was selected as a vaccine candidate for a phase I/II clinical trial. The planned activities focused on a broadening of possibilies for Tn presentation are challenging, and promising strategies for preparing conjugates of GalNAc-glycopeptides of mucin epitopes and the universal CD4+ T cell epitope have been worked out. Here, an evaluation for therapeutic properties against breast and/or pancreas tumors is planned.

Also the research line of synthesizing glycoconjugates as antivirals to fight AIDS can be considered as original. The conjugates are built up from mCD4g, a new 26AA mini CD4, and a heparine fragment (6 repeating sulfated disaccharides), coupled via the single lysine residue present. The resulting mCD4-HS12 product turned out to be a very potent anti-HIV drug when evaluated on peripheral blood mononuclear cells. The planned activities will focus on the in vivo potency of the drug whereby higher amounts of material are necessary, the exploration of more simple HS analogues including peptide-based HS mimics, and a further evaluation of their inhibiting properties.

Besides the mentioned main stream activities there is a continuous need for synthesizing relevant peptides for other IP internal and external projects, e.g. NEMO inhibitors, cell penetrating peptides, and diagnostics tests against paratuberculosis, all projects that are of high relevance.

In conclusion, overall the quality of the synthetic activities is good and the impact of the results so far is highly promising.

Output 2005-2010:

48 Scientific papers, although only 15 as first and/or last author by group members, in good to very good chemistry or biochemistry journals (1 J. Biol. Chem., 1 Nat. Chem. Biol., 1 Glycocon. J.) biology journals (2 J. Immunol. and 1 Blood) and chemistry journals (1 Glycobiology, 1 Tetrahedron, 1 J. Org. Chem., 1 Glycoconj). Collaborative work was published in a paper in JACS, a paper in PNAS and more in J. Biol. Chem., Blod and Vaccine. The group deposited 13 patents and 1 thesis was submitted. The published papers are of good quality, and taking into account the type of research (synthesis of carbohydrates, glycopeptides, and peptides in a biological / medical context), the various journals, chosen for the output, clearly reflect the multidisciplinarity of the work.

The various collaborations of the group, necessary to reach optimal results with the compounds synthesized, and to get insight into the relevant interaction phenomena, are of good quality and stable.

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

In 2004, the group leader has received the BioVision 2004 Award from Aventis Pasteur. In the period 2005-2010 the group has presented 41 scientific lectures and 15 poster presentations. Of the 41 scientific lectures, 13 were presented as invited speaker at national or international meetings.

The research lines give clear possibilities for raising funds in different ways from various sources. For the moment international grants are donated by the Research Council of Norway (ENTVAC) and by the EU (FP7 ; STOPENTERICS, an international network, wherein 14 institutional partners are involved), national grants by MENRT, ANRS, and ANR PCV, and an institutional grant by DARRI. It is expected that the type of work is of high interest for industrial collaborations. Also the Mizutani Foundation for Glycoscience will be a new possibility to raise extra financial support. For industrial collaboration, the outcome of the clinical trials with the S. flexneri oligosaccharide-TT conjugate vaccine candidate (infectious disease) and the MAG-Tn3 vaccine candidate (cancer) will be of the utmost importance.

The recruitment of high level scientists is restricted by internal rules of Institut Pasteur. The recruitment of more post-docs and PhD students needs special attention.

- **Appreciation on the scientific strategy and the project**

The planned future activities have been thoroughly worked out, are highly relevant, and will bring the total activities to an even higher level. They are defiant and appear all feasible. So far, they are restricted to an organic chemical approach, but it may well be that alternative routes finally have to be explored to reach the planned results. In this context the demonstrated possibilities of combining chemical and enzymatic routes is challenging. In view of the great expertise in the group, problems are not expected. In order to carry out the synthesis of larger amounts of material for the clinical trials under GMP rules, subcontractors have been included.

The various research lines have been chosen very careful and are original. Although strong competition exists in the field of developing carbohydrate-based vaccines against different types of infections and cancer, the specific topics explored in the group can compete with related activities in the glycobiology and glycomedicine field. The importance of developing carbohydrate-based drugs has been stressed in the European Science Foundation Policy Briefing no. 27 (July 2006) « Structural Medicine: The Importance of Glycomics for Health and Disease ».

- **Conclusion :**

— Summary

The research on developing innovative chemical/enzymatic strategies towards probes, diagnostic tools, glycotherapeutics, or glycovaccines is of high quality. The major activities are focused on glyco-related topics and are highly promising. The very specialistic expertise that is necessary to bring such challenges to success, is very well present. The arrangement of the various activities is in good balance. On one hand, the initial synthetic work has led to promising vaccine candidates, ready for further evaluation in clinical trials, whereby subcontractors are involved in synthesizing the right amounts. On the other hand, the academic activities in the group are focused on new synthetic leads and a better understanding of the biomolecular interactions between the synthetic molecules and their counterparts.

— Strengths and opportunities

-The available infrastructure and the knowledge of the leading scientists are perfect for doing the chosen research.

-The chosen projects make clear how great the opportunities of combined carbohydrate and peptide chemistry are in the battle against diseases.

-The growing interest in glycoscience worldwide, in relation to medical problems, can give the group (and Institut Pasteur) a dominant position in this field.

-The group could also function within the Institut Pasteur as a center of knowledge for glyco-related questions (fungal and bacterial polysaccharides, glycosylated proteins and lipids, proteoglycans), i.e. a center of (chemical) glycobiology.

— Weaknesses and threats

The weaknesses are mainly in the low number of PhD students and post-docs. In view of the chosen projects, there are no real threats. However, the visibility of the group as a whole should be improved since only one of the external presentations was done by another than the group leader.

— Recommendations

- Attention should be paid to the possibilities of recruiting more PhD students and post-docs.

- Apart from the group leader, the two other senior scientists should also present their work in invited lectures at national and international meetings.

URA 2128 E2 Chemistry and Biocatalysis (Sylvie POCHET)

- **Staff members**

URA 2128 E2	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2,6	2,6
N2A : Number of full time researchers Pasteuriens	1	1
N3: Number of postdoctoral fellows	1	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of technicians and administrative staff (Form 2.6 of the application file)	3,4	3,4
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	1
N7: Number of staff members with a HDR or a similar grade	3	3

- **Appreciation on the results**

The group is composed of 2 chemists being experts in nucleoside chemistry and 2 biochemists with expertise in nucleoside related enzymes. It is divided in three teams: The first is involved in the synthesis of nucleosides analogues as potential therapeutic agents, the second in the development of biocatalysts and therapeutic targets from nucleoside metabolism whereas the third team deals with the essay development and chemical library screening.

The group is involved in the identification of inhibitors to develop compounds as therapeutic agents against *M. tuberculosis* TMPK, NADK from Gram-positive bacteria, NDT family etc. Different strategies like structure-based drug design, fragment–based approaches and screening of chemical libraries are used to identify inhibitors. Another focus of the group is to identify nucleoside analogues as biochemical tools for the investigation of biochemical processes. During the last 4 years the group identified potent inhibitors of TMPKmt which may represent a new class of anti tuberculosis inhibitors. Different classes of compounds were synthesized as substrate mimics based on benzyl-pyrimidine skeletons. Compound optimization is underway in collaboration with two teams, one in Spain and one in Montpellier.

Another interesting target is UMPKmt that has been very recently characterized and behaves like a Gram-positive bacterial UMPK. The 3D structure of UMPKmt/GTP was determined by X-ray crystallography and structure-activity relationships are underway with the « Institut Curie ».

Moreover, using a fragment-based approach, they synthesized a library of various nucleotides (250 compounds) based around selected scaffolds. The importance of this fragment approach strategy has been recognized by the attribution of an ANR blanche grant and allowed a specific recognition of nucleosides analogs by NAD Kinases and the discovery of micromolar inhibitors with bactericidal activities. This methodology is very promising and the design of the compounds will be reviewed to improve affinity, specificity and biological stability. This work will be done in collaboration with a group in Montpellier and in Bergen, Norway.

A new member of the NDT family has also been characterized with unprecedented specificity: the synthesis of unnatural 2'-deoxynucleosides has been performed by an enzymatic process using NDT-II from *L. leichmannii*. For the investigation of enzymatic mechanisms, the group developed efficient access with original synthetic schemes to a

series of nucleoside analoguess based on an imidazole skeleton efficiently converted into the corresponding 2'-deoxynucleosides using NDT.

The screening facility allows them to identify hits as anti-infectious and anti-cancer agents. This facility is open to collaborations with other groups at Pasteur Institute.

In conclusion the topics involved in this group are promising. Compound optimization is underway in each ongoing project using the expertise in chemistry and may lead to fine-tuning the inhibition of the corresponding enzymes.

Output 2005-2010:

29 Scientific papers but only 7 of these have first and/or last authors from the group members (2 in J. Biol. Chem and 1 in J. Mol. Biol.). Collaborative work was published in Ang. Chem. Int. Ed. (Engl.), Nucl. Acids Res., J. Biol. Chem., PNAS and Blood. 10 Patents were deposited including one licensed by Roche ; 1 thesis defended in 2006. The published papers in journals of chemistry are good showing the expertise of the group for the efficient synthesis of nucleoside analogs. The papers in biology and medicinal chemistry reflect the high number of national and international collaborations leading to co-publication with many authors. In the screening activities two patent applications have been filed and one is underway. A start-up will be created at the end of 2010 based on these 2 patents.

Various collaborations exist with national and international partners specialized in each field leading to co-publication.

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

No awards have been received. One invitation for a seminar was reported in order to present the screening facility at Pasteur Institute and two oral communications have been given at national conferences. This group has to increase the occasions to present their work.

During the last 4 years the group received national funding (1ANR-2 Carnot) and institutional funding from Pasteur institute. No private funding was mentioned.

Various collaborations exist with foreign partners in Spain for the development of NMPKmt inhibitors, in Bergen, Norway for NADK inhibitors, in Cornell and Baltimore for the NDT family project and in Japan for the investigation of biochemical processes.

10 Patents including one licensed by Roche have been filed.

The recruitment of more PhD students is important. Chemical synthesis is time-consuming and needs a lot of hands. Apart from that, students keep laboratories lively and push established personnel to new vistas.

- **Appreciation on the scientific strategy and the project**

The team will be pursuing ongoing projects with the aim to optimize recently identified inhibitors for the development of antibacterial agents.

In the research program concerning the enzymes NMPKs (nucleoside monophosphate kinases) including UMPKmt, the development of dedicated fluorescent nucleosides to investigate the catalytic sites of NMPKs has been proposed.

- **Conclusion :**

— Summary

Good chemistry group with good potential that can considerable contribute to their important research projects. Taking into account the identified inhibitors in ongoing projects, the future is promising and needs a fine-

tuning of the chemical structure of the inhibitors to obtain better activities or better investigations of the biochemical processes.

— Strengths and opportunities

The expertise in organic chemistry is indisputable and it would be very useful to improve the activity of inhibitors in each project.

— Weaknesses and threats

The visibility of the group is minimal and needs to be reinforced. The group needs to concentrate more on its own research subjects and publish on the group subjects. They should learn how to sell their results obtained in these highly relevant topics, which also means publications in higher impact factor journals.

One of the important weaknesses is also the lack of PhD students because if the chosen projects are to be successful the number of students must be improved.

— Recommendations

This big group with four senior scientists needs to work hard on getting younger people and publish papers on its own research rather than on research in collaboration and in higher standard journals. They also need to improve their national and international visibility.

URA 2128 E3 Medicinal Chemistry (Yves JANIN)

- **Staff members:**

URA 2128 E3	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N2A : Number of full time researchers Pasteuriens	0	0
N3: Number of postdoctoral fellows	2	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of technicians and administrative staff (Form 2.6 of the application file)	0,10	0,10
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	0
N7: Number of staff members with a HDR or a similar grade	1	1

- **Appreciation on the results**

In the period 2006 to 2010 the scientific themes were divided in two parts:

- The synthesis of a dibenzofurane family with antimycobacterial effect was done in collaboration with a team at the Université Paris Descartes and was supported by a grant from IP and a European Community project (ND4TB).

Little success from a biological point of view was obtained, but it has allowed the development of efficient new synthetic accesses to benzofuran-featuring compounds.

- Alkoxypyrazoles with anti infectious potential, in collaboration with a team at ICSN supported by Medicen "Pôle de Compétitivité" and the Ile de France region, were synthesized and the activity of 3-alkoxypyrazoles was explored. The reactivity of these 3-alkoxypyrazoles was then studied and new synthetic pathways were developed giving access to new pyrazole derivatives. The intellectual properties aspects of these efficient methodologies are being evaluated by the Department of Valorisation of the Pasteur institute. Among these is the biological activity of a series of new chemical entities as original antimycobacterials.

Output 2006-2010:

The results of the group demonstrated a good expertise in the synthesis of pyrazoles derivatives (6 publications, 3 patents). Taking into account the small team, the scientific production is good; 16 publications (14 of which with the group leader as senior author) in journals of organic and bioorganic chemistry with good impact factor and a total of 4 patents during the period.

Collaborations were developed essentially outside the Pasteur institute for the design and synthesis of chemicals.

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

-The work done in this group should be more presented outside the Pasteur institute at national and international conferences. There has been only one invitation to give a seminar at Romainville and 3 oral communications in national congresses.

-During the period 2006-2010, no PhD student has been recruited in the laboratory. Four post-doc students were hired in the group since 2006 and only one is currently in the laboratory.

-National funding (2 Medicen-1 Carnot) and international (1EU) and institutional (6 IP) grants have been obtained and allowed to buy consumables and pay salaries for the post-doc students.

-There are a number of collaborations inside of the Pasteur Institute and with other groups in Paris but not outside.

-Although the chemistry has been patented, the biological consequences of the molecules are not known mainly because of solubility problems.

- **Appreciation on the scientific strategy and the project**

No clear scientific project is presented other than continuing the chemistry on past projects.

Two parts are relevant in the future:

- New chemical entities have been pointed out with an unprecedented effect on *M. bovis* BCG, and analogues will be synthesized introducing various substituents and SAR will be performed. Furthermore, a new synthetic approach in only three steps will be developed.

- Some structure-activity relationship studies on an original target against malaria in collaboration with a group at the Pasteur institute is undergoing.

- **Conclusion :**

— Summary

This small group (one permanent researcher) involved in medicinal chemistry proved to have an excellent expertise in pyrazoles synthesis and to be efficient in the synthesis of various chemical entities. However, to

efficiently develop activities in medicinal chemistry and to force the discovery of biologically active compounds, this group needs more hands for the chemistry part, although the hiring of students is restricted because of a too small current laboratory surface. The question is therefore whether the Pasteur Institute wants to increase the impact of medicinal chemistry. If not this group has no chance to be more active. A more intensive collaboration with other groups at Pasteur institute will also be relevant in order to identify series of compounds to be synthesized and screened for their biological activities.

— Strengths and opportunities

Considering the very small size of the group the amount and quality of publications was rather good.

— Weaknesses and threats

The group is presently too small without PhD students. The national and international visibility is almost absent. There was no clear scientific project presented.

— Recommendations

This group should either be reinforced at the Pasteur Institute or the group leader should look for a different and more adapted environment in order to make better use for his good chemical expertise.

URA 2185 E1 Structural Biochemistry (Pedro ALZARI)

- **Staff members**

URA 2185 E1	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	1
N2A : Number of full time researchers Pasteuriens	3	2
N3: Number of postdoctoral fellows	3	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of technicians and administrative staff (Form 2.6 of the application file)	5	4
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	3
N7: Number of staff members with a HDR or a similar grade	2	2

- **Appreciation on the results**

The group studies molecular mechanisms of signal transduction and regulation in bacteria with special emphasis on *Mycobacterium tuberculosis*. Initially, the group was involved in a structural and functional genomics approach to identify and validate novel drug targets in *M. tuberculosis*. During the last five years, the group has been focusing on fewer classes of regulators and processes such as eukaryotic-like kinases and phosphatases in mycobacteria, histidine kinases and two-component systems and bacterial regulators. The work of this group is original and potentially of great relevance for human health. The structural information is taken as a starting point for further mechanistic validations (i.e. site-directed mutagenesis, enzymatic analysis, inhibitors, etc.).

Output 2005-2010

The scientific productivity of the group is high with 80 manuscripts published 2005-2010, 41 of which with a first and/or last author from the group. Results of the group are generally published in good international journals (3 J. Biol. Chem., 2 J. Mol. Biol., 1 Nucl. Acids Res., 1 Biophys. J., 3 PNAS, 3 Mol. Microbiol., 2 Structure, 1 Nature Chem. Biol.). However, relatively few publications are in the highest profile journals. Highlights during the reviewing period since 2005 have been the structural and biochemical analysis of the *Trypanosome cruzi* proline racemase (PNAS, 2006). PPM posphatase from *Mycobacterium smegmatis* (Structure, 2007), the structure-function analysis of a thermosensor histidine kinase from *Bacillus subtilis* (PNAS, 2009) and in collaboration the development of small molecule activators of the protein kinase PDK1 (Nat. Chem. Biol., 2009).

The group had been part of a previous, coordinated effort at the Pasteur Institute but now involves fewer groups at Pasteur Institute. The work was recently supported by the renewal of a European grant. The group continues to play a central role in running and developing different platforms including HT crystallization, protein production and biophysical characterization.

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

The group is well visible through participation in international conferences, teaching and network activities at the local and international level. The group leader obtained the Prize Jacques, George and Elias Canetti for research on tuberculosis (2006).

Roughly 1/3 of the group consists of postdocs (3) and Ph.D. students (3), while other group members are either scientists (5) or technicians (4). There are relatively few postdocs and Ph.D. students that have been internationally recruited.

The group is well supported through national and international grants. From 2005-2010 the group obtained 6 ANR grants. In addition, it was supported by an EU grant from 2006-2010 that will be renewed from 2011-2015.

The group is part of a stable scientific network based on its work on *Mycobacterium tuberculosis*. In addition, the group is well integrated into the European crystallography/structural biology community.

Work of the group resulted in a great number of crystal structures with some of them being potential drug targets. In the case of the human phosphoinositide protein kinase 1, small molecules activators were developed.

- **Appreciation on the scientific strategy and the project**

In the future the group proposes to pursue three different major topics in the area of bacterial signaling processes:

1. The role of mycobacterial PknA/PknB in the control of morphogenesis and cell division.

2. Phosphorylation dependent control of glutamate metabolism in mycobacteria.

3. Molecular basis of signal transduction and catalysis regulation in bacterial two-component *B. subtilis*.

The proposed projects are an extension and continuation of work currently pursued in the group. The projects are independently pursued by three developing subgroups but considerable cross-talk and synergy is expected. Focusing on particular biological pathways and processes appears as a sensible decision. Two of these research projects concern mycobacterial systems where the group has broad experience and well established collaborations.

As outlined in the proposal the group wants to progressively organize itself into three internal teams. No plan was presented how much this reorganization would also lead to the reallocation of resources. Unfortunately, the two junior group leaders were not present and their qualities as team leaders was therefore difficult to assess.

The structural biology of the projects is very well developed. In contrast, plans how the structural information could be further validated are less concrete. High-throughput chemical screening to identify leads for drug

development, systems-biology approaches with modeling of signaling pathways or cell biology approaches could be possible directions.

- **Conclusion :**

— Summary

The group has been mainly focusing on eukaryotic-like kinases and phosphatases in mycobacteria, histidine kinases and two-component systems and bacterial regulators. In particular, the work on mycobacterial proteins is original and of great relevance for human health. The group has been very productive with 80 manuscripts published since 2005. However, relatively few of them are in high-profile journals.

— Strengths and opportunities

The group is well visible in the international mycobacterial and crystallography communities. The group is well supported by national and international fellowships. It also plays an important role in the Institute Pasteur as the group leader oversees several platforms related to protein science. The proposed research plan is focusing on a few important bacterial signal processes where considerable synergy can be expected.

— Weaknesses and threats

The structural biology of bacterial cell signaling is well developed in the ongoing work and future plans. In contrast, follow-up studies, additional validation and the translational aspects of the structural biology work are less well developed. The group wants to reorganize into three different subgroups. The organizational and budgetary consequences of this reorganization of this reorganization need to be better defined.

— Recommendations

The research plan on bacterial signal processes with a strong focus on mycobacterial signaling appears justified and reasonable. Better integration of the structural work with microbiology, cell biology and chemical biology through in-house and/or external collaborations might increase the impact of the planned research. Reorganization of the group in three subgroups could be beneficial, but will strongly depend on the qualities and leadership skills of the three team leaders.

URA 2185 E2 Structural Dynamics of Macromolecules (Marc DELARUE)

- **Staff members**

URA 2185 E2	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N2A : Number of full time researchers Pasteuriens	0	0
N3: Number of postdoctoral fellows	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of technicians and administrative staff (Form 2.6 of the application file)	1,5	1,5
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	3
N7: Number of staff members with a HDR or a similar grade	2	2

- **Appreciation on the results**

The group of Structural Dynamics of Macromolecules is formed by two permanent researchers and two administrative/technical staff. In the past five years the Unit has produced world-class output in terms of quality.

The group uses a large array of experimental approaches (crystallography, SAXS, mutations and testing activity, biochemistry) that are often joined with computational approaches for which the group has developed new programs that are available on websites. They have tried to approach reality as much as possible without making the calculations too heavy. They study dynamics in proteins and calculate conformational paths between two end states.

The subjects are DNA polymerases involved in repair or non homologous end joining. They have determined structures, tested mutations based on structure that change dependency on template, flexibility, involvement of divalent cations outside the active site and performed structure based drug design. In collaboration with another group in IP outside the department, they work on Cys-loop receptors, allosteric receptor that changes shape and ion permeation after ligand binding (this work led to two Nature papers), simulation of molecular dynamics, anesthetics binding and designed mutants leading to the closed form. A structure inspired drug design project on an enzyme from Trypanosomas has now ended and present work on drug design on topoisomerases from Mycobacterium is ongoing. The results were published in very good to excellent journals.

Output 2005-2010

In the reporting period there were 24 publications, 17 of which with a first and/or last author belonging to the group, in journals like Nucl. Acids. Res. (5), RNA (1), Phys. Rev. Lett. (1), PNAS (1), Biophys. J. (2) and two papers in Nature (2009 and 2010). The group also wrote a book chapter and deposited a patent. This young group produced its first PhD thesis during the review period and contains presently 4 students.

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

The group has a strong attraction on foreign post docs that afterwards go on to post docs or permanent positions in France or abroad. The group has an excellent small low ratio of permanent to non-permanent staff and is strongly involved in training of young scientists as in the organisation of national or international workshops. The group leader has a very high international visibility and the other scientific member is editor of PLoS One. The group runs 3 web sites providing tools for the analysis of the dynamics of macromolecules that are widely used by the international structural biology community.

Finances were obtained from 2 ARC grants and partnerships in an ANR and an EU project. The Apple company provided funding for equipment. During the reporting period the group leader was an ARTS laureate (Apple) and received the "Prix La Case Policart-Lacassagne" from the Académie des Sciences.

- **Appreciation on the scientific strategy and the project**

This small group focuses on the study of proteins involved in DNA metabolism and cancer. One remarkable feature of this Unit is the excellence in completely different approaches to structural biochemistry. While crystallography and modelling are mostly used, other experimental techniques such as SAXS have been used. The different techniques are used simultaneously contributing to the elucidation of biological questions that single techniques have not been able to answer. Importantly, the modelling aspects are not dealt with standard approaches, but a number of original approaches have been proposed and exploited for the interpretation of experimental results. The Unit has numerous productive collaborations with different Units at IP, and with external groups for the theoretical and computational aspects of their research. The broad network of interactions established by the Unit is certainly one of its strengths. Both the proposed directions in experimental science and for the development of new methods and computing techniques are highly promising.

- **Conclusion :**

— Summary

The group of Structural Dynamics of Macromolecules has consistently performed at world-class level in the past five years in terms of research output.

— Strengths and opportunities

Its main strength is an interdisciplinary approach that combines experimental techniques, mostly, but not limited to, crystallography. There are number of opportunities of extending the collaboration to other experimental groups in IP, but also to look for synergies with the Unit of Structural Bioinformatics, particularly in the validation of alternative approaches to determine the pathways connecting alternative conformations of macromolecules. Proving the ability of theoretical approaches to help in the discovery of novel drugs or therapies needs broad synergies.

— Weaknesses and threats

The main weakness of the Unit is to be small, and the interdisciplinary approach used would benefit of specialists in different fields (although it requires coordination and focus on a well-defined agenda).

— Recommendations

For this very good group, the number of permanent staff is relatively low. The development of high-resolution cryoEM at the Pasteur Institute will be very beneficial for this group.

URA 2185 E3 Nuclear Magnetic Resonance of Biomolecules (Muriel DELEPIERRE)

- **Staff members**

URA 2185 E3	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N2A : Number of full time researchers Pasteuriens	4	4
N3: Number of postdoctoral fellows	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of technicians and administrative staff (Form 2.6 of the application file)	2,5	2,5
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	4
N7: Number of staff members with a HDR or a similar grade	5	6

- **Appreciation on the results**

The group has done well in the past four years with 56 publications in international journals. The cutting edge character of the publications is due to the combination of state of the art NMR spectroscopy with excellent biologists mostly working at Pasteur. The group has excellent output given the moderate level of the equipment that cannot be compared to the level of the equipment at other places in France. Of course this also means that the group is not always in the drivers' seat when a paper is written up. This explains why some of the most important papers listed don't have scientists from the group in the first or last position. However, it is also very obvious from these papers, that they could not have been done or published at the same level if the NMR part had been missing. The group has established itself as one of the best in France in addressing questions of biological interest.

A long standing system under investigation is the Has haeme transport system where the group has made important contributions to the field. Other projects, on transcription factors of hyperthermophilic archaea and adenylate cyclase toxins are well under way. The projects with the Rabies group at Pasteur have revealed a very interesting mechanism by exploring the weak and not so weak protein-protein interactions defining the destiny of infected neuronal cells.

Output 2005-2010

In the reporting period there were 56 publications, 25 of which with a first and/or last author belonging to the group, in journals like Biochemistry (3) J. Mol. Biol. 5), J. Biol. Chem. (5) and two papers in JACS and one in Nature Protocols. Collaborative work was published in Science and another Nature protocols. Three patents were deposited and 5 PhD theses were defended in the period and all PhDs then went on to do a post doc in excellent laboratories. The PIs were invited to numerous national and international meetings.

The Has project has been going on for more than 10 years and here the group is in the driver seat "recruiting" collaborators e.g. for crystallization studies. The rabies project is a collaboration with other groups at Pasteur as is the project on hyperthermophilic archaea and adenylate cyclase toxins. These collaborations have only just started or are going on for a longer time. Therefore, the group appears to have reliable and competent collaboration partners. Further long term collaborations are within the department but also beyond with the NMR centre in Florence (It).

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

The group contains 4 PhD students and one postdoc, indicating the potential of the group to attract students, although it seems to be desirable to increase the number of postdocs. The group consists of high level scientists which would easily become group leaders at other places. Most of them have done postdoctoral studies in Oxford or Cambridge, UK.

The group attracts money in top down calls as well as in bottom up competitions such as four ANR projects. The ANR Jeunes Chercheurs testifies the competitiveness of the projects applied for by the young PIs in the group. The group is also successfully raising funds by co-application with other departments and gets funding from the Carnot Institutes for applied research in biomedicine but is not involved in EU contracts. Given the resources the group has, the amount and quality of the funding is impressive. The high esteem that the biological NMR community has for the group leader is also reflected in the invitation of the ICMRBS committee asking her to organize the ICMRBS in Lyon in 2012. After the CNRS bronze medal in 1989, the Thérèse Lebrasseur prize of the Fondation de France in 1997, the group leader received the "Chevalier de l'Ordre National du Mérite" in 2007.

- **Appreciation on the scientific strategy and the project**

The group has worked on biologically interesting projects with state of the art NMR methodology making sure that the biological question could be answered with NMR methods. This has led to success and the occupation of a unique niche in France. This direction will be continued in the future by continuation of the above mentioned projects and new projects such as the one on hydrophobins that are interesting in terms of structural biology (aggregation) and biologically significant, since they are important for the virulence and escape mechanisms of fungal spores in the lung. This project calls for the combination of liquid state and solid state NMR spectroscopy which is technologically cutting edge and done by a growing number of excellent laboratories worldwide. These measurements have to be done outside of Pasteur since the required equipment (solid state NMR spectrometers) is missing. A solid state NMR spectrometer would even further increase the competitiveness of the group when basic experiments could be done at Pasteur and only those experiments that require higher field elsewhere. The projects of the group are adapted to the available resources, which are also enhanced by going to Florence and Utrecht for measurements. Given the excellent funding of the group, there was no restriction of resources observed.

- **Conclusion :**

— Summary

The NMR group is essential to the department and has found its niche of excellent performance combining state of the art NMR with interesting biological questions of which the major part originated at the Pasteur Institute, thus reinforcing its strength.

— Strengths and opportunities

The group has performed interesting projects in which NMR spectroscopy is optimally suited to answer biological questions. It has identified future projects which are investigated at Pasteur because the biology is excellent at Pasteur. Some of the projects combine several techniques of structural biology such as NMR, X-ray and electron microscopy and are therefore at the heart of the mission statement of the department to do integrative structural biology.

— Weaknesses and threats

The group proposes projects that require the use of solid state NMR spectroscopy for internationally competitive results. This is due to the direction of the group picking interesting biological projects which cannot be geared in such a way that only liquid state NMR is required. Solid state NMR is not represented in the department and there is also no strong group in the close vicinity for such a collaboration. The next group would be in Lyon, but it is difficult to do such experiments because there is no person with a strong background in solid state NMR in the group. On the side of the equipment, the group has to be congratulated for its excellent scientific output in the past years despite the fact that a 600 MHz NMR spectrometer is the highest field at Pasteur, which is not competitive any more if one wants to address the most challenging questions in structural biology. This is a clear threat which today is

compensated by the reputation and the track record of the scientists running the group. However, when they will retire in the coming years, this success story may not continue.

— Recommendations

The group has to be equipped to be competitive with respect to instrumentation. This requires higher fields (800 MHz plus) as well as the possibility to perform solid state NMR spectroscopy at least with a 600 MHz wide bore instrument. A department that has the mission to perform integrated structural biology (which is specifically highly applauded), needs these possibilities in order to provide the most optimal data to feed into the sparse data software developed by the bioinformatics group.

URA 2185 E4 Structural Biology of Bacterial Secretion (Remi FRONZES)

- **Staff members**

URA 2185 E4	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N2A : Number of full time researchers Pasteuriens	0	0
N3: Number of postdoctoral fellows	1	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of technicians and administrative staff (Form 2.6 of the application file)	2	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	1
N7: Number of staff members with a HDR or a similar grade	0	1

- **Appreciation on the results**

First class results on a type IV secretion system were obtained during the post doc of the group leader. The group leader started at IP end of 2009 and the work was started after the installation of the laboratory only in April 2010. The first crystal of a protein involved in DNA translocation across the bacterial membrane has been obtained.

First author papers in Nature and Science were published in 2009 from the post doc lab as were a series of high-flying reviews (TIBS, Nature Rev. Microbiology, EMBO J.). There were no independent publications yet from the present laboratory at the Pasteur Institute.

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

The group leader has already obtained ANR funding (2010-2013) and will apply for other funding for which there is a very significant chance in obtaining it.

- **Appreciation on the scientific strategy and the project**

The project concerns the structural biology of bacterial transformation. Bacteria have a system for binding external DNA which is then translocated across membrane through a channel with the help of ATPases. The DNA is then integrated into the chromosomal DNA and expressed. Naturally transformable bacteria express 20-50 proteins implicated in this process and the complexity of structures involved may be compared with the complex secretion systems that the group leader worked with during his post doc. It is proposed to do crystallography of all soluble and membrane components, cryo-EM on reconstituted complexes and 2D crystallization of membrane proteins. The first results are on the crystallisation of ATPases of *P. pneumoniae* and the first crystals have been obtained. This project is ambitious but is likely to give major results over the next 4 years.

The project is very relevant as transformation is one of the mechanisms through which bacteria exchange genetic information and can acquire antibiotic resistance. The research project combines multiple methods of structural biology in an original way.

- **Conclusion :**

— Summary

Very strong project by a group leader who has previously shown that he is capable of taking such a study to competitive results.

— Strengths and opportunities

Multiple structural biology approaches, has started to attract major funding and will be performed in a very good structural biology and microbiology environment.

— Weaknesses and threats

One of the weaknesses is not due to the group leader but to the absence of electron microscopes dedicated to this group. The group leader must also be careful to publish independently of the post doc lab in order to receive recognition of independence.

— Recommendations

This very promising young group has a very good and ambitious project. The Pasteur Institute should ensure that this group has unlimited access to electron microscopy.

URA 2185 E5 Biochemistry of Macromolecular Interactions (Daniel LADANT)

- **Staff members**

URA 2185 E5	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N2A : Number of full time researchers Pasteuriens	3	3
N3: Number of postdoctoral fellows	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of technicians and administrative staff (Form 2.6 of the application file)	1.25	1.25
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	2	3

- **Appreciation on the results**

This team has focused on the study of molecular mechanisms of protein–protein and protein–membrane interactions. The model system has been the bacterial toxin adenylate cyclase (CyaA) of *Bordetella pertussis* which causes whooping cough. The aim is to clarify how this toxin enters the cell; in crossing the plasma membrane, it translocates its N-terminal catalytic domain as a unique entry mechanism which still remains largely unknown in detail. Nevertheless, the team has demonstrated that this mechanism may be exploited for targeting T-cell epitopes into antigen-presenting cells, for instance, in immunotherapeutic trials to combat malignancies. The same approach has been used to induce antibody responses, e.g. against HIV-1. The team has also employed CyaA as a basis for a two-hybrid technology for assembly of protein complexes. All these approaches are well described, and the work can be characterized as original and of high quality.

Output 2005-2010

In the reporting period there were 42 publications, 16 of which with a first and/or last author belonging to the group, in journals like Cancer Res. (1), J. Mol. Biol. (3), J. Biol Chem (2). and Nucleic Acids Res. (1). With collaborative work published in PNAS, EMBO J. and PLoS Path. Apart from original work the group also published an impressive list of 14 book chapters mainly with first and/or last authors from the group. Members of the group were also part of two patent applications. Although there were no thesis defended during the period (the group presently has two students) one permanent researcher defended the HDR.

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

In the past the group has only had a few post docs and mainly Master students. Presently there are only two students and two postdocs. The members of the group have good international visibility and have given multiple presentations in national and international meetings. The group leaders is an active member of the national scientific community and has rendered many services to this community. National and international collaborations with groups

in the UK mainly involve the use of the CyaA technology developed in the group for vaccine design and two hybrid studies.

The groups received financing through the ANRS, ARC, is collaborator in two EU projects and coordinates and ANR grant. One of the temporary group members is honorary professor of IP and has received very many international distinctions.

- **Appreciation on the scientific strategy and the project**

The research directions for 2011-2014 are to continue to study the physico-chemical properties of CyaA and how this enzyme penetrates the cell membrane. These studies are necessary for the large scale production of protein for vaccine use. It is planned to characterize protein interactions in multi molecular machineries with the CyaA-based two-hybrid system developed by the team, and this methodology will be improved. One of the subjects of study will be the characterisation of the bacterial cell division complex. The future plans are well described and the team has a good collaborative national network.

- **Conclusion :**

— Summary

Solid biochemistry group that, through focussed research on a biological system, was able to develop a novel two hybrid system and a new way of making vaccines.

— Strengths and opportunities

The clear strength of this group is its position in the Pasteur Institute that permits fruitful development of the vaccination approaches and its position in the structural biology unit that will be essential for the biophysical characterisation of the molecules produced.

— Weaknesses and threats

The relatively small number of students and post docs may lead to reduced high risk and highly visible research. The group has solid result published in solid journals but no exceptional papers.

— Recommendations

This group should continue their good work and try and increase the non-permanent: permanent ratio.

URA 2185 E6 Structural Bioinformatics (Michael NILGES)

- **Staff members**

URA 2185 E6	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N2A : Number of full time researchers Pasteuriens	3	3
N3: Number of postdoctoral fellows	3	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of technicians and administrative staff (Form 2.6 of the application file)	2,5	2,5
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	3
N7: Number of staff members with a HDR or a similar grade	3	4

- **Appreciation on the results**

The Unit of Structural Bioinformatics has been established in 2001 and since it has consistently performed, in terms of scientific output, at the highest level in the field. The five senior scientists in the Unit lead independent research on a number of diverse topics in theoretical biology and computational biophysics. The common denominator is a rigorous and physically sound approach. Exceptional work was performed combining computational methods with experimental approaches and new algorithms for sequence alignment. Members of the group are part of extensive international networks, in particular providing methods for NMR data analysis and structure determination (ARIA).

Output 2005-2010

The group published 84 papers, 35 of which had a first and/or last author from the group. The quality of papers was generally good to very good with some exceptional papers; Phys. Rev. Lett. 2007, PNAS 2006 and 2010, PLoS Comput. Biol. 2005 and 2008, JACS 2005, and Science 2005. Collaborative work was published in 2 Nature Methods papers, several JACS and Angew. Chem. Int. Ed. (Engl.) and PNAS papers. There were 7 theses during this period and 3 patents deposited.

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

The head of the group is the most visible scientist in the URA and in the whole Department, ranking among the best in the world in the field of structural bioinformatics but even beyond in the broader field of structural biology. Although the methods applied are in the field of theoretical biology, the connection with relevant experiments, with biological important questions, and with medical and pharmacological applications, is always present. Sustained links with international and national partners are present and the unit has no problems in recruiting top graduate students and postdoctoral researchers. Even more important, links with other units in the Pasteur Institute are strong, both in the past and in the future plans.

The group is highly visible internationally and all senior scientists have extensively presented their work in national and international meetings and have taught in international courses. The group leader has received the Thérèse Lebrasseur prize (Fondation de France) in 2010.

Members of the group are involved in 4 EU networks, either as partner or coordinator, 2 ANR and 2 ACI contracts and have received several foreign grants (UK, USA, Canada, Israel).

- **Appreciation on the scientific strategy and the project**

The future projects are important in the context of the global challenges in the post-genomic biomolecular sciences. They cover an interesting range of problems and involve different and complementary methods. The integrative approach to structure determination that has been developed in the group is highly promising, particularly in its extensions to low resolution and sparse data which are increasingly available from a number of rapidly developing techniques such as cryo EM, mass spectrometry, FRET and solid state NMR. Investments in expanding such techniques at the Department of Structural Biology and Chemistry will certainly have a higher return thanks to the presence of the Unit of Structural Bioinformatics. In turn, the group will benefit enormously from the availability of data in order to benchmark and rate different approaches to structure determination. Synergy between experiment, theory and modelling is crucial in the field of structural biology and this group is at the forefront in the endeavour to push this synergy further. This was also presented as the defining topic of the whole department of structural biology and the definition of this mission to develop an integrative structural biology requires the existence of such a department where approaches can be tested on examples that do not necessarily have to be of upmost biological importance. The approaches developed in the group can be extended to characterize intrinsically disordered or partially disordered proteins, whose relevance in biological processes is increasingly evident. One of the lines of research in the group consists of developing methods to predict transitions between different conformations of a protein. The prediction of the correct pathway and of the transition state could lead to the design of ligands that could prevent or enhance the transition. Valuable and promising for the future is the development of novel concepts for the analysis of genomic data. The use of probabilistic concepts to handle non-linear laws seems in most cases more reliable than the methods currently used. For this reason, it would be very useful if those methods were made available to the scientific community through web interfaces or as plug-ins in tools developed by others.

- **Conclusion:**

— Summary

This group has performed very well in the past and its future plans are realistic, so we believe that it will perform as well in the next four years.

— Strengths and opportunities

Excellent physical and mathematical approaches in biology combined with experimental data. This group will be strengthened even further by the development of high resolution cryo-EM and higher level mass spectroscopy at the Pasteur Institute.

— Weaknesses and threats

Like most groups in the Department, the ratio of permanent compared to non permanent personnel is rather high and the activities of the group would benefit from an increase in the number of postdocs and graduate students.

— Recommendations

The committee recommends that the group maintains all the autonomy it needs in the administration of their computer facilities and on the decisions related to their exploitation and upgrade. It also recommends support for the maintenance and further development of open-access software and web-based tools. These, and ARIA in particular, have a large audience. ARIA is used in structure refinement by about half of the NMR groups worldwide and its association with Pasteur Institute positively contributes to its reputation in the NMR community. Investments in developing or strengthening cutting-edge structural biology experimental techniques such as cryo EM, mass spectrometry, FRET and solid state NMR at the Department of Structural Biology and Chemistry will strengthen the group of Structural Bioinformatics.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
DÉPARTEMENT DE BIOLOGIE STRUCTURALE ET CHIMIE - URA 2185	**A**	**A+**	**B**	**A**	**A**
STRUCTURAL BIOCHEMISTRY [DELARUE-ALZARI]	A+	A+	Non noté	A	A+
STRUCTURAL DYNAMICS OF MACROMOLECULES [DELARUE-DELARUE]	A+	A+	Non noté	A	A+
NUCLEAR MAGNETIC RESONANCE OF BIOMOLECULES [DELARUE-DELEPIERRE]	A	A+	Non noté	A+	A+
STRUCTURAL BIOLOGY OF BACTERIAL SECRETION [DELARUE-FRONZES]	Non noté	A	Non noté	A	A
BIOCHEMISTRY OF MACROMOLECULAR INTERACTIONS [DELARUE-LADANT]	A	A	Non noté	A	A
STRUCTURAL BIOINFORMATICS [DELARUE-NILGES]	A+	A+	Non noté	A+	A+
DÉPARTEMENT DE BIOLOGIE STRUCTURALE ET CHIMIE - URA 2128	**A**	**B**	**A**	**B**	**A**
MEDICINAL CHEMISTRY [POCHET-JANIN]	A	B	Non noté	Non noté	B
CHEMISTRY OF BIOMOLECULES [POCHET-MULARD]	A+	A	Non noté	A+	A+
CHEMISTRY AND BIOCATALYSIS [POCHET-POCHET]	A	B	Non noté	B	B

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

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

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

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

• SVE1 Biologie, santé
- **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
- **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
- **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
- **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
- **SVE1_LS5 Neurosciences**
- **SVE1_LS6 Immunologie, Infectiologie**
- **SVE1_LS7 Recherche clinique, Santé publique**

• SVE2 Ecologie, environnement
- **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
- **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
- **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

Nos réf. : GM/RR/AERES/N°345

AERES
Section 2
Evaluation des unités de recherche

Institut de chimie
Le directeur scientifique

www.cnrs.fr

Campus Gérard-Mégie
3, rue Michel-Ange
75794 Paris cedex 16

T. 01 44 96 40 99
F. 01 44 96 53 70

Paris, le 13 MAI 2011

Objet : rapport préliminaire du comité de visite de l'AERES concernant l'URA2128 « Unité de chimie organique » (UCO) - Paris

L'avis de l'Institut de chimie est totalement conforme à celui transmis par Madame Sylvie POCHET, directrice de l'URA2128, que vous trouverez ci-joint.

L'Institut de Chimie tient à remercier les membres du comité d'évaluation de l'URA2128 « Unité de chimie organique ».

Régis REAU

PJ : observations de l'URA2128

INSTITUT PASTEUR

Unité de Chimie Organique
CNRS URA2128

Paris, 15 avril 2011

Monsieur le Président du Comité AERES

Objet : Réponse au comité de visite AERES du Département de Biologie Structurale et Chimie – URA2128

L'ensemble du personnel de l'Unité tient à remercier le comité d'experts de l'AERES qui a bien voulu examiner le bilan et les projets de l'URA2128 dans le contexte de l'évaluation du département Biologie Structurale et Chimie de l'Institut Pasteur. Nous souhaitons également remercier le comité pour le travail d'évaluation réalisé et la qualité du rapport d'évaluation fourni à l'issue de la visite.

Nous avons pris connaissance du rapport préliminaire du comité de visite AERES et avons apprécié les points forts remarqués. Une lettre de réponse au comité AERES a été adressée par chacune des trois équipes qui composent l'URA:

- l'Unité de Chimie des Biomolécules dirigée par Laurence Mulard,
- l'Unité de Chimie et Biocatalyse dirigée par Sylvie Pochet,
- le laboratoire de Chimie Médicinale dirigé par Yves Janin.

Les erreurs factuelles ont été consignées dans des fichiers séparés.

Les recommandations émises par le comité seront prises en considération. Nous serons particulièrement attentifs à augmenter notre visibilité nationale et internationale. Le comité a souligné à plusieurs reprises le faible nombre de thèses soutenues pendant la période 2005-2010. Il convient de rappeler que la restructuration des groupes de chimie survenue entre 2006 et 2007 n'a pas été propice à un engagement de long terme. Par contre, un grand nombre d'étudiants M2 et de post-doctorants financés sur contrats propres ont été accueillis, et ce dans la limite de la capacité d'accueil autorisée (effectif total maximum de 12 personnes pour les unités).

Les suggestions et remarques du comité constitueront une aide précieuse pour l'évolution de l'unité dans le contrat à venir.

Je vous prie d'agréer, Monsieur, l'expression de mes respectueuses salutations.

Sylvie Pochet
Directrice de l'URA2128

Institut Pasteur
25-28 rue du Docteur Roux
75724 Paris Cedex 15
Téléphone : 06 85 42 49 47
Télécopie : 33 (0)1 45 68 84 04

INSTITUT PASTEUR

Paris, April 15, 2011

Département de Biologie Structurale et Chimie
CNRS URA 2185 / CNRS URA 2128

AERES
Section of Research Units

Dear Sirs,

in the name of the department of structural biology and chemistry I would like to thank the members of the AERES Site Visit Committee for conducting a thorough and efficient evaluation of our department, and for their constructive comments and remarks. The committee's comments and recommendations are very supportive of our vision for the future development in structural biology on the Pasteur campus.

One of the major concerns of the committee was the geographic distribution of the department on campus, a situation that we cannot change. Certainly, the task of efficient communication is made difficult by the fact that the department is spread over almost as many buildings as it has groups. We would like to stress, however, that many activities are in place in particular for the students (journal clubs, guided tours through the department for new students, representatives for students and postdocs in the department council, ...), activities that we could not document sufficiently during the very brief time that the committee spent on campus. We realise, however, that we have not been sufficiently proactive to make sure that all students benefit from these activities, and will increase our efforts.

Sincerely yours,

Michael NILGES
Head of department

Alain ISRAEL
Directeur de l'Evaluation Scientifique
Institut Pasteur

25-28 rue du Docteur Roux
75724 Paris Cedex 15
Téléphone : +33 (0)1 45 68 82
30 Télécopie : +33 (0)1 45 68 87
19

INSTITUT PASTEUR

Paris, April 6, 2011

Unité de Biochimie Structurale
URA 2185 CNRS

AERES
Section of Research Units

Dear Sirs,

I would like to thank the members of the Site Visit Committee from the AERES for conducting a thorough and efficient evaluation of our Department of Structural Biology and Chemistry. We very much appreciate their constructive comments and remarks concerning our past and future research activities in the field of structural microbiology.

Sincerely yours,

Pedro M. Alzari
Chef d'Unité
Institut Pasteur

25-28 rue du Docteur Roux
75724 Paris Cedex 15
Téléphone : +33 (0)1 45 68 86 07
Télécopie : +33 (0)1 45 68 86 04

INSTITUT PASTEUR

Unité de RMN des Biomolécules
CNRS URA 2185

Paris 14th April 2011

To whom it mays concern

The committee raises concerns on the future of the Unit after my retirement (2017) and on our equipment. I am however confident that the success story of our Unit will continue as it has been built over more than fifteen years with the three young group leaders currently in the Unit. Moreover, the group leaders take full scientific responsibility of the projects they lead, have been active and successful in fund raising and have shown their capacity to develop independent research. At present, we have access to very high-field NMR machines either in national or European large-scale facilities and we are partners of the Equipex project "Paris in resonance" which was selected by the ANR and would give access to an 800 MHz liquid/solid state spectrometer. This configuration should help to overcome our equipment limitations temporarily. However, we do plan to apply for a higher field spectrometer in the near future

Muriel Delepierre

ALAIN ISRAËL
DIRECTEUR DE L'EVALUATION SCIENTIFIQUE
INSTITUT PASTEUR

Département de Biologie
Structurale et Chimie

28 rue du Dr. Roux
75724 PARIS Cedex 15
Téléphone: +33 (0) 1 45688871
Fax: +33 (0) 145688929
e-mail: murield@pasteur.fr

Dr Rémi Fronzes, Chargé de recherche, CNRS
Unité Biologie structurale de la sécrétion bactérienne,
Institut Pasteur, 25-28 rue du Docteur Roux
75724 Paris Cedex 15, France
Tel: +33(0)145688864
Email: remi.fronzes@pasteur.fr

Paris, 5th of April 2011

To the AERES committee,

The group "Biologie structurale de la sécrétion bactérienne" or "Structural biology of bacterial secretion" was created in October 2009 at institut Pasteur. It is composed of a CNRS scientist, three post-doctoral fellows, a research assistant and a research technician.
Our research aim is to decipher the molecular mechanisms that support DNA transfer events between bacteria, in particular during natural transformation and conjugation. We use structural biology (X-ray crystallography and high-resolution electron microscopy) and biochemistry techniques to study the architecture of the membrane protein complexes involved in these events.

We would like to thank the AERES committee for its evaluation of our activity and projects. We have no particular comments except that we are aware of the weaknesses and threats pointed out by the committee : scientific independence and access to electron microscope.
We would like to reassure the committee by saying that:

- The major project of the laboratory concerns bacterial transformation systems. This project is only distantly related to the previous work of the group leader and is performed independently from the laboratory where he was a post-doctoral fellow (Gabriel Waksman's laboratory at Birkbeck college in London). It is crucial that our scientific independence is recognized.
- The access to the electron microscope is not unlimited but is improving. For the moment, our projects are not limited by the access to this equipment.

Yours sincerely,

Dr Rémi Fronzes

Alain ISRAËL
Directeur de l'Evaluation scientifique
Institut Pasteur

INSTITUT PASTEUR

Daniel LADANT
Biochimie des Interactions Macromoléculaires
Département de Biologie Structurale et Chimie

Paris, April 12, 2011

To the AERES committee members

Object: Response to the AERES evaluation report

Team : **URA 2185 E5 Biochemistry of Macromolecular Interactions**
(head : Daniel Ladant)

Comments of Daniel Ladant on the report from the visiting AERES committee

First, I would like to thank the committee members for the time and efforts spent to evaluate the team.

We have highly appreciated the very positive comments of the committee on the originality and quality of our work.

We take good note of the recommendations of the committee in particular regarding the suggestions to increase the ratio of non-permanent scientists versus permanent ones.

Sincerely

Daniel Ladant
DR2 CNRS
Responsable de l' Unité de Biochimie des Interactions Macromoléculaires

28, Rue du Docteur Roux
75724 Paris Cedex 15
Téléphone : +33 (0)1 45 68 84 00
Télécopie : +33 (0)1 40 61 30 42
e-mail : daniel.ladant@pasteur.fr