IBITEC-S - Service d'ingénierie moléculaire des protéines (SIMOPRO)

Rapport Hcéres

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

Section des unités de recherche

AERES report on the unit:

Service d'Ingénierie Moléculaire des Protéines

From the

CEA

May 2010

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et de l'enseignement supérieur

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From the

CEA

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

May 2010

Unit

Name of the unit: Service d'Ingénierie Moléculaire des Protéines

Requested label: Service du CEA

No. in case of renewal:

Unit director: M. Vincent DIVE

Members of the expert committee

Chairperson:

Ms. Solange LAVIELLE, Université Pierre et Marie Curie, Paris

Reviewers:

Ms. Francesco-Xavier AVILES, UAB, Barcelone

Mr. Guy BRANLANT, Université Henri Poincaré, Nancy

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Mr. Daniel LADANT, Institut Pasteur, Paris

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Mr. Bernard ROQUES, Université Paris Descartes

Reviewer(s) nominated by the staff evaluation committees (CNU, CoNRS, CSS INSERM ...):

Representatives present during the visit

Scientific delegate representing AERES:

Mr. Jacques BARATTI

Research organisation representative :

Mr. Jacques NEYTON, CEA

Mr. Nathalie GRAS-NAULIN, CEA

Report

1 • Introduction

• Date and execution of the visit

The committee spent one full day (Friday, March 19th from 8:00 to 18:00) in the SIMOPRO laboratory, CEA, Saclay. The visit mainly consisted, as set up by the AERES delegate, in the presentation of the Unit by the director and of the results and projects of the seven teams of SIMOPRO by the Group Leaders. Three special sessions were devoted to meetings with i) the CEA representatives, ii) the staff (researchers/engineers and technicians, respectively) and iii) the director and co-director. The deliberation of the committee took place the day after (Saturday March 20th from 9:00 to 12:45) at the Ecole Normale Supérieure, Paris.

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

The SIMOPRO Unit, located on the CEA site at Saclay, is one of the five iBiTec-S Units, ("Institut de Biologie et de Technologies de Saclay"), created in 2007 after the reorganisation of the DSV (Direction des Sciences du Vivant) in distinct Institutes. The SIMOPRO Unit represents part of the previous DIEP (its director retired in 2006), implying that some rearrangements have occurred, notably with some group leaders and research themes. The SIMOPRO's staff in 2009 consisted in 27 AI (researchers and engineers, CEA nomenclature), 15 AII (technicians, CEA nomenclature) with a permanent position and 25 with a non-permanent position.

The main objective of SIMOPRO researches is to conceive/design new molecules, from pseudopeptides to miniproteins, with well-defined pharmacological activities and potential applicability in health care. The common point or red thread of SIMOPRO researches is peptide/protein engineering. This Unit is a typical interdisciplinary laboratory that gathers complementary expertises ranging from chemistry to computational and physical chemistry, bioinformatics to structural biology, molecular biology to cell biology, immunochemistry to immunology, all these disciplines being interconnected to achieve the common objective. This Unit must be considered as a laboratory working at the interface of chemistry and biology, where the molecule is the central part of all researches. Thus, criteria for this evaluation are those relevant to the chemistry/bioorganic chemistry field even though this Unit is in a Life Sciences department and in the Life Sciences AERES Committee.

• Management team

SIMOPRO, with a director and a vice-director, is organized in seven teams, (which will be presented below), with either one Group Leader or (for two of them) two Group Leaders (history from the 2007 rearrangement). The "administration" consists in three persons in charge of most of the administrative duties; some of the technicians/engineers are devoted to the running of the four core facilities, which are crucial for the lab activities considering the diversity of techniques necessary to develop the multidisciplinary approaches.

- Staff:

	In the report	In the project
N1: Number of professors (see Form 2.1 of the unit's dossier)	2	2
N2: Number of EPST, (Public scientific and technological institution) or EPIC, (Public industrial and commercial institution) researchers (see Form 2.3 of the unit's dossier)	27	27
N3: Number of other professors and researchers (see Form 2.2 and 2.4 of the unit's dossier)	0	0
N4: Number of engineers, technicians and tenured administrative staff members (see Form 2.5 of the unit's dossier)	15	14
N5: Number of engineers, technicians and non-tenured administrative staff members (see Form 2.7 of the unit's dossier)*	21 AI + 12 AII	4 AI + 6 AII
N5*: Number of post-docs for an average 18-24 months period (Form 2.7 of the unit's dossier)*	16	8
N6: Number of doctoral students (see Form 2.8 of the unit's report dossier and 2.7 of the unit's project dossier)	14	5
N7: Number of persons accredited to supervise research and similar	11	11 (+ 3 expected in 2010)

* Numbers (N5 and the following item in blue) were difficult to calculate in the iBiTec-S document, with more than 81 persons/names for SIMOPRO with various "status", i.e., post-docs, CDD AI or CDD AII, "stagiaires", "intérimaires"…. So, these numbers need to be confirmed.

2 • Assessment of the unit

- Overall opinion.

The overall opinion of the committee is highly positive, almost all of the so-called « objective » criteria being very good. SIMOPRO within the Life Sciences Department of CEA highly fullfil the CEA demand in terms of participation to CEA programmes (some of them being strategic, as for the Biodefense programme) and to fundamental researches associated to numerous and important applications in health care. The director and vice-director should be acknowledged for their work at the head of SIMOPRO, prior projects initiated in DIEP are still actively pursued and several evolved in a very promising way.

This Unit is one of the few laboratories in France working at the interface of chemistry/biology with all competences and technical facilities required for a productive Chemical Biology. All these theoretical competences are devoted to the design of new molecules, such as small inhibitors of enzymes, proteins or mini-proteins for diagnostic or vaccine applications or new strategies for radioimaging. The previous reputation of the work done on toxins in DIEP has been enlarged successfully to new application domains, such as a miniCD4, a lead molecule as a microbicide and/or for prophylactic vaccine candidate. The expertise in the enzymology of MMPs and ADAMs proteases are internationally recognized and may be key for the understanding and regulation of membrane-exposed MMPs. Similarly, the expertise in immunochemistry / immunology on the understanding in CD4 T cell response in human in the perspective of developping new tools (diagnostic, vaccines) and safe therapeutic proteins is a major asset in the different on-going and future projects of SIMOPRO.

- Strengths and opportunities:

The strengths of SIMOPRO come in part from i) the strength of the CEA (funds and organisation), but also from ii) the diversity of competences of the 27 researchers of the Unit, with a technical staff of 10 persons devoted to impressive core-facilities, iii) the dynamism in raising funds and recruiting non-permanent staff, such as post-doc fellows or technicians, attracted by the well-known technical core-facilities, and iv) an unwavering commitment to go into biomedical application(s), which is a major asset of their researches.

In some domains SIMOPRO is at the edge of successful applications of some works initiated almost ten years ago, with patents with licences. In one case, clinical trials with results expected by the end of 2010 might assess the strategy of miniproteins scaffolds associated to the study of immunogenicity. If successful the overall project of the Unit on mini-proteins will be funded (see below).

- Weaknesses and threats:

The weaknesses are at two levels, a first one that is intrinsic to the SIMOPRO organisation: too many small teams, with two « leaders » in two of them, and a second one that comes from the decrease in the funds provided by CEA to iBiTec-S in 2010 and the forthcoming years.

The organisation of SIMOPRO will have to be readjusted, specifically in 2011, after consideration of the results from the expected applications. The director/co-director and the current Group Leaders will have to admit that i) a Unit reorganization into fewer groups, each with a higher number of permanents positions and one Group Leader, (since egos may not be the best key to a successful organisation), and ii) a re-focusing of the competences onto specific projects, will most probably be required. This, inasmuch the threats which have been presented to the Committee by the director and the CEA representatives for the next two years (or maybe more ?) are considered.The CEA will decrease its financial support, all the Units will have to find funds to support their research, only salary and « housing » will be provided by the CEA, no new « permanent » or post-doc position will be available for the next two years (or maybe more ?). SIMOPRO, as all Units not strongly connected to University circuits, has a hard time to recruit PhD students (for 2010 only 4 PhD students). The only source for PhDs funding will be national grants or EU grants.

- Recommendations for the unit director:

The Committee summarizes its recommendations in three points, for more details see the « strenghts and weaknesses » section.

The Unit might need a reorganisation of the seven teams in fewer but larger teams, each with a single Group Leader. In several cases the number of permanent team members appears subcritical and might require a better balance.

This reorganisation might probably require also a re-focussing in the objectives and in the goals of the Unit, choices will have to be made but they may depend on the success of the projects close to medical applications. This would probably result in an increase in the number of publications for some “permanents”, as well as a “better” choice of the journals in terms of impact factor.

The productivity of the SIMOPRO is highly depending on competences but also on the impressive core facilities, maintaining all the equipements at the top level in the forthcoming period might represent one bottleneck for the Unit, the Committee has to say that members of SIMOPRO might be very vigilent and active in raising funds.

- Data on work produced:

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

A1: Number of *produisants* (professors and researchers whose names appear in a minimum number of "publications" over a 4-year period) listed in N1 and N2 in the project column ° one of the "non-produisant" has been affected during this 2005-2009 period as responsible of all the "immobilier" problems, a full-time charge .	25
A2: Number of *produisants* among the other staff listed in N3, N4 and N5 in the project column * Technicians "working at the bench"	6/10 *
A3: Proportion of *produisants* in the unit [A1/(N1+N2)]	25/27
A4: Number of theses for accreditation to supervise research defended	11
A5: Number of theses defended	14

3 • Detailed assessments:

- Appreciation on the results

The originality of SIMOPRO researches resides in a well-organized multidisciplinary strategy, centred on molecules and their mechanisms of action, all researches being supported by four well-equipped core facilities. Three criteria assess for the quality of the researches: the quality/number of the publications, the number of patents and licenses, the capability to find funds at the public or private level. All three criteria are clearly positive, see below.

Relevance of the SIMOPRO objectives within the CEA: (1) solid fundamental research oriented towards applications and (2) strong involvement in specific transversal projects of CEA (i.e., projects related to national and international Biodefense).

The results obtained during the past four years have been published in 192 papers, (for 25 "produisants" for 27 researchers), in the most important journals in all domains: in March 2010 one paper in Cell, in Angewandte Int. Ed, JACS, Nature Chemical Biology, PNAS, J. Immunology, J. Biol. Chem., Biochemistry.... with a mean impact factor> 5.15, and 55 publications with an IF>5, (which is good, considering that besides Angew. Chem. Int. Ed. Engl., none of the chemistry journal has an IF >10).

The group leaders have been invited to 13 international conferences, including three Gordon conferences.

All the teams have filed patents with PCT, for a total of 21 patents with three licences for years 2005-2009. Two start-ups were created during this term with the participation of CEA, two members of SIMOPRO being co-founders of these start-ups.

Previously known as the DIEP, SIMOPRO was created with the present configuration in 2007 after the reorganisation of the DSV at Saclay. So, it can be said that the "core'" of SIMOPRO researches has been maintained or renewed for several years in the CEA organisation.

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

The group leaders have been invited to 13 international conferences, among them three Gordon conferences. Only a few post-docs have been recruited via the "international" recruitment CEA programme, this highly competitive programme has provided up to 2008 a limited number of post-docs per year for all the iBiTec-S. Because of CEA fundings decrease this post-doc programme has been interrupted in 2008. So, most of the post-docs have been hired through specific grants, and the recruitment has to satisfy CEA policy.

Concerning the PhD students in the period 2005-2009 14 PhD have been defended in 4-5 years. SIMOPRO is affiliated to various Ecoles Doctorales, but even if some "permanents" are involved in teaching programmes this activity remains marginal. The only solution is either grants or the CEA PhD programme, which for the past years concerned an average of 20 PhD students per year for the 5 units of the Institute.

All the teams filed patents with PCT, for a total of 21 patents in the period 2005-2009 with three licenses. Two start-ups were created during this term. All teams have been very successful in raising financial supports from national programmes in 2005-2009 for a total amount in 2010 of 774 kEuros plus 643 kEuros for the NRBC project (Biodefense).

SIMOPRO has long-term partnership with different labs both at the national and international levels.

Considering that the main objective of the SIMOPRO researches is focussed on applications, the committee remarked as a weakness too rare connexions/partnerships with clinicians teams. This partnership should be improved, to better or more rapidly assess/validate the targets and the corresponding delivered molecules.

Concrete results : 21 patents with PCT, three licenses during the 2005-2009 period, with one molecule entering in 2010 in clinical trials in a consortium project with Novartis, USA, as HIV microbicide candidate and as a new prophylactic vaccine candidate. Two group leaders are co-founders of two new start-ups, with CEA participation.

Finally, all teams have been very successful in 2005-2009 in raising financial supports from national programmes: (4 ANR, 2 ANRS, 2 INca and 5 grants from private companies: UCB, Servier, Protéus, Novartis US), and international programmes: 6 EU (6th and 7th PCRD) and 2 from NIH. To "give an idea" of their dynamism, the total amount for 2010 will be 774 kEuros plus 643 kEuros for the NRBC project (Biodefense). These partnerships underline also the dynamism of all teams to initiate and maintain collaborations with French, European, American and Japanese laboratories.

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

In the document, the SIMOPRO Unit is "separated" in two laboratories with a total of seven (4 + 3) teams, nevertheless, this separation in two labs was barely used in the presentation and discussions. The only justification for these two labs could be the "size" of the molecules they are focusing on (small one versus large proteins). It is the opinion of the Committee that such a division has no real meaning neither in terms of science or even technical relevance.

The various researches in SIMOPRO require availability of a large variety of techniques, materials and equipments, of which the most expensive (radioactive labelling, in vivo radioimaging, mass spectrometry, protein recombinant techniques, purification, crystallisation as well as in vitro and in cellulo assays) are well-organized as in-house core facilities.

The scientific animation of SIMOPRO is organized at different levels. At the team level: a seminar every two weeks. At the Unit level: a monthly seminar gathering all permanent and non-permanent staff. At the iBiTec-S level: every year is organized: i) a post-doc PhD seminar, ii) two Institute Workshops, iii) 3-4 "prestigious seminars". After discussion with the SIMOPRO staff (researchers, technicians, PhDs and post-docs) the Committee could appreciate a common feeling of satisfaction regardless management research organisation (i.e., governance, communication policy, etc.). The committee has no further comment on that point, as people seem happy to work in SIMOPRO Unit. The major concern which must be mentioned is the "carrier" plan for the technicians, who mentioned difficulties in being promoted and the long and difficult endeavour of upgrading from "technician" to "principal technician" or (worse) to "engineer", with personal motivation as the only "fuel". Besides, mobility from one laboratory to another appears to be difficult. It is obvious that these concerns are not specific to SIMPORO but should be addressed at the general level of the CEA institution. (See at the end of this report, as meetings with the staff).

The architecture of SIMOPRO was reconsidered in 2007 with a new organisation in seven teams with some young leaders. This reorganization had to face: i) the departure of one team leader to the Minister of Research, ii) the retirement of the past director and iii) the death in 2005 of one of the Group Leader, the three of them considered the founders of most of the research activities still going on. Beginning of 2010, this reorganisation and new leaderships can be considered successful. The only downsides to this coordination concern: i) two teams ("Molecular Modelling and Engineering of Tc-containing peptide and protein imaging agents" team 25 and "Transfer of binding sites through miniprotein engineering, team 26) having both two group leaders (as previously mentioned, the Committee's opinion is that such an organisation cannot be the "best" configuration). In the case of team 25, both leaders have distinctive expertises (computational chemistry and labelling of small molecules and proteins) and the coherence of such a juxtaposition (starting in 2007) has not been found up to now evident. However, both competences are key for the Unit and needed in most of the current and future projects of the Unit. Two of the current teams (team 25 imaging agents, and team 30 non ribosomal biosynthesis) recently received technical and financial supports, respectively one and two AI transfers within the Institute plus one post-doc for each team. From the director's point of view, this was to assess within the Unit and iBiTec-S the competences of team 25 and the importance of the recent results of team 30. One of the seven teams of the Unit appears critical in size with only two researchers and one technician. However, their work is highly focussed on specific applications. Depending on the successful results (clinical trials are in due course this year) this team might be either reinforced, or the three persons might be transferred to other subjects. In fact, their competences and the results they obtained up to now will be helpful for other themes within the Unit.

All the permanent staff is composed of CEA employees and as known the connexion to teaching programmes in University/Schools is only on a voluntary basis, even at the INSTN affiliated to CEA. Seven "permanents" from SIMOPRO have been teaching for the past five years for about 110h (total) per year from 2009 to 2008 and 172h in 2009, in various programmes, mainly at the M2 level (Universities, Engineering Schools or Museum National d'Histoire Naturelle (MNHN), Technicians Schools, BTS).

At the regional level this unit is involved in transversal programmes within the CEA and via the national Biodefense programme with the coordination of 26 teams within this NRBC programme, five projects are currently developed in SIMOPRO. Since 2010, SIMOPRO has been collaborating within two different CEA translational projects: Nanotox with the DSM and SCBM Units and Health technology (diagnostics and imaging).

During the visit, the committee members met independently the researchers, the technicians and the PhD students and postodoctoral fellows

Researchers : Concerning the organization of the Unit, they are quite satisfied. However, their major concern is the financial support provided by CEA. The budget of the unit decreased by 40% in 2010 as compared to last year, 20% of this loss is due to internal budget restriction (starting 2010, CEA pays only salaries and fixed cost of the buildings). Thus, the unit has also to finance on its research budget things like building repair compulsory for safety (roof windows securization for instance). The researchers were asked how this budget restriction impacts their research. They cancelled recently all the maintenance contracts of apparatus like HPLC. Their problem is mainly the fact that due to the absence of research financing by CEA, they have to run for grants every year (private or public), which means that they can't focus anymore on long term and risky research, as they did up to now. They estimate that they have to focus now on short-term research with immediate results in order to apply for the grants for next year (public research). They also have to focus on applied research to obtain private funding. Accordingly, the result and impact of their research in fundamental research could be lower in the future while this is still a mission given to the CEA by the government. The significant amount of time spent in applying for grants, now impacts on the time spent on research, (comment added by the committee: as for everyone in public laboratories). Concerning the possibility to have PhD students, they think that they have difficulties to find good students since they don't have enough connection with universities. (Comment added by the committee: At this respect, perhaps it might be useful to suggest them to establish "marketing campaigns" focused on Universities, reinforced by "collaborative fellowships" open to good students involved in the lastest years in related careers (Chemistry, Biology, Biotechnology ...etc), to facilitate their recruitment.

Technicians : Most (if not all) of the permanent and non-permanent "bench" and "office" technicians of the Unit were present. Some of the bench technicians are associated to a team while others are associated to a core facility. They raised no particular complain about the one or the other situation besides a "more and more administrative duties" issue. Three major points were raised:

- The very limited carrier evolution and opportunities within the CEA organization: the "fuel" that keeps them going forward is their personal motivation and/or curiosity, two parameters that can

vanish with time if not buttressed by carrier rewards. Being promoted from "first class technician" to "principal technician" takes about 20 years. For the category A2 to category A1 promotion this can take even longer. In short, most of the technicians are young and for now they keep being highly motivated, but they would appreciate having a more attractive "future" in terms of in-house promotion steps and rates. It is obvious that these concerns are not specific to SIMPORO but should be addressed at the general level of the CEA institution.

- The limited opportunities for internal formation: except for those formations that are mandatory within the CEA or Unit organization, it is becoming difficult or impossible to access specific scientific or technical formations. Considering that formations can help them enhance their expertise level or range, and hence be more efficient in their work, they would appreciate be offered more opportunities.

- The planned reduction or suppression of the shuttle service currently provided by the CEA. The shuttles pick them up at various locations all around the county and bring them to the labs (and return). The lab is far from any transportation facility ("in the middle of nowhere") and most of those people that use the shuttle have no, or limited only, other transportation means. This would lead to a detrimental situation and this point is a major concern for almost all of the technicians.

PhD students and postdoctoral fellows During the meeting with PhD students and Post-doc fellows the committee could appreciate a very good organisation of the research activities they are involved in the different teams of the SIMIPRO Unit. In particular the team leaders and the permanent staff members organise together with all the students monthly one-day meetings during which each person working in the different teams can present the results obtained in the last month or reporting the most important papers recently published. All the students demonstrated that they can share expertise and competences, characteristic of the different teams to advance in their research project. Needs of new equipment and/or material are clearly defined between the different teams and the Director/co-Director have regular meetings with the team leaders to organise such expenses during the year. From the discussion the committee understood that even if funds available at CEA are decreasing, the students have always the best conditions to follow their research projects. The interaction with the core facilities of SIMIPRO but also with other Units at CEA is considered optimal. PhD students have regular classes at the PhD School they are associated with. Regarding their feeling on the possibilities for future work positions they aspire to get, it is clear that CEA would be for them one of the best possibility to work with a permanent position in research. Nevertheless, they are aware that few positions at CEA will be available in the future. On the other hand, most of them will try to get a position in the industry (considered the most stable), very few in the Universities. All of them believed that funding start up or spin off companies for R&D activities linked to their results would be very risky.

- Project assessment:

The main objective of SIMOPRO is to perform a fundamental research (the CEA policy implicitly states that about 30% of the funds should be dedicated to fundamental researches) and to look for possible applications. This point has been examined at different levels, that is team by team, this will not be discussed here, (see below) and a transversal programme (discussed in that section).

The transversal programme within SIMOPRO aims at "engineering" mini-proteins for therapeutic purposes. Based on the success story of the mini-CD4 molecule, they want to pursue this adventure with other molecules and other targets. This objective is a highly federative project, which requires all the competences present in the Unit, from bioinformatics, chemical grafting of functional motif onto identified scaffolds (toxins or not), to protein expression including site-directed mutagenesis, bioassays, radiolabelling for imaging, with the goal of diagnostic and/or therapeutics applications. In this project, as for the mini-CD4, the strong competences in immunochemistry of team 27 will be required and fundamental to "erase" immunogenicity.

This project will be presented to French pharmaceutical companies for partnership and a grant proposal will be submitted at the European call related to protein engineering (FP7-2011, call Health.2011.2.1.-2: Proteins and their interactions in health and disease.)

This project is considered as original since only in that Unit are all the competences present to undergo such a transversal programme. The members of the Committee estimated that the risk is possibly not at the scientific level, even if it is an ambitious programme. In fact, choice(s) will have to be made and intensive discussions with all teams will be necessary to concentrate all forces to a limited number of targets and molecules. The Committee believes that

an association with medical teams to validate the first defined targets and molecules would be an asset in this process, and recommends that this partnership be defined since the very beginning of the process.

4 • Appreciation team by team

Team 1: Function of zinc metalloproteases

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers	1	1
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	4
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	5 AI + 1 AII	2 AI + 1 AII
Number of post-docs for an average 18-24 months period (Form 2.7 of the unit's dossier)	2	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	1
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

The Group Leader is internationally recognized as a leader in the field of matrix metallopeptidase, this team has analysed in details the mechanism of action of these superfamily of enzymes (more than 35 types or subtypes), which play a crucial role in physiopathological processes. The most critical problem encountered with these proteases is to find a strategy aimed at designing one selective substrates and particularly inhibitors. This is one of the reason for which the clinical assays of MMPs inhibitors in cancer chemotherapy have been deceptive very likely due to a lack of specificity. To overcome this problem, the team has introduced in collaboration with a leader laboratory, the solid-phase synthesis of pseudopeptides containing as zinc chelator the phosphinic group. By this way, the team has been able to design the first highly potent and selective inhibitor of MMP12, a peptidase expressed in inflammatory situations, which seems to play a critical role in atherosclerosis. Moreover, the team was the first to obtain the probes necessary to investigate the physiological role of the two sites of ACE as well as ACE2 the role of which remains to be establish.

Many other innovations have to be developped in the team such as affinity capture of MMPs allowing to extract these enzymes from a given tissue (tumor for example). However this method has to be compared with the determination of corresponding mRNAs. Some preliminary results show that the challenge to find new MMP inhibitors devoid of zinc chelating group is possible.

The quality of the publications is of high standard taking into account the journals in relation with the research programm (25 papers and 2 patents). However in a number of publications (13), only the name of the Group Leader is present. These papers obviously are at least partly based on the use of the probes developped in the team. It should

be important in the future to ask the main authors to introduce at least one other member of the CEA team (if justified), and not only the name of the Group Leader.

Excellent for both hands this may be underlined regarding the quality of the international collaborations in more than 7 different countries.

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

Number and reputation of the awards obtained by staff members, including invitations to international conferences and symposia: Excellent, the Group Leader is regularly invited at the Gordon conferences on zinc metallopeptidases and peptide chemistry symposia.

Ability to recruit high levels scientists, post-docs and students, and more particularly from abroad: This is a point which warrants to be improved but is probably difficult due to the CEA politics for recruitement of post-doctoral fellows. Nevertheless 3 these have been defended during the lastest 5 years.

Ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters: Very good with various grants from european and international organisations as well as financial support from pharmaceutical industries.

Participation to international or national scientific networks, existence of stable collaborations with foreign partners: Excellent but warrants to be improved with clinicians and molecular biology laboratories to rapidly obtain the proof of concept of their innovations in the field of MMPs.

Concrete results of the research activity and socio-economic partnerships: Numerous collaborations with the parmaceutical industry, clinicians etc… Two patents and two molecules expected to give either biomarkers or drugs.

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

The team organisation seems efficient. The single remark concerns the papers in collaboration with external laboratories (the chemist who has synthesized the probe used in the study) of the team in addition to that of the leader should be introduced.

- Appreciation on the project

The projects are vey ambitious but feasible in 4 years and their interests are very high. The new strategy to design zinc metallopeptidase inhibitor essentially directed towards the recogition of the subsites and with only a weak interaction with the zinc atom is particularly interesting because a better bioavailabities of the inhibitors could be expected. The team has a long experience in the use of crystal data and computer modeling and some preliminary results seems already promising.

- Conclusion :

  - Summary

The team has the expertise to carry out the project, which has several components. The collaborations with well-recognized laboratories is perfectly adapted to the project and should be amplified in particular for the project concerning the detection of instable plaque, which is of major interest. It could be interesting not only to continue the studies on animal (use in parallel of KO MM12 and inhibitor binding to investigate the general distribution of MM12 not only restricted to the plaques). The detection of MMP active forms is also very interesting and the chemical approach very innovative. Nevertheless, it should be interesting to associate this quantification of expressed proteins with their corresponding mRNAs.

  - Strengths and opportunities

    - Excellent participation to international or national scientific networks. The Group Leader is regularly invited at the Gordon conferences on zinc metallopeptidases and peptide chemistry symposia.
    - Very good ability to raise funds, with various grants from european and international organisations as well as financial support from pharmaceutical industries.

- Excellent participation to international or national scientific networks, with stable collaborations with foreign partners.
- Numerous collaborations with the parmaceutical industry, clinicians etc… Two patents and two molecules expected to give either biomarkers or drugs.

– Weaknesses and threats

Few, but some subject warrants to be cautionously explored even if they are financially supported. Thus, inhibitors of zinc metallopeptidases putatively used in cardiovascular diseases is a highly competitive and risky domain. Vasopeptidases inhibitors targeting ACE and NEP have failed in clinic due to angioedema hypothesized to be due to inhibition of BK cleavage by NEP. In fact, this is not NEP, which is mainly involved but aminopeptidase B and unfortunatly omapatrilat is a rather good inhibitor of this BK degrading enzyme ! The involvement of these enzymes as well as ACE2 via apelin in other diseases (cancer etc…) seems to be more promising.

– Recommendations

All projects are interesting and obiously the problem is the choice. The committee thinks that except for MMP12, the interest for MMP is decreasing while that for MMPTM is increasing and the team has all the abilities to enter in this field. Moreover, the more fundamental projects on characterization of active sites, biomarkers etc… remain of major interest.

Team 2 : Molecular Modelling and Engineering of Tc-containing peptide and protein imaging agents

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	5
N3: Number of other researchers	0	0
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	0
Number of post-docs for an average 18-24 months period (Form 2.7 of the unit's dossier)	4	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	1
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

The research activities of this relatively new team were focused on four different themes coordinated by two different group leaders. In particular, one of the Group Leader developed his activity on structuring of small peptides and pseudopeptides through Technetium/Rhenium coordination by recurrent chelation motif for both diagnostic imaging and radiotherapeutic applications respectively. On the other hand the activity of the other Group Leader used novel TcO peptide sequences for protein and peptide Tc labeling. However, the central part of his research activities consists in developing a general approach for the design of mini-proteins able to interact at particular binding sites and important *in silico* methods to design protein-ligands.

The team was involved in INCa grant and many collaborative projects at the national level as demonstrated by some important common publications.

The level of publication of this relatively small group is excellent both qualitatively and quantitatively (41 articles in peer-reviewed journals and one European patent application on Tc or Re chelating peptide tags in 2005-2009). The expertise of the team in the field of Tritium labelling of proteins, peptides and pseudopeptides is also demonstrated by the technical support coordinated by one of the Group Leader for *in vitro* and *in vivo* experiments at SIMOPRO and other groups at CEA, as well as various academic and industrial partners.

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

The team is expert in: i) the field of peptide and protein labelling for the development of imaging agents and ii) of in silico methods to design mini-protein ligands. Both expertises up to now translated only into some collaborations with national research groups (INSERM 698, INSERM Paris, INSERM Strasbourg, CNRS Chatenay-Malabry, ESBS Strasbourg) should possibly be extended in the next four years also at the international community. Moreover, it could be interesting to organize the technical support already provided by one of the Group Leader in a real platform for peptide and protein labelling. Besides, some emphasis might be put on the recruitment of foreign post-docs and/or students.

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

Both protein labelling and in silico methods are critical research activities in SIMOPRO and generally speaking in CEA. Nevertheless this team suffers of a poor management possibly because of its quite young union. Common research policy is strongly recommended.

- Appreciation on the project

The project let expect an important impact in the next four years in the field of in vivo imaging. In fact combinatorial synthesis and screening of new complexes (possible stable Tc/Re locked templates) should lead to innovative tracers to be applied to specific and selective imaging agents. We strongly suggest making a careful choice of the targets. In this sense it is expected that the relevant projects mentioned as funding applications in the diagnostic field, if accepted by ARC, Ligue contre le cancer, ANR emergence, as well as TecScan will already consider specific and relevant tumor selection. If not, a detailed impact analyses will be strongly recommended.

In silico mini-protein design approach is also an extremely relevant project. Methodological development of molecular simulations and force field analyses could lead to a strong integration with the research topics of Team 24. This strong partnership should facilitate future obtainment of common resources.

The competence of team 25 is highly complementary to that of the other research teams within SIMOPRO. Both expertises of this team should be an asset for the advancement of several projects of the research Unit, in particular for the development of therapeutic mini-proteins. A strong effort in a common strategic management will be instrumental to the life of the Research Unit SIMOPRO.

Team 3 Transfer of binding sites through miniprotein engineering

- Staff members

	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
N3: Number of other researchers	0	0
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2 AI	0
Number of post-docs for an average 18-24 months period (Form 2.7 of the unit's dossier)	3 + 1 intérimaire	1
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

This team, coordinated by two Group Leaders, developed its research activities mainly in three different subjects, included in two areas: i) Design of an optimized miniCD4 as HIV microbicide candidate; and ii) Design of a new prophylactic vaccine candidate, based on a miniCD4-Env construct,

They focused attention on CD4, a primary receptor used by HIV-1 (through its gp120 envelope protein) to initiate access to host T cells. T cells with CD4 receptors suffer a progressive reduction in number with HIV infection, and the CD4 count is used as an evaluator for patient treatment. Therefore, CD4 is important at basic research and clinics of HIV infection. They isolated and minimized the CD4-binding surface of gp120 glycoprotein onto a small scorpion toxin scaffold and optimized their binding affinities, of those constructs or derived minipeptides (i.e., M48-U1), to subnanamolar level, for various envelope subtypes. This optimization was patented and used with different biological-biomedical purposes: i.e., M48-U1 totally abolished virus infection in *in vivo* models, and was one of the team repertoire elements to look for antiretroviral-microbicide strategies. Also, the CD4 and derived minimized motifs were used to analyze the development of a prophylactic vaccine against HIV because their binding to gp120 (*i.e.,* after injection of gp120-smallCD4 fusion protein to macaques) elicited CD4i antibodies, which were correlated to virus infection. This and related findings gave rise to another international patent, and to the establishment of a consortium, chaired by a large pharma (Novartis, USA).

The team enjoyed two French ANR grants and participated in two projects at European level, as well as in an NIH-USA based project. Besides the two international patents, the team had a scientific productivity based on 10 papers in journals of intermediate impact factor, in 4 of which it seemed to play a leading role. Certainly this number of publications (period 2005-2009) is modest, and somehow correlates with the small size of the group but, this number of publications is compensated by the significant number of patents (two with PCT), grants (four) and links with clinics and pharma industry.

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

It is surprising how a team with such small size and moderate productivity (in publications) succeeded in receiving invitations to join several international consortiums and grants, keeping excellent collaborative inks/partnership at national and international levels. In contrast, apparently they got no awards or oral invitations in international Congresses and had a null capacity to recruit new members and young scientists-collaborators (see 3 also). These clearly are points for improvement.

The clear applicative strategy of the team, particularly in protein and peptide-based approaches for fighting HIV infection, at its links with clinics and pharma industry, indicates a relevant socio-economic value of their projects.

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

This is a point of difficult judgment, among other reasons because of the very small size of the team (with 3 permanent members). Probably this strongly correlates with the history of the team, in which its formal leader left it recently, and with the co-leadership of two of its members, (in apparent contradiction with its small size). From the positive point of view, and by now, it seems that such a dual-leadership does not affect the life of the research team, and might help in grant writing and raising. However at the medium-long run this could have a negative impact in the capability of the team to face compromises and productivity (i.e., in the participation in Consortiums-large grants), in keeping a minimum "internal life" for a group, and on its external valorisation.

The team should consider diverse possibilities to expand, such as through the recruitment of foreign post-docs and/or students (now inexistent), as well in merging (functionally or formally) to other teams, as nº26, with whom they have many complementarities. The involvement in future teaching activities, now apparently absent, might also help in such desirable trends.

- Appreciation on the project

The proposed project for the next years, quite based in the previous success with international consortiums-grants, pharma industry and clinical applications, seems to be highly interesting and feasible. The three selected subjects: i) single-domain antibody inhibitors; ii) analysis of the basis of HIV virus resistance to treatments with mini-CD4s; and iii) development of specific and targeted anti-retroviral microbicides, are well-focused and attractive subjects at basic, applicative and technology-development level. For instance, the latter one might involve protein overexpression with incorporation of unnatural aminoacids, an issue of large biotechnologic interest and impact, if achieved.

Therefore, the perspectives are excellent, the policy for allocation of resources seems to be correct (if they keep the success in obtaining French and international grants), and the originality of the project is all right.

Apparently, the continuation of the team with such small number of members although it might seem highly risky for its future, might be an acceptable risk given its recent history and productivity (overall). However, they should try to compensate for these uncertainties and unbalances increasing the size of the Group (i.e., engineers-technicians to be hired by specific grants), incorporating PhD students and post-docs, and increasing the number and/or quality of publications. The establishment of collaborative links with other teams of the Institute, like nº 25 because of complementarities, and nº 27 to go deeper inside immunochemistry issues, would also be highly beneficial. Also, they should use their excellent international links and consortia to get invited in conferences as speakers, and improve some of the above-mentioned unbalanced points.

Team 4 Immunochemistry of the cellular immune response

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers	0	0
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4 AI + 3 AII	1 AI + 2 AII
Number of post-docs for an average 18-24 months period (Form 2.7 of the unit's dossier)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	0
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

This research team is focused on the understanding of CD4 T cell responses in human. In the past years they have developed specific technologies to identify CD4 T cell epitopes and characterize immunogenicity of proteins in human, including HLA class II specific binding assays and quantitative T cell stimulation assays. During the period 2005-2009, the team members have characterized CD4 T cells epitopes in a variety of pathogens, allergens or therapeutic proteins. They also identified CD4 T cells epitopes in tumor associated antigens and also discovered a novel tumor antigen.

The expertise of the team in the analysis CD4 T cell responses has given the group a large international recognition. The team is involved in many collaborative projects at the national and international levels. Most of these projects are supported by various dedicated grants (European FP7, NIH/NCI-NIAID, INCA, ANRS, NRBC).

The level of publication of this relatively small group is excellent both qualitatively and quantitatively (40 articles in peer-reviewed journals in 2005-2009). In addition the team has a very active valorization policy (7 patents filed and 1 license). The expertise of the team also led to a very close partnership with a biotech company. The group leader also co-founded another biotech company in 2009.

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

The team is internationally recognized for its work and expertise in the field of CD4 T cell immune response analysis. This translated into fruitful collaborations with both national and international research groups as well as strong partnerships with 2 biotech companies. The team obtained a number of competitive grants (at national and international levels) to fund the different lines of research.

The team has also an in-site collaboration (with SIMPOPRO Team 28), although its expertise in the characterization of protein immunogenicity could be certainly better exploited in the development of the various projects of the Research unit, in particular those aimed at developing therapeutic mini-proteins.

Besides, some emphasis might be put on the recruitment of foreign post-docs and/or students.

- Appreciation on the project

The project is in direct line with current research of the team. Building on their current knowledge they will expand their studies of immunogenicity of various pathogens or therapeutic proteins. They will develop new approaches to identify peptides that are endogenously processed by dendritic cells. These projects are developed mainly in the framework of long-term collaborations with academic laboratories or biotech partners. This strong partnership should facilitate future obtainment of resources through grant applications of private contracts.

The competence of the team is highly complementary to that of the other research teams within SIMOPRO. The well-established expertise of Team 27 in immunochemistry should be an asset for the advancement of several projects of the research Unit, in particular for the development of therapeutic mini-proteins.

- Global Appreciation on the team

Team 27 has been very successful in the past period achieving an excellent productivity and attracting a wide recognition at national and international level. The group has established numerous collaborations with both academic laboratories and private partners. The competence of the team in immunochemistry is highly complementary to that of the other research teams within SIMOPRO and should be valuable for the development of various projects of this Research unit.

Team 5 Toxin-Membrane Interactions

- Staff members

	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
N3: Number of other researchers	0	0
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4 AI + 2 AII	1 AII
Number of post-docs for an average 18-24 months period (Form 2.7 of the unit's dossier)	3	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	1
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

The research group "Toxin-Membrane Interactions" studies the mechanism of translocation of two bacterial toxins, the diphtheria toxin (DT) and the botulinum neurotoxin (BoNT) type A. Using site directed mutagenesis, they demonstrated that the six histidine (His) residues of the Diphteria Toxin T domain act in a concerted manner as pH-sensors leading to the unfolding of the protein (Perier et al. 2007, J Biol Chem). They have also shown that BoNT/A T domain exhibits a behavior very different from that of the DT T domain.

In the framework of the interministerial program of R&D against RNBC (Radiological, Nuclear, Biological and Chemical) threats conducted by CEA, this research group developed also inhibitors of bacterial and plant toxins, focusing mainly on BoNTs, ricin and Shiga toxins (Stxs). Screening 4 librairies of 30 000 compounds, four synthetic

compounds were identified as inhibitors and patented. Two compounds were able to protect mice from nasal instillation of ricin at an LD90. A manuscript has just been accepted in "Cell".

They also work on the design of an inhibitor of the growth factor HB-EGF, which is derived from the receptor binding (R) domain of DT. They also designed membrane anchors derived from the diphtheria toxin translocation (T) domain and the bee venom phospholipase A2 (PLA2) for cell engineering and cellular vaccine applications.

Accordingly, this group works on topics of relevant interest on a scientific point of view, since the understanding the mechanism of translocation of these toxins may help to design inhibitors and adapt these mechanisms for the delivery of therapeutic proteins into cells. Furthermore Ricin is considered as a potential bioterrorism weapon for which no antidote exists.

The quality and the impact of the results are well illustrated by the publications in either good to outstanding peer review journal (J. Biol Chem, Cell in 2010).

Number and quality of the publications, scientific communications, thesis and other outputs: 19 publications have been produced including in Cell, J. Mol. Biol., JACS, J. Biol. Chem, J. Immunol., FEBS Lett., J. Neurochem, Anal. Chem. The publications/researchers ratio is good (but not outstanding). Nevertheless the quality of the publications is pretty high.

The Group Leader communicated in seven conferences abroad (three as an invited speaker). The committee invites him to reinforce this aspect, especially taking advantage of the Cell paper.

Quality and stability of partnerships: Internal partnership with team 27 is appreciated. Several external partnerships with the Curie Institute, the AFSSAPS, etc..

- 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 communicated in three conferences abroad as invited speaker. No other recent awards

Ability to recruit high levels scientists, post-docs and students, and more particularly from abroad: Acceptable.

Ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters: Funded by NRBC program, ANR 2009 Emergence Bio call

Participation to international or national scientific networks, existence of stable collaborations with foreign partners: NRBC programs with USA

Concrete results of the research activity and socio-economic partnerships: The Group Leader is coordinator of the biological axis of the R&D interministerial program against RNBC threats conducted by CEA. Besides CEA, AFSSA, AFSSAPS, CNRS, Institut Curie, INSERM, IRSN, MNHN, Institut Pasteur and some Universities… iBiTec-s plays an essential role with the team leader co-ordinating about 25 projects, which involve 30 different teams, five being from SIMOPRO.

- Appreciation on the project

The interest of the project is excellent and in line with the previous 4 years. Their expertise associated with the general competences and technological platforms of the whole unit, allows them to expect for very interesting results in the next 4 years.

The policy for allocation of resources seems to be correct.

The prospects for the project are excellent and the originality of the proposed research is all right.

- Conclusion

  - Summary

This group works on topics of relevant interest, The quality and the impact of the results are well illustrated by the publication in good to outstanding peer review journals (J. Biol Chem, Cell).

– Strengths and opportunities

This group could take advantage of the interesting work recently accepted in Cell in order to get a better international recognition.

– Weaknesses and threats

- No major weaknesses or threat.

– Recommendations

- Increase the number of publications.
- Reinforce the number of communications abroad in general in order also to get more invitation as invited speaker. The good level of science made is in this group allows its mambers to do it.

Team 6 Toxins, Receptors and Channels

- Staff members

	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)	4	4
N3: Number of other researchers	0	0
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3 AI + 3 AII	1 AI + 2 AII
Number of post-docs for an average 18-24 months period (Form 2.7 of the unit's dossier)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file) (form 2.8)	1	none
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results:

Research in the straight line of that successfully carried out by this team and former department over more than a decade. Pertinent focus on two recently identified peptidic effectors targeting two poorly described transmembrane receptors of physio/pathological relevance. Challenging project within the international context. Well-defined methodological strategy consistent with the team expertise and buttressed by internal and external collaborations. Excellent correlation with the unit transversal projects and scientific endeavors.

Number and quality of the publications, scientific communications, thesis and other outputs: Thirty one publications in international journals, of which 1/3 shared by several members of the team (means IF, 4.7) and 2/3 related to external collaborations through one or two team members. Numerous communications in international and national meetings. Regular training of M2 and PhD students. Responsability of or contribution to high level grants (ANR 2006, ANR 2007, EU-FP6). 1 patent.

Quality and stability of partnerships : National and international partnerships providing access to a panel of expertises complementary to those present in the team or available in the lab.

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

Number and reputation of the awards obtained by staff members, including invitations to international conferences and symposia: Good, although essentially centered onto the team leader.

Ability to recruit high levels scientists, post-docs and students, and more particularly from abroad: Good, considering the limited opportunities in this area. Regular presence of a post-doc

Ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters: Good: 2 ANR grants, 1 EU-FP6 project, etc

Participation to international or national scientific networks, existence of stable collaborations with foreign partners: Good: EU-FP6 project, several long-term collaborations with national and foreign teams

Concrete results of the research activity and socio-economic partnerships: Good and regular: 31 publications, 1 patent

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

Strongly organized team with 4 researchers (including the group leader), 1 research technician, 1 PhD and/or post-doc fellow. The three researchers beside the group leader might want to direct some efforts toward individual (or at least shared) recognition in talking (best, getting invited) in meetings.

A fruitfull continuation of the orginal work initiated by the DIEP director on the isolation of toxins and the use of toxin as scaffold to graft motif. This team can be viewed as central for the mini-proteins SIMOPRO transversal project.

The Group Leader and one researcher teach for about 30 + 15h per year, considering the overall implication of the Unit in 110h-170h teachings per year.

- Appreciation on the project:

Existence, relevance and feasability of a long term (4 years) scientific project: Good – The local and collaborative technical expertise and facilities, human means, and ability to raise fundings are all consistent with the project. No doubt that successful data will be gathered within the next 4 yrs.

Existence and relevance of a policy for the allocation of ressources: Good, considering that all the teams now have to raise their own bench fees and temporary salaries

Originality and existence of cutting edge projects: Good – the two families of receptors addressed by this team need to be documented.

- Conclusion :

  – Summary

This is a solid team with a good record and a good project. It is well-positioned and recognized in the SIMOPRO unit and at the national and international levels. This team has been efficient in raising funds and promoting collaborations.

  – Strengths and opportunities

Excellent expertise in molecular toxinology, biochemistry and chemistry of small proteins, pharmacology. Right in the line of the general unit project.

  – Weaknesses and threats

Not many publications with the other teams.

– Recommendations

The three researchers beside the group leader might want to direct some efforts toward individual (or at least shared) recognition in talking (best, getting invited) in meetings.

Team 7: Enzymology and Non Ribosomal Peptide Biosynthesis

- Staff members

	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)	4	4
N3: Number of other researchers	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1 AI + 1 AII	
Number of post-docs for an average 18-24 months period (Form 2.7 of the unit's dossier)	2 + 2 intérimaire	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	1
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

This is a team (originally present in the DIEP and headed previously by Dr R. Genet, this team was completely renewed in 2005 after R. Genet left from CEA, with M. Gondry becoming the group leader) with high competences/activities in identifying and characterizing enzymatical systems responsible for synthetizing bioactive molecules produced by microorganisms but which are not dependent on the ribosomal machinery. Two interdependent enzymatic systems have been studied. The first one is a cyclodipeptide synthase, i.e., Cyclo(L-Phe-L-Leu) which belongs to a new synthesizing cyclo peptide enzyme family and whose activity is dependent on aminoacyl tRNA as substrates. The second enzymatic family, called the cyclopeptide tailoring family, is responsible of modifying the cyclopeptide produced by the cyclopeptide synthase. In the case of Mycobacterium tuberculosis, a specific P450, CYP121, whose gene is essential for M.T cell growth and viability, forms a C-C bond between the side chains of the cyclopeptide Tyr-Tyr, the mechanism of which remains to be determined. One of the final objectives is to synthezize selective inhibitor against CYP121. The results obtained so far are significant and are competitive at the international level.

The quality of the publications (those directly in the fields) is at a high/top level, but the quantity remains relatively low, it should be noted that the Group Leader has only published 9 publications for the period 2005-2009, plus five patents, the other publications are from, the bilan of whom is already included in team 25. The patents have been deposited in 2006-2008, which might explained the relatively low number of publications, since the most impressive publications (1 Nature Chemical Biology and one PNAS appeared at the end of 2009). The ratio publications/researchers is correct except for one researcher but who was recruited very recently (07/2008). Scientific communications is relatively modest. The number of Ph.D defence during the 2005-2009 period is 1.

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

Number and reputation of the awards obtained by staff members, including invitations to international conferences and symposia: This is a point, which needs to be significantly improved in particular for the Group Leader. The results obtained recently, which are of high level, deserve to be presented in top congress as invited speaker.

Ability to recruit high levels scientists, post-docs and students, and more particularly from abroad: In the present context, due to the policy of the CEA (few Ph.D and post-doc positions available), the ability to recruit post-docs and more particularly Ph.D students is thus difficult. A possibility would be to recruit via ANR grants but this implies to apply sucessfully to ANR program (thematic or "blanche").

Ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters: Only one grant was mentioned.

Participation to international or national scientific networks, existence of stable collaborations with foreign partners: This part could be improved at the international level although one national collaboration with a geneticist team from Orsay is remarkable and very efficient, plus one collaboration with KYOWA, Japan.

Concrete results of the research activity and socio-economic partnerships: Five patents.

- Appreciation on the project

The project is of high level and interest and should be feasible within the next 4 years. Yet, it will need high expertise in enzymology which includes to dominate sharp expertise for instance in "radical enzymology".

- Conclusion:

  – Summary:

The team has the expertise to carry out the project whose one of its main interest is to open a new route to block Mycobacterium Tuberculosis. Collaborations with teams from SIMOPRO and iBiTec-S (3-D structure, design and synthesis of selective inhibitor against CYP 121) and from also teams from University are already engaged that are essential for the success of the project.

  – Strengths and opportunities:

Good expertise in the fields and good reseaux of collaborations at the national level.

  – Weaknesses and threats:

The team needs to be more visible at the national and international levels and should apply successfully to ANR to obtain financial support.

  – Recommendations:

The team has initiated in the recent period a very promising project which mixes academic research of high level and potential applications in health care. This will help the team, in particular his PI, to acquire a national and international visibility.

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

Nom de l'équipe : FUNCTION OF ZINC-METALLOPROTEASES

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

Nom de l'équipe : MOLECULAR MODELLING AND ENGINEERING OF TC-CONTAINING PEPTIDE AND PROTEIN IMAGING AGENTS

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

Nom de l'équipe : TRANSFER OF BINDING SITES THROUGH MINIPROTEIN ENGIINEERING

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

Nom de l'équipe : IMMUNOCHEMISTRY OF THE CELLULAR IMMUNE RESPONSE

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

Nom de l'équipe TOXIN – MEMBRANE INTERACTIONS

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

Nom de l'équipe TOXINS, RECEPTORS AND CHANNELS

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

Nom de l'équipe : ENZYMOLOGY AND NON RIBOSOMAL PEPTIDE BIOSYNTHESIS

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

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L'Administrateur Général

Monsieur Pierre GLORIEUX
Directeur de la section des Unités de recherche

AERES
20, rue Vivienne
75002 PARIS

Saclay, le 07 mai 2010

N/Réf. : DPg/AN/np/2010-132

Objet : Observations du CEA sur le rapport d'évaluation du « Service d'ingénierie moléculaire des protéines » (iBiTec-S/SIMOPRO)

Monsieur le Directeur,

Je remercie tout d'abord l'AERES pour la qualité du rapport d'évaluation sur l'activité du « Service d'ingénierie moléculaire des protéines » situé au sein de l'Institut de biologie et de technologies de Saclay et pour la pertinence des recommandations qui ont été faites.

En tant qu'Administrateur Général de l'Etablissement CEA, ce rapport n'appelle pas de commentaires particuliers de ma part. Je puis vous assurer que je prêterai la plus grande attention à la mise en œuvre des actions qui permettront de répondre aux recommandations formulées par l'Agence.

Veuillez agréer, Monsieur le Directeur, l'expression de mes cordiales salutations.

Bien cordialement,

Bernard BIGOT

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DIRECTION DES SCIENCES DU VIVANT
INSTITUT DE BIOLOGIE ET DE TECHNOLOGIES DE SACLAY
SERVICE D'INGENIERIE MOLECULAIRE DES PROTEINES

Mr le Dr Jacques Baratti
Comité d'évaluation AERES du SIMOPRO

Saclay, le 13 avril 2010

Réf : DSV/iBiTec-S/SIMOPRO/10/094/VD

Monsieur Baratti,

Vous trouverez ci-dessous les observations que m'a inspiré la lecture détaillée du rapport du comité d'évaluation désigné par l'AERES sur les activités du SIMOPRO.

- ***Sur le SIMOPRO :***

Page 5: Weaknesses and threats : **The weaknesses are at two levels, a first one that is intrinsic to the SIMORPO organization: too many small teams…..**

Concernant la taille des équipes et le nombre de projets développés, il faut garder en mémoire la restructuration récente du DIEP (11 équipes) en SIMOPRO (7 équipes), qui date seulement de 2007. La réduction du nombre d'équipes entre le DIEP et le SIMOPRO a été l'occasion de renforcer certaines équipes du SIMOPRO. Cependant, afin de préserver une certaine productivité scientifique (reconnue par l'AERES) et de faire en sorte que la restructuration du SIMOPRO soit vécue de la meilleure façon, un équilibre délicat entre le nombre d'équipes et le maintien des projets ont été des paramètres importants à prendre en compte pour la structure du SIMOPRO. L'augmentation de la productivité scientifique du SIMOPRO par rapport au DIEP (nombre de publications, brevets, budget sur contrats) semble valider ce choix. Une fois la restructuration du SIMOPRO réalisée et vécue de façon positive par les équipes, on pourra certainement comme suggéré par l'AERES renforcer certaines équipes par regroupement thématique ou, sur la base d'une excellence scientifique, par l'obtention des postes nécessaires, provenant du CEA ou bien d'autres organismes.

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Page 7, paragraphe 5: **considering that the main objective of the SIMOPRO researches is focused on applications, the committee remarked as a weakness too rare connextions/partnerchips with clinician teams:**

La relation avec des cliniciens est un problème difficile à résoudre dans l'axe thérapeutique. Elle se fait une fois validé l'intérêt des composés dans différents modèles animaux. Plusieurs composés développés au SIMOPRO ont été récemment analysés dans différents modèles animaux avec de très bons résultats. Malheureusement, compte tenu des coûts d'une étude clinique, la relation avec les cliniciens ne peut se faire que dans le cadre d'un partenariat avec des firmes pharmaceutiques, si celles-ci s'intéressent aux composés du SIMOPRO. Cependant, dans le cas du projet mini-CD4, le SIMOPRO a réussi à convaincre la société Novartis de réaliser une étude clinique chez le Macaque.

Dans le cas des agents de contraste, la situation est plus simple, car nous travaillons directement avec des médecins responsables de plates-formes en médecine nucléaire (JB Michel et D. Le Guludec à Bichat et D. Fagret à Grenoble). Par ailleurs, une fois les composés validés chez l'animal, le passage à l'homme se fait plus facilement et les études nécessaires peuvent être soutenues financièrement par des programmes spécifiques de l'ANR (Tecsan).

- ***Team 1 :***

Page 10, troisième paragraphe: **However in a number of publications (13), only the name of the Group Leader is present.**

La présence de 13 publications dans lesquelles n'apparaît que le nom du groupe Leader vient d'une part de l'étude de composés ayant été développés avant la présence des chercheurs actuels dans l'équipe et d'autre part de travaux collaboratifs avec une équipe de chimistes Grecs, résultant de discussions scientifiques sur la chimie des peptides phosphiniques.

Page 11, troisième paragraphe: **Ability to recruit high levels scientists, post-doc and students, and more particularly from abroad: this is a point which warrants to be improved….**

Après avoir fonctionné longtemps avec des post-docs étrangers, grâce notamment aux nombreux contrats Européens, ces dernières années l'accent a été mis sur des post-docs français, pouvant être présentés à l'embauche au CEA, une stratégie ayant abouti au recrutement des deux seuls chercheurs du groupe actuellement.

- ***Team 3 :***

Page 16: troisième paragraphe: **However at the medium-long run this could (size of the team) have a negative impact**…

Le recrutement d'un chercheur pour cette équipe est la priorité du SIMOPRO en matière d'embauche. Dans un contexte fort morose, le SIMOPRO, grâce à un départ à la retraite en 2010, espère obtenir satisfaction.

- ***Team 7 :***

Page 23, deuxième paragraphe: **The quality of the publications (those directly in the field) is at high/top level, but the quantity remains relatively low (publications), it should be noted the Group Leader has only 9 publications…**

La découverte d'une nouvelle famille d'enzymes reste un événement rare en enzymologie, justifiant le dépôt de 5 brevets par M. Gondry et l'intérêt d'un industriel Japonais. A partir de 2007, les options qui ont été prises par cette équipe ont été d'élucider d'une part la structure 3D d'un des membres de cette famille (travail non publié) et d'autre part de clarifier le mécanisme enzymatique. L'établissement de ce dernier a été plus difficile que prévu, en effet personne ne pouvait imaginer raisonnablement que le substrat était du type aminoacyl tRNA. Cette découverte, bien que longue, a néanmoins assuré la publication du travail dans Nature Chem Biol. On a donc choisi dans ce cas une stratégie de brevets et de publications en faible nombre, mais de fort impact. Il en est de même pour la structure de l'enzyme résolue depuis 2 ans, mais dont la publication ne se fera que cette année, après avoir réalisé l'ensemble de la mutagenèse du site actif, permettant aujourd'hui une reprogrammation effective de ces enzymes, en les faisant produire des cyclo-dipeptides non codés (résultat présenté au comité le 19 Mars dernier). Ce travail exhaustif permettra encore une fois une publication de très fort impact, au lieu de plusieurs papiers moins importants.

Cordialement,

Dr. Vincent DIVE
Chef du SIMOPRO