SIMOPRO - Service d'ingénérie moléculaire des protéines

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Service d'ingénierie moléculaire des protéines

SIMOPRO

Under the supervision of the following institutions and research bodies:

Commissariat à l'énergie atomique et aux énergies alternatives

Institut National de la Santé Et de la Recherche Médicale - INSERM

December 2013

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr Didier HOUSSIN, president
- Mr Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Mr Jean-Luc GALZI, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the expert committee, the composition of which is specified below.

The assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Service d'ingénierie moléculaire des protéines
Unit acronym:	SIMOPRO
Label requested:	CEA and INSERM
Present no.:	
Name of Director (2013-2014):	Mr Vincent DIVE
Name of Project Leader (2015-2019):	Mr Vincent DIVE

Expert committee members

Chair:	Mr Jean-Luc GALZI, CNRS, Illkirch, France
Experts:	Mr Jean-Jacques FOURNIÉ, Cancer research center Toulouse (representative of INSERM CSS)
	Mr Cesare MONTECUCCO, University of Padua, Italy
	Mr Didier ROGNAN, Laboratory of therapeutic innovation, Strasbourg
	Mr Shu YE, William Harvey Research Institute, London, United Kingdom

Scientific delegate representing the AERES:

Mr Jacques BARATTI

Representative(s) of the unit's supervising institutions and bodies:

Mr Jean-Marc GROGNET, IBITECs CEA

Ms Marie-Josephe LEROY-ZAMIA, INSERM

Mr Eric QUEMENEUR, Direction des Sciences du Vivant, CEA

1 • Introduction

History and geographical location of the unit

The SIMOPRO laboratory is located in Saclay near Paris, within one of the historical research campuses of the Commissariat à l'Energie Atomique et aux Energies Alternatives. The laboratory belongs to the life sciences division which was originally founded to work on Biological, radiological, nuclear and explosive risks. Accordingly, its main focus is on new chemical and biochemical entities with potential applications in diagnostic and therapeutic areas.

SIMOPRO was created in 2008, under the supervision of its present director with the aim to understand architecture and function of proteins and to engineer selected proteins into useful scaffolds for basic and applied research. SIMOPRO ("the laboratory") gathers two laboratories (or "departments") comprising three teams each. There are in addition 5 technological platforms with expertise in analytical chemistry, protein production and purification, cristallogenesis, and animal housing. The fith platform is very specific to the CEA as it ensures production of radioactively labelled small molecules (^{3}H, ^{125}I, ^{99m}Tc, ^{14}C).

Management team

The management team is composed of a director and a vice-director, supported by an executive board of team leaders and a laboratory council of elected members. A 4-person administrative team is in charge of budget, secretary, building maintainance, orders processing and laundry.

AERES nomenclature

SVE1-LS7

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent researchers from Institutions and similar positions	24	22
N3: Other permanent staff (without research duties)		
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	22	22
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	46	44

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	5	
Theses defended	12	
Postdoctoral students having spent at least 12 months in the unit	19	
Number of Research Supervisor Qualifications (HDR) taken	13	
Qualified research supervisors (with an HDR) or similar positions	11	

2 • Assessment of the unit

Strengths and opportunities related to the context

The research done by members of the unit is globally of high quality in both basic and applied research.

The laboratory is clearly a leader in the field of molecule labeling, structural biology of mini proteins and enzymes and masters several technologies in the field of protein production, purification, mutagenesis, structure solution and molecule design based on miniproteins.

The association of all teams to the LabEx LERMIT is fundamental for the future of the laboratory and for its integration in the forthcoming structuration of the Saclay-Paris Sud research campus.

The coupling of basic and applied research with major national defense issues is an added value to the activities of the laboratory, which is recognized nationally and internationally for its expertise in the protection against biohazards and potential bio terrorist attacks. The laboratory thus maintains important interactions with government organizations (Army, ministries of defense, domestic affairs, foreign affairs …) and has acquired reputed expertise in bacterial, chemical, nuclear risks management. This also ensures (CBRNe funding) part of the funding for basic and applied research on toxins mechanisms of action and antidotes development. To increase SIMOPRO ability to recruit high levels scientists, post-doc and students significant efforts have been dedicated to establish many International collaborative projects. Thus, SIMOPRO' teams were/are involved in 11 European Projects (One as coordinator, Venomics) and two NHI projects over the evaluation period.

A number of high quality technical facilities are available to cover needs in protein expression, radioactive and other isotopes labeling of molecules, cristallogenesis, in vivo imaging. These would deserve upgrading to maintain the high level of services that are expected in the future.

Overall, there are excellent opportunities for translational science with envisaged of miniproteins as tool for basic research, but also for tissue addressing systems and therapeutic or diagnostic applications. Apart the mini-CD4 project leading to several publications and two European projects, new miniproteins have been tailored and tested for therapeutic applications, such as the mamba-quaretine toxin for kidney polykistoses and hyponatria and the development of an inhibitor of HB-EGF from its natural ligand, diphtheria toxin, for the treatment of rapidly progressive glomerulonephritis and other HB-EGF-related diseases. In addition, based on their results, two groups from SIMOPRO are involved in international projects funded for the next 5 years, comprising preclinical evaluations in animal model and phase I human clinical trial.

Weaknesses and threats related to the context

There is a serious and actual risk, linked to budget cuts and reduction in personnel recruitment, that the unit will not be able to manage all current research topics in the future.

The task force in biology on the CEA campus in Saclay is pretty limited. Scientific animation presently relies mainly on initiatives from the LabEx LERMIT, the center of gravity of which is rather far from Saclay. Attendance to seminars is thus not easy and causes long travel periods of time. There appears to be a limited number of invited scientists who could give seminars within the unit and promote the education of the younger investigators (Ph.D. and post-docs which appear to be rather isolated).

Contribution of laboratory members to teaching efforts is very heterogeneous. Some researchers are deeply involved and teaching and have thus numerous contacts with students for master training while others could certainly do better.

Recommendations

The laboratory should consider a future strategy to cope with the significantly reduced possibilities to hire researchers and important cuts in recurrent budget coming from the CEA. All teams are therefore strongly invited to focus their activities around a central common theme, e.g. miniproteins with therapeutic and diagnostic potential that is the most recognized core expertise of the laboratory.

Although the laboratory takes part to the LabEx Lermit which offers scientific events, local scientific animation should be further developped to counterbalance the relative isolation of the laboratory that results from poor representation of biology on the campus in its present configuration. Regular conferences given by invited external speakers might be regarded as a possibility, particularly considering the large scientific community near Paris.

Information to personnel about unit strategy and decisions is scarse. Laboratory internal communication deserves improvement through, for instance, general assembly venues, and more frequent consultations of the laboratory council.

Sustained efforts should be devoted to participation in training in order to attract doctoral fellows more efficiently. The laboratory has a unique expertise (synthetic biology applied to protein engineering and NRBCe research) that deserves dissemination in the university and in other research centers.

3 • Detailed assessments

Assessment of scientific quality and outputs

Globally, during the past period, the unit members have published 205 articles in peer reviewed journals, including 7 of high to exceptional level (1 Cell, 2 NAR, 1 Plos Pathog, 1Blood, 1 PNAS, 1 Nat Chem Biol). Approximately half of the articles are issued from the laboratory as can be judged from authorship analysis, however, for the high impact articles corresponding authors belong to SIMOPRO.

Laboratory members gave 104 invited conferences at national and international congresses (including 8 Gordon conferences) and gave another 51 talks/seminars in research institutes. Research themes are globally original (MMP inhibitors with important physiological roles, studies on immunogenicity, modeling and production of miniproteins for therapeutic purposes, analysis of toxins mechanisms of action) and some groups are clearly leaders in their field at the international level. Yet, the team-by-team analysis (below) shows heterogeneity in the average amount and quality of publications.

Assessment of the unit's academic reputation and appeal

Some indicators of the laboratory reputation are detailed above, such as the number of invited lectures at international conferences and research centers, but an important factor is the capacity of attracting fund for research which is to be considered very high.

The coordination of national (10 ANR/INCA grants), several DGA/NRBC (10) contracts, eu-projects/networks as coordinators (1), Work package leader (1) or co-investigators (10) well illustrates the reputation on the laboratory teams at the national and international level.

The participation of all teams to the LabEx LERMIT (and of one team to a second LabEx: VRI – Vaccine Research Institute), to the Idex project MABIO and to the Investment for the future DIGIDIAG (Santé & biotechnologies call 2011; coordination of WP14) also highlight the pivotal position of the unit in the structuration of the research campus in Saclay-Paris Sud that is underway.

Two teams have received grants from the NIH for 4 years.

In addition, it should be noted that the laboratory succeeded in attracting three scientists from the CNRS and one Emeritus Research Director to join the group working on venom toxins to develop toxinology in the peripheral and central nervous system. This team extension is particularly important because it will expand the scientific collaboration on marine neurotoxins which is a scientific suject of major importance as well as a matter of paramount concern for a major French industry.

Master students are applying for their laboratory training. Yet, the internal CEA rules renders their recruitment too expensive to afford enroling as many as teams or projects could accommodate.

Assessment of the unit's interaction with the social, economic and cultural environment

During the past five years the laboratory globally increased its income in research contracts (1,36 M€ in 2012), which represent a 35% increase as compared to 2009. This increase is couterbalanced by a significant reduction of CEA recurrent support to the unit which has passed from 800 k€ to 470 k€ in the same period.

Simopro researchers have filed 16 patents in the past period and launched two start-up companies : Vaxeal and VenomTech to which they have licensed some of the patents.

One of the team leaders is coordinator for biology of the joint ministerial program of R&D against chemical, biological, radiological, nuclear and explosives (CNRBe) risks. As such, he supervises 20 research programs involving 30 laboratories from the CEA and 15 other french laboratories from CNRS, INSERM, and universities. The activity also includes contracting with public and private bodies and promoting technology transfer to industrial partners and to the Biotox-Piratox network in charge of public health and safety. Another team leader is in the advisory board of the Labex LERMIT, supervising the 35 research programs currently run by 45 laboratories from the Labex and is a member of the INSERM national committee 8.

Products, know-hows and detection methods developped in the unit were transferred to companies such as Abraxis, Novakits, GeneSystems, NBC-Sys,Antabio, Sanofi, UCB Pharma.

Several researcher are members, and one of them is president, of the French society of toxinology (SFET).

Assessment of the unit's organisation and life

The laboratory is headed by its director assisted by a vice-director and an administrative team comprising a secretary, one financial administrator and two persons for general laboratory maintenance.

Team leaders meet regularly to discuss science issues. Informations however do not come down at the researcher and technician levels.

A laboratory council does appear in the rules of procedures of the laboratory but does not indeed meet regularly. Thus collaborators complain about poor internal communication and absence of general assemblies to share information.

Isolation is a problem for some categories of researchers (no tradition to organize seminars) particularly the younger people who need to participate to congresses, specialized schools, training courses etc.

Technicians would take advantage of internal mobility offers being published and would be interested to attend continuous training programs.

Assessment of the unit's involvement in training through research

Several members of the laboratory assume teaching duties, but to a limited extent on average.

20 PhD thesis defenses were held during the past five years, showing a remarkable dynamism of teams to train PhD students.

Altogether, the laboratory staff provides more than 100 hours of lectures in several universities, mostly in Paris and South of Paris, in toxicology, protein engineering, biomolecular engineering.

Several researchers have also organized or co-organized conferences including national meetings on toxin research, one Gordon conference, round tables and workshop on biohazards and biodefense, among others.

Assessment of the strategy and the five-year plan

For the future period, the laboratory capitalizes on its expertise in mini proteins design, synthesis and structural biology, to develop engineering for therapeutic and diagnostic purposes. It is supported in this effort by its own solid assets as well as by the task force of the LabEx LERMIT that provides complementary expertise, especially in animal models, and access to hospital services and clinical research.

This strategy is in line with the need to focus on major task forces of the laboratory and justifies the orientation of the unit towards medical research institutions.

4 • Team-by-team analysis

Team 1 : Function of Zinc metalloproteases

Name of team leader: Mr Vincent DIVE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	5	5
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	6	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	11	5

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	7	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	2	3

• Detailed assessments

Assessment of scientific quality and outputs

The team leader is an internationally recognized leader in the development of matrix metalloproteinases inhibitors. The team has developped a selective MMP12 inhibitor. This work is novel as no other selective MMP12 inhibitor is currently available. The team has since demonstrated in a mouse model that this inhibitor can stabilize atherosclerotic plaque, which has a potential in translational medicine because the rupture of unstable

atherosclerotic plaques is the commonest cause of coronary heart disease complications such as myocardial infarction. Other important findings and methodology developments from this team include the detection of an endogenous MM12 active form with a novel broad spectrum activity-based probe, and the finding of simple pseudo-dipeptides with a P2' glutamate as a novel inhibitor family of MMPs and other metzincins. Another recent and important novel finding is that MMP-12 inhibitors might represent a novel class of antiviral agents (Nature Medicine, in press). Regarding novel technologies, the group has/is involved in several International programs dealing with the toxicology of nanoparticles (Nanogenotox FP7, Nanomile FP7) and use of nanoparticles in nanomedicine (Nano-Athero, FP7). These programs will help the team to collaborate with the Labex NanoInnove located in the Paris-Sacaly Campus. From 2008 to 2013, the team published 38 papers, many of which are in leading journals in their research field, such as FASEB J (1), ATVB (1), JACS (1), JBC (5), J Med Chem (1) and J Prot Res (1).

Assessment of the team's academic reputation and appeal

The group has a very high impact in the community. Its international recognition and visibility are reflected by their participation in a number of international conferences (x12) as invited speakers or session chairs, and also by a number of international research programs (NIH grant (x1) and European grants (x4)). The work of the team involves extensive collaborations with researchers in Canada and many European countries.

At the national level, the team is involved in several ANR contracts and is a member of the LabEx LERMIT. The team leader is in the advisory board of the Labex LERMIT and is the co-leader of the Lermit workpackage « new strategies in drug targeting in cardiovascular diseases and a member of the INSERM national committee 8.

Assessment of the team's interaction with the social, economic and cultural environment

The team has a long-term collaboration with a biotechnology company Vect-Horus. They have 2 patents and other one pending.

Assessment of the unit's involvement in training through research

The group shows no implication in teaching besides training of PhD students.

Assessment of the strategy and the five-year plan

The research strategy and plan for the next five years is ambitious and innovative, with potential for medical applications.

The planned research program is an expansion of the current research of this team, with scientifically sounds objectives. These objectives should be feasible to achieve because the team has relevant expertise and technical skills, a number of research grants, and access to a range of facilities and tools.

Conclusion

- **Strengths and opportunities:**

The team is internationally recognized in its field of research and thus benefits from many national and international collaborations that are already funded for the next five years.

The team has a strong track record of publications and research grants.

Their research program is innovative with strong potential for medical application.

They have wide international connections/networks with other leading researchers in the field.

The team leader is deeply involved in all international protease networks.

- **Weaknesses and threats:**

As a consequence of poorly established links with pharma industries and clinical research, patents are not yet licensed.

The very limited, to almost non-existent, involvement in teaching renders very diffcult to attract students for PhD training as well as post docs. This is of particular importance if one considers that CEA will not recruit new researchers in the next five years.

- **Recommendations:**

It is recommended that the team continue to extend their research in developing protease inhibitors and methods for detection of active proteases, and their potential for medical applications. The team leader should thus pay more attention at identifying partners for drug development as this is the logical progression of the work carried out.

To attenuate the difficulties linked to the drop of personnel recruitment at the CEA, the team should make efforts in teaching and other sort of training programs in order to attract young scientists and perpetuate excellence in the field.

Team 2 : Modelling and molecular engineering

Name of team leader: Mr Philippe CUNIASSE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	6	4

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students		
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	3	

• Detailed assessments

Assessment of scientific quality and outputs

During the evaluation period 41 per reviewed publications and one patent have been produced. Among them, there are only 10 publications in which a team member is either first or last contributing author. A significant amount of papers concern the study and valorization of the artificial mini-protein (mini-CD4) designed using the grafting approach. One third of the scientific production (theoretical physical chemistry) is related to the development of POLARIS(MD), a new generation force-field incorporating an advanced physical model that takes explicitly polarization into account for application in bio-molecular simulations and chemical applications. About half of the 40 papers

published during the period are not related to the PI's activity but signed by one member of the team, Dr Loïc Martin that recently joined it.

Assessment of the unit's academic reputation and appeal

There are 3 permanent scientists in 2 ANR Committees and a participation to 3 EU projects. The team is a member of LERMIT LabEx, but its attractivity is difficult to assess, if any. Strong weakness in the team's visibility with a single member (not the PI) being invited to national and international congresses.

Several local and international grants are of unknown amounts.

Assessment of the unit's interaction with the social, economic and cultural environment

POLARIS(MD) is developed in collaboration with INTEL corporation for optimization of the performance of the code. STAMPS and POLARIS(MD) are protected by copyrights via a deposit at the French association for software protection (APP).

Assessment of the unit's involvement in training through research

The team belongs to the École Doctorale 'Innovation Thérapeutique' and has hosted 6 post-docs but a single PhD and a single Master student. No teaching activities are reported.

Assessment of the strategy and the five-year plan

The project deals with the design of artificial protein ligands by grafting functional residues on (mini-)protein scaffolds. These scaffolds are identified using the STAMPS software developed in the MIM team. The objective of the project is the design of artificial mini-proteins for therapeutic and diagnostic applications. The strategy in based on the grafting of functional motifs of residue on mini-protein scaffolds. The currently developed applications concern important human-health topics like blood-brain barrier crossing, LDL regulation for cholesterol control and tumour targeting. This work lie in the general context of "biologics" with the aim of designing protein ligands as alternative to antibodies for therapeutic or diagnostic applications, a domain of intense activity during the last decade. One key asset of the protein binder design method developed in the MIM team is the complete mastery of the IP. The MIM team has an important contribution to the transversal project of SIMOPRO for designing mini-proteins for therapeutic and diagnostic applications. Indeed, one strategic orientation of the section relies on the in silico design of the first generation artificial mini-protein binders using the method and the bioinformatics tools developed in the MIM team.

Conclusion

- **Strengths and opportunities:**

Past experience has led to a a single proof of concept that should be extended.

Existence of a collaborational network (Labex and international Network).

- **Weaknesses and threats:**

Missing strategy explains the relatively low scientific output. Biological aims and perspectives are missing.

Strong dependence on collaborations outside of the lab.

Teaching students are missing.

No benchmark of developed software with state-of the art approaches to estimate its true value.

- **Recommendations:**

Computational biology could be transferred to a research platform without affecting SIMOPRO's project.

Team 3 : Immunochemistry of the cellular immune response

Name of team leader: Mr Bernard MAILLÈRES

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	6	2

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	1	

• Detailed assessments

Assessment of scientific quality and outputs

The team investigates the prediction of immunogenicity in humans with the perspective of developing new vaccines, new diagnosis tools and safe therapeutic proteins. They produced on this topic 40 articles from Jan 2008 to Jun 2013 in good IF journals and filed 4 patents. They characterized the CD4 T cell epitopes of LAGE and Survivin tumor antigens, depicted the CD8 and CD4 T cell responses to the tumor antigen Midkine and showed that the immunogenicity of therapeutic antibodies and erythropoietin can be predicted by quantifying TCR repertoire.

Assessment of the unit's academic reputation and appeal

The team is member of LabEx LERMIT and LabEx VRI, it is involved in three international programs supported by NIH, IMI and FP7, and three national collaborative projects supported by ANR (one as coordinator) and NRBC funding.

Assessment of the unit's interaction with the social, economic and cultural environment

The team was recently granted by the NIH for 4 years to run T cell epitope mapping and from IMI (ABIRISK) to delineate immunogenicity of therapeutic proteins.

The team created a commercial service in collaboration with PROTEUS and licenced a patent to INDICIA.

They licenced 3 patents to the VAXEAL to develop therapeutic vaccines against cancer and chronic viruses.

They are part of CELLESTIM (sponsored by ANR) to improve the methods of T cell investigation.

Assessment of the unit's involvement in training through research

One PhD student, teaches 9h/year in Master 2 at AgroParistech.

Assessment of the strategy and the five-year plan

The project is to evaluate the affinity of peptides for HLA class II molecules and the number of specific CD4 T lymphocytes among normal donors PBMC. They have been applied to vaccine candidates and therapeutic proteins. The project is sound and of very good quality, although it might have been more ambitious.

Conclusion

- **Strengths and opportunities:**

The group has a good production rate, appropriate equipments and in house technologies that ensure competitiveness.

Past experience has led to a proof of concept.

Collaborative network (Labex and international Network).

Continuation of former strategy and projects.

- **Recommendations:**

The team should enlarge its range of technologies to warrant publication is highest journals in the field.

The LabEx environment will be useful to acquire expertise in clinical issues linked to the topic.

Team 4 : Toxin-membrane interactions

Name of team leader: Mr Daniel GILLET

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	6	3

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	1	

- Detailed assessments

Assessment of scientific quality and outputs

The team explores the development of therapeutics from bacterial and plant toxins. They also manage the biology projects of the Joint ministerial program of R&D against CBRNe threats (encompassing 30 research teams from 15 academic entities).

They identified protective inhibitors of ricin, Shigatoxins and other pathogens. They produced an inhibitor of HB-EGF, which causes kidney destruction in glomerulonephritis, and they characterized the successive steps through

which the diphtheria toxin and the botulinum neurotoxin interact with a membrane to initiate their lethal membrane translocation.

They produced 18 (11+7) publications in good to very high IF including 1 in Cell , NAR and JACS. In summary, an excellent production for 6 ETP.

Assessment of the unit's academic reputation and appeal

The team, which is a member of LERMIT LabEx, manages the biology projects of the Joint ministerial program of R&D against CBRNe threats, representing 20 research projects involving 30 research teams in 15 academic entities.

Team members were invited speakers in 4 national, 9 international conferences, 13 seminars, 2 round tables; Yearly organization of Bio CBRN Scientific Day of Joint ministerial program of R&D against CBRN risks.

The PI has been awarded Knight in the Order of the Academic Palms.

Assessment of the unit's interaction with the social, economic and cultural environment

The team has a total of 6 patent applications and one contract with the small pharma Antabio to develop anti-ricin drug.

The team is a member of the Labex LERMIT and obtained grants from DGA, ANR, 1 UCB Pharma, 1 CEA Life Sciences Division, 1 Irtelis PhD program, 5 yearly Joint ministerial R&D program against CBRNE risks.

The team has several membership: member of the evaluation committee of the French National Research Agency call "Astrid" in 2012 and 2013; member of the Biotox-Piratox Scientific Committee since 2009; member of the Scientific Prospective Bio Comittee of the High Commissioner on Nuclear Energy (2007-2012).

There are collaborations in France, UE and USA.

Assessment of the unit's involvement in training through research

Member of the boards of the CBRN Master at Ecole du Val de Grace – UPMC and the TMMCE Master at the National Museum of Natural History. Organization of 3 teaching units of 9 ECTS.

3 PhD thesis have been defended during the evaluation period.

Assessment of the strategy and the five-year plan

An excellent strategy focussed on 2 themes:

1) characterize the protection mechanisms against Ebola, rabies, dengue viruses and Leishmania (in collaborations). Run new screens against toxins acting on small G proteins and cell signaling inducing innate and adaptive immunity.

2) study the therapeutic effect of the HB-EGF inhibitor against RPGN.

Conclusion

- **Strengths and opportunities:**

- Excellent scientific project;

- Excellent production;

- Outstanding socioeconomical significance of the research;

- Excellent collaborational network;

- A wise strategy of continuation of former projects.

- **Weaknesses and threats:**

None, expect the low number of sponsor origins.

Team 5 : Toxins, receptors and channels

Name of team leader: Mr Denis SERVENT

Workforce :

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	4	7
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	6	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	10	7

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	3	5
Qualified research supervisors (with an HDR) or similar positions	3	

• Detailed assessments

Assessment of scientific quality and outputs

This group has established itself at the front line of current research in the field of animal toxinology and is a leader in the study of novel peptide/protein toxins that bind to ion channels and to receptors, with particular attention to the G protein coupled receptors.

The group has characterized novel toxins that act on specific muscarinic receptors, and other receptors of this class, and, using protein engineering, is trying to improve and extend the binding to other receptor isoforms to obtain novel therapeutics and novel tools for research.

The group has identified a vasopressin 2 receptor binding toxins that it is under evaluation for treatment of the polycystic kidney disease. Another potentially important discovery is the fact that toxins may recognize dimeric forms of G protein coupled receptor. This may lead to new exploration in this still debated issue in the field.

As a whole, the group is highly productive in terms of scientific publications (36 publications out of which 19 as PI, in toxinology and pharmacology journals + 4 book chapters), particularly if one considers its small size.

Assessment of the unit's academic reputation and appeal

The group leader is highly regarded as an expert by animal toxinologists. He is in addition president of the French toxinology society and has been invited as speaker in the most important symposia in animal toxins (Leuven 2008, Recife 2009, Zermatt 2011, Hawai 2012, Oxford 2012, Rio de Janeiro 2013). Several team members are regularly invited in French and foreign laboratories to present their work and to establish collaborations.

The team is member of the LabEx LERMIT and is coordinator of one European network dedicated to venomics. It is also member of a second European network (Conco) aiming at discovering novel cone toxins with potential therapeutic properties.

An external group (three CNRS researchers and one emeritus director) from the CNRS campus in Gif/Yvette will join the team in 2014 to strengthen toxinology studies, especially in the peripheral and central nervous system, with emphasis on a group of neurotoxins which contaminate marine invertebrates and are therefore of paramount importance for France.

Assessment of the unit's interaction with the social, economic and cultural environment

This is a quite performant team in its area. It is/was associated or coordinating 5 ANR grants in association with SMEs.

Following the discovery of new snake toxins, the group has been involved in a spin-off company: the Venome-Tech start-up.

The group has been involved in NRBCe (nuclear, radiological, biological and chemical threats) programs for its expertise in Microplate detection of toxin-receptor interactions.

Assessment of the unit's involvement in training through research

Members of the team have good records in this domain: they are strongly involved in teaching in Paris-Sud 11 University, the University Pierre et Marie Curie in Paris, and in the National Museum of Natural History (MNHN). Habilitated researchers have supervised 3 PhD and 6 Master students.

Assessment of the strategy and the five-year plan

The prospective activities and aims are a logical continuation of the previous work and are likely to provide very important results. One major event for the near future is the arrival of a group headed by one of the best electrophysiologist of the neuro-muscular system, which will potentiate the collaborative effort on the study of marine neurotoxins. This is a major problem for public health care and marine industry, an issue of paramount importance for France.

Conclusion

- **Strengths and opportunities:**

The group is a recognized expert of venom toxins purification, identification and engineering, as well as recognized for its capacity to study and characterize ligand-receptor interactions.

Its capacity to work on mini proteins design perfectly matches with the strategic orientations of the unit in the future.

- **Weaknesses and threats:**

Competitivity currently requires to more deeply characterize the new pharmacological systems.

The group limits its explorations to the molecular and cellular levels. Animal models are nowadays important to provide high impact results, especially to confirm toxin specificities in complex systems.

- **Recommendations:**

The group has published a respectable number of papers, sometimes at the expense of quality/impact. Less numerous articles with impact beyond the specific domain of toxinology would help improving the visibility of the research carried out by the group.

It is advisable that the group leader puts some effort in hiring a talented post-doc to expand the study on the biological activity of the toxins using different cell types and tissues. This should allow the group to report their activity in higher impact journal to promote further the scientific status of the group.

Team 6 : Enzymology of nonribosomal peptide biosynthesis

Name of team leader: Ms Muriel GONDRY

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	5	4

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	1	2
Qualified research supervisors (with an HDR) or similar positions	1	

• Detailed assessments

Assessment of scientific quality and outputs

This group has identified and characterized an enzyme, and then a family of enzymes, that catalyse the formation of cyclic dipeptides, based on an original mechanism of action using aminoacyl-tRNAs but no template RNA. Sequence comparison indicates that this is a novel class of bacterial enzymes: the cyclodipeptide synthases, some of which are produced by pathogenic bacteria. The role of cyclic peptides has not been clarified yet, and this is one of the prospected activity, but the group hints that they could be developed as novel antibiotics, though it is not clear

how this could be achieved. These findings have been published in high impact journals. The group has also performed a high quality characterization of one cytochrome P450 enzyme from Mycobacterium tubercolosisis.

The scientific production is of very high quality. The 15 published articles appeared in high impact journals such as NAR, PNAS, Nat Chem Biol, JBC, Chem Biol, Nat prod rep.

Assessment of the unit's academic reputation and appeal

The group is member of the LabEx LERMIT and its leader serves on its board.

Team representatives have been invited as speaker in several important meetings, although limited to national congresses.

Assessment of the unit's interaction with the social, economic and cultural environment

The work has great potential for future developments in synthetic biology design of new metabolite factories, with the help of the two, and probably still to discover, families of amino acid metabolizing enzymes.

Assessment of the unit's involvement in training through research

The group leader is teaching biomolecular engineering at the Master "Biology and Health" at the University of Paris Sud 11. She has trained two Ph.D. students who have obtained their degree.

Assessment of the strategy and the five-year plan

The prospective activity is a logical continuation of previous research and it is proposed to determine the whole range of cyclic dipeptides that are formed by different cyclo-dipeptide synthases and to perform various biological screenings to determine their possible biological activities. This is a labour intensive approach that may provide interesting results and applications. Applications in the field of synthetic biology are considered as a possibility to generate new dipeptide motifs with further modifications by means of combining dipeptide synthases with cytochromes of different origins.

Conclusion

- **Strengths and opportunities:**

The identification of a family of widely distributed, but still poorly investigated, enzymes that catalyse the synthesis of original molecules of presently almost unknown functions, is an original field that deserves investigation for potential future therapies controlling bacterial growth and applications in the field of bioengineering.

The size of the family of enzymes holds promises and many totally unexplored chemical reactions might be exploited to increase chemical diversity in biotechnology applications for drug discovery.

- **Weaknesses and threats:**

The activity of the group does not appear to be exquisitely integrated in the laboratory strategy. As such, the necessity to elaborate a group strategy that matches laboratory future scientific policy is a concern that the group leader should not underestimate. Nonetheless, the objective to extend the diketopiperazine repertoire through molecular evolution of CDPSs will expand the engineering technologies present in SIMOPRO.

The group is poorly visible at the international level as manifested by the almost absence of international conferences attendance and presentation of the work.

- **Recommendations:**

Although carrying a research that can be qualified as very original with expected important basic and applied developments in the future, the group should consider its closer integration in the laboratory as a major issue to sustain and improve its productivity.

The team leader should put efforts on creation of a European and wider network of collaborations to enlarge the range of research funding, especially in basic research.

5 • Conduct of the visit

Visit date:

Start:	wednesday, 18, december, 2013, at 8.30 am
End:	wednesday, 18, december, 2013, at 7.00 pm

Visit site:	Service d'ingenierie des protéines
Institution:	CEA, Saclay site
Address:	DSV / iBiTec-S / SIMOPRO
	Bât. n°152 / point courrier n°24
	F-91191 Gif-sur-Yvette

Programme of visit:

08:30	Welcome to the committee
	Scientific part
8:45	Presentation of AERES evaluation and of committee members
	(Mr Jacques BARATTI and Mr Jean-Luc GALZI)
8:55	Presentation of the unit project: Vincent DIVE
	Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members
9:35	Scientific Presentation Team 1 – Mr Vincent DIVE
	Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members
10:15	Break
10:30	Scientific Presentation Team 2 – Mr Philippe CUNIASSE
	Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members
11:10	Scientific Presentation Team 3 – Mr Bernard MAILLÈRES
	Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members
11:50	Lunch - buffet / discussion
13:20	Scientific Presentation Team 4 – Mr Daniel GILLET
	Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members
14:00	Scientific Presentation Team 5 – Mr Denis SERVENT
	Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members
14:40	Scientific Presentation Team 6 – Ms Muriel GONDRY
	Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit member
15:20	in parallel the committee splits into three groups

	Meeting with researchers Meeting with technicians
	Meeting doctoral students and post doctoral fellows
	Attending: Committee members, AERES scientific delegate, without the leaders, representative of institution, without the direction of the unit and without team leader
15:50	Break
16:05	Meeting with representatives of Institutions
	Attending: Committee members, AERES scientific delegate, representatives of CEA (Mr Gilles BLOCH and Mr Jean-Marc GROGNET) and INSERM (Ms Marie-Josèphe LEROY-ZAMIA)
16:35	Meeting with the unit director
17:05	Deliberation of the committee (closed hearing)
	Attending: Committee members, AERES scientific delegate
19:05	Thanks and leave of the committee
19:15	End

Specific points to be mentioned

The director of the Doctoral School was not present during the visit. The rattachment of the unit to this ED was during the last year.

6 • Supervising bodies' general comments

DE LA RECHERCHE À L'INDUSTRIE

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Monsieur Pierre Glaudes
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 Paris France

Fontenay-aux-Roses, le 17 mars 2014
Objet : Rapport AERES E2015-EV-0912281K-S2PUR150008212-006634-RT Service d'Ingénierie Moléculaire des Protéines
N/Réf. : DSV/DIR/2014-111/GB/guc

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport d'évaluation du Service d'Ingénierie Moléculaire des Protéines (SIMOPRO) dirigé par le Dr Vincent Dive, dont le CEA exerce la tutelle. Le comité de visite a réalisé un remarquable travail d'évaluation et souligne la grande qualité scientifique de la recherche fondamentale et appliquée qui y est développée.

Le CEA se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions. Les points d'améliorations suggérés par le Comité seront discutés avec le directeur d'unité dans un esprit constructif pour l'avenir de la recherche au CEA.

Vous trouverez joint à ce courrier les éléments de précisions que Monsieur Vincent Dive a souhaité apporter au Comité à la lecture du rapport.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de toute ma considération.

Gilles BLOCH

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Direction des sciences du vivant
Le Directeur

Saclay, le 12 Mars 2014

Nom de l'unité : Service d'Ingénierie Moléculaire des Protéines
Acronyme : SIMOPRO
Nom du directeur pour le contrat en cours : Dive Vincent
Nom du directeur pour le contrat à venir : Dive Vincent

Référence AERES: E2015-EV-0912281K-S2PUR150008212-006634-RT
S2PUR150008212 - SIMOPRO - Service d'Ingénierie Moléculaire des Protéines - 0912281K

A l'attention des membres du Comité d'évaluation AERES:

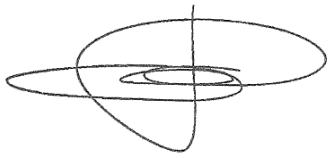
Je remercie tout d'abord l'ensemble du comité AERES pour le temps accordé à l'évaluation de notre unité et l'excellent travail réalisé. Les avis positifs sur l'unité, les groupes, mais aussi les critiques adressées sont des éléments extrêmement importants pour améliorer la qualité des recherches réalisées dans nos unités.

La recommandation faite par le comité de veiller à recentrer les activités de cette unité sur sa thématique de base « l'ingénierie Moléculaire des Protéines, est tout a fait logique. Cette recommandation se justifie d'autant que les exemples d'interpénétration dans cette thématique entre les différents projets développés au sein du SIMOPRO ont été présentés et appréciés par le comité.

A cet égard, il nous semble important de rappeler que l'équipe du Dr Cuniasse, qui a fait l'objet d'un jugement assez sévère, apporte une contribution importante aux projets transversaux du SIMOPRO. Le travail théorique sur la recherche de plates-formes fonctionnalisables pour leur conférer de nouvelles fonctions diagnostiques ou bien thérapeutiques est centrale dans la stratégie du SIMOPRO. Deux raisons à cela, d'une part les moyens de calcul dans les années à venir vont exploser et d'autre part les

groupes ayant des logiciels propriétaires, avec des codes adaptés pour tirer le meilleur parti de ces nouvelles puissances de calcul, auront des avantages stratégiques évidents. Le développement des programmes STAMPs et POLARIS répondent exactement à ces opportunités et se combinent par ailleurs avec l'implication du CEA sur le calcul intensif. L'activité du groupe du Dr Cuniasse est un atout indéniable pour l'avenir de l'unité.

L'axe thérapeutique choisi par le SIMOPRO est une activité à haut risque et par nature, une activité à fort taux d'attrition. Le succès des anticorps thérapeutiques résulte d'une très longue période de recherche. C'est un pari sur l'avenir, mais nous pensons que demain, des protéines optimisées par l'activité humaine prendront une place importante dans l'arsenal thérapeutique. Néanmoins, en accord avec le rapport du comité AERES, de tels objectifs ne pourront être atteints que si le SIMOPRO veille à ces objectifs premiers, renforce son potentiel humain, et développe les partenariats sur le plan National et International indispensables pour réaliser cette ambition.



Dr Vincent Dive
Service d'Ingénierie Moléculaire des Protéines