SPI - Service de pharmacologie et d'immuno analyse

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit:

Service de Pharmacologie et d'Immunoanalyse

From the :

CEA

May 2010

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

Section des Unités de recherche

AERES report on the research unit:

Service de Pharmacologie et d'Immunoanalyse

From the :

CEA

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

Mai 2010

Research Unit

Name of the research unit : Department of Pharmacology and Immunoanalysis

Requested label : Service du CEA

N° in the case of renewal :

Name of the director : M. Christophe CREMINON

Members of the review committee

Committee chairman :

M. Philippe NAQUET, Université Aix-Marseille 2

Other committee members :

M. Jacques BARBET, Université de Nantes

M. Jean Paul BORG, Université Aix-Marseille 2

M. Joachim KOPKA, Max Planck Institute

Ms. Anne Marie HONNEGER, University of Zürich

M. Daniel HARTMANN, Université Claude Bernard Lyon 1

M. Bruno DOMON, ETH Zurich

Committee members suggested by CNU, CoNRS, CSS INSERM, CSS INRA, INRIA, IRD

Observers

AERES scientific advisor

M. Jacques BARATTI

University, School and Research Organization representatives

Mme Nathalie GRAS-NAULIN, CEA

M. Jacques GRASSI, CEA

M. Jacques NEYTON, CEA

1 • Introduction

• Date and execution of the visit

The visit was held on March 9 2010 and followed the classical schedule: briefing, presentation by the Unit Director and discussion, scientific presentations by 4 research teams and discussion, poster visit, discussion with teams members, conclusion with the Unit Director and final review report.

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

This unit belongs to the CEA DSV (Direction des Sciences du Vivant) and is a member of the IbiTec Institute (Institut de Biologie de Saclay). The unit was created 25 years ago from two laboratories (LEMM and LERI) with a competence in immunodetection and biophysical analysis. The main activity of this research unit was devoted to methodological developments and consequently generated numerous interactions with industry and biotechnology.

The unit was later joined by an INRA laboratory with expertise in food allergies and in 2008 by a fourth team specialized in protein engineering and molecular biology.

Presently, this unit gathers significant technological expertise in four directions: immunoanalysis, mass spectrometry, biochemical analysis and molecular biology.

This unit has access to L3 lab space used for research in prion and infectious diseases.

The major field of activity concerns methodological and analytical developments although a small fraction of the activity also deals with fundamental research. The key strategic axes of research deal with the technology of monoclonal antibodies and analytic tools based on technics such as mass spectrometry and cell culture models.

Budget: > 1 million euros / year (industrial developments, national and international programs)

• Management team

The institute is organized in 5 teams of 16-21 persons, half being permanent staff members approximately. Only four teams will be the object of this scientific evaluation (LERI team 18, LEMM1 team 19, LEMM2 team 20 and LIAS team 21). The presence of a significant number (around 20 on permanent or contractual positions) of engineers and technicians is a characteristics of this department.

The Director of the unit is himself a senior scientist of the first team. A significant originality of this department is that it depends mostly from external contracts for its financial support, unlike other CEA departments. Consequently, research is highly dependent upon successful interactions with external partners and the quality of the scientific and technological developments is directly related to the ability to generate new interactions.

• Staff members

It is composed of roughly 100 persons among which 33 are permanent CEA staff (engineers, technical staff), 30 permanent staff of public/private partnerships (INRA, University, industry) and 25 collaborators on fixed-term contracts and students.

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file) CEA	18	18
N3: Number of other researchers (Form 2.2 and 2.4 of the application file) INRA	4	4
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	14	13
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	7	6
N6: Number of Ph.D. students (Form 2.7 of the application file)	21	20
N7: Number of staff members with a HDR or a similar grade	11	11

2 • Overall appreciation on the research unit

- Summary

This research unit composed of 100 people organized in 5 teams is essentially devoted to methodological and analytical developments in the area of health biotechnology. Three keywords characterize their scientific priorities: biosecurity, health and nanosciences. Fundamental research exists but is not their primary goal in agreement with CEA expectations. Funding comes from numerous external contracts with academic and private institutions and valorization via patenting, licensing, joint public/private labs and spin offs is efficient.

Research is organized around specific expertises in monoclonal antibody production and immunoanalysis for team LERI, mass spectrometry and pharmacology for team LEMM and protein engineering and immunotherapy for team LIAS. The team LI2A was not evaluated. This biotechnological research is generally of very good quality and the working spirit is excellent. A limitation to this organization mode is the extreme dispersion of research axes driven by funding opportunities rather than scientific choices; this may hamper the development of high risk/high profile scientific or technological discoveries. Despite this criticism, it is worth reminding that this organization allowed very efficient mobilization of human expertise towards prioritary goals such as the Bovine Spongiform Encephalitis epidemics and now bioterrorism. Indeed, this up-todate readiness for solving emergency challenges in these two fields may be one of the essential functions of this research units.

In conclusion, this research unit is well positioned within CEA, has an important potential for technological transfer and fund raising, and corresponds to a need. Its impact on science and biotechnology could benefit from a more focused research.

- Strengths and opportunities

- Excellent technological expertise in monoclonal antibody production, mass spectrometry and protein engineering
- Excellent ability to mobilize analytical expertise to specific unforeseen emergency tasks
- Good interface with industry providing diversified sources of funding
- Certification for Good Laboratory Practice

- Weaknesses and threats

- Limit dispersion which could lead to a deficiency in breakthrough fundamental or biotechnological research and high-impact publications

- Better evaluate the risk when embarking new technological developments in highly competitive areas such as immunotherapy, human monoclonal antibody production or microbial diagnosis.

• Recommendations to the head of the research unit

This unit is composed of highly qualified researchers and technicians and globally the scientific evaluation is highly supportive. In contrast to most 'french research units', this one is very technology-driven and problem-solving oriented (it is a fact and not a weakness). However, a general recommendation would be to better define the priorities for the different projects: it would be advantageous for the long term existence of the unit, to set up priorities, define a very few 'truly scientific programs', resource them adequately, which should lead to publications in high impact journals (e.g Nature Methods or Nature Biothech).This recommendation could apply to different contexts.

- Indeed a bottom-up project identification is clearly acknowledged within the unit, but it might be necessary to clarify the decision tree when new projects are embarked to limit the risk of dispersion of responsabilities and efforts.
- The activity of research teams is sometimes closer to that of a high quality platform and this leads to a significant dispersion of research interests. It might be important to clarify the responsabilities of each project leader in this organization.
- New technological developments are naturally encouraged but it might be useful to have a scientific council helping in prioritizing the projects that should benefit from a major investment.

Globally, we would advise to establish a more homogenous research profile of expertise for the whole research unit and amplify internal synergisms that may be exploited towards a more concise set of expertises.

• Production results

A1: Number of lab members among permanent researchers with or without teaching duties who are active in research (recorded in N1 and N2)	20
A2: Number of lab members among permanent researchers with or without teaching duties who are active in research (recorded in N3, N4 and N5)	18
A3: Ratio of members who are active in research among staff members [A1/(N1+N2)]	100%
A4: Number of HDR granted during the past 4 years	3
A5: Number of PhD granted during the past 4 years	10

3 • Specific comments

- Appreciation on the results

This unit has accomplished significant work in biotechnology leading to significant scientific results but mainly towards new technological developments. This expertise is well recognized by institutions which do not hesitate to give them specific missions (FIDGI program with the LERI team for example). Many of these developments give rise to patenting (all teams have patents, often licensed), technological transfer (joint lab between academic and private companies, project of creation of a national IBISA metabolomic platform) and in some cases new projects lead to the initiation of start up companies (SPI-MET, CIME).

This unit has a strong expertise in biosecurity and health biotechnologies.

Most researchers and PhD participate to publications. Many publications derive from collaborative work within each team and with diverse external partners. A majority of original articles from all teams are published in very good journals of biochemistry and biotechnology (JBC, Anal Chem, J Proteom Res, J Immunol Methods, Antimicrob Agents Chemother to name a few representative examples). PhD theses are defended in most teams and PhD students directly participate to articles and patents. Furthermore, these PhD easily find jobs in the field of biotechnology and industry.

A major strength of this unit is the large number of partnerships with pharmaceutical industries.

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

No award but invitations to scientific congresses and meetings

Several PhD and postdocs mostly from France work within the SPI environment. Security reasons might explain this bias towards national recruitments.

Excellent partnerships guarantee comfortable funding although one might wonder if some of them might be more opportunistic with regard to the developed analytical technologies rather than motivated by hypothesis-driven basic or applied science.

These teams are engaged in national or international projects (DGA, ANR, EU) with researchers, clinicians and industrial partners.

All teams have approx. 2-3 patents, a good fraction being already licensed. Furthermore all teams set up either platforms (IBISA request for the LEMM lab) or spinoffs to provide external access to the developed technologies (start up projects for the LEMM teams)

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

There is a good working spirit in this unit among researchers and technicians who readily accept the missions of this unit.

The management is somewhat variable between all teams and efforts have been made to focus resarch activities.

A bottom-up strategy for identification of research programs is encouraged but might lead to the initiation of too many dispersed long term projects requiring significant investments for small research teams. This aspect may require more thinking to optimize the efficiency of the unit and to create a more concise scientific profile for the research unit.

The unit includes one Professor and one associate Professor from the University Paris 7. Many researchers teach either in academic or industrial environments regularly, either in Ile de France or in biotechnology schools (Compiègne, Sophia Antipolis).

- Appreciation on the project

Many long term projects have been presented with a common goal: provide new technological and analytical tools that can be transferred to institutions via platforms or industrial partners. These objectives are centered around a common theme: health technology.

Some long term goals will require heavy investments to be fully successful, notably in the field of immunotherapy (human monoclonal antibody for therapeutic purposes in cancer, toxicology), diagnosis (predictive tools in infectious, neurological or toxicological problems).

It might be advisable to select specific projects for which significant funds and staff could be devoted to guarantee their success and high impact.

Ambitious projects exist and would benefit from a deeper risk assessment and could be prioritized in a long term. More specifically, means and criteria used to close or reduce the funding for unsuccessful projects should be clarified.

4 • Appreciation team by team

Title of the team LERI, Immunoanalysis and research laboratory

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	7	7
N3: Number of other researchers (Form 2.2 and 2.4 of the application file)	0	0
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	5
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	5	4
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

This research team is mainly devoted to technological innovation based on the development of monoclonal antibodies and immunoaasays. Among the recent achievments, two main axes can be identified. The LERI team has developed a novel type of lateral flow immunoassay for rapid detection of various toxins which should be soon commercialized. The second axis deals with the development of highly specific monoclonal antibodies that were very successfully applied to Prp detection in the last years with major financial return for CEA and the SPI unit. Based on these encouraging results, the team is trying to apply these reagents to immunotherapeutic applications such as the prevention of Prp spreading and more recently to toxin neutralization in vivo with some interesting preliminary results. Humanization of some antibodies is envisaged by designing chimeric human/mouse antibodies.

This team has generated an impressive collection of antibodies generating a significant number of scientific publications (46 Articles with Reviewing committee) but a large number derive from collaborations. Around a third

originate from LERI team's work and are published in very good journals in the field of biochemistry (JBC, Anal Chem) and immunoanalysis (J Immunol Methods, Mol Immunol).

2 PhD theses were defended and 3 patent applications were filed.

This research team is well identified for its ability to raise high quality immunodetection assays and has a long tradition of valorisation through industrial but also national contracts with institutions such as the Pasteur Institute, Veterinary schools and more recently the Ministry of Defense (DGA). The FIDGI program (submitted to confidentiality) represents a preponderant activity currently (70% of man power, with very strict deadlines and expectations) and will end within two years. The objective is to develop efficient immunoassays in the field of bioterrorism.

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

Team members regularly participate to conferences where both posters and talks are given.

The team is mainly composed of CEA researchers and technicians as well as contractual project-based technicians.

This team is engaged in numerous collaborative works due to the type of technological research developed. It plays an essential role in bringing financial return to the unit and to CEA.

Collaborations with institutional and private partners, some of them abroad (i.e. Biorad, Hercules, CA, USA)

The main application of their work is devoted to patented technological developments followed by valorization through local start ups (SPI-Bio) or external licensing.

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

The team is well organized and has the ability to rapidly adapt to new and urgent needs (Prion detection in the past, bioterrorism now) based on national priorities.

This item could be considered as a weaker point as scientific innovation is not a main feature of this team.

Teaching is not a main activity of this team. In contrast, they provide monoclonal antibodies and related technologies to other team units which generate efficient internal collaborations.

- Appreciation on the project

The project has three main objectives:

- enhancing immunodetection sensitivity through technological developments using immunoliposome based detection. Although the idea is not new, this team has already obtained promising results.

- designing novel immunoassays for the detection of pathogens. Although little was said about the FIDGI project, the goal is to identify new antigenic targets for Yersinia Pestis and Bacillus anthracis and relies on extensive collaboration with the Pasteur Institute which should ultimately bring new expertise to the LERI team in microbiology.

- producing human monoclonal antibodies. This last project seems less advanced and may suffer from two pitfalls: the choice of a technology based on chimeric murine/human reagents and the development of truly human B cell-derived antibodies without a clear expertise and dedicated human power for this ambitious and highly competitive project.

Projects cannot be considered as truly original but the mission of this team is rather based on technological than only scientific breakthroughs. However, the Unit Director insisted on the ability of members of the unit to promote bottom-up projects which were then internally tested.

- Conclusion :

  - Summary

The main goal of this team is the development of new immunoassays involving both technological developments and identification of novel antigenic targets. The team has a well known recognition in this highly specialized field and has the potential to provide the scientific and industrial community with high quality tools.

  - Strengths and opportunities

The team has demonstrated its potential for fast adaptation and reactivity to needs for new immunoassays (prion, bioterrorism), innovative technological application (lateral flow technology, immunoliposome based sensitivity) that were efficiently transfered to external users (industry, nation, ...).

The team has a recognized competence in monoclonal antibody production.

Scientific articles are regularly published in recognized journals in the field of immunoanalysis and immunotechnology.

There is a very good adequation between the philosophy of the team and the acceptation by the team members.

This team has an excellent record in fund rising through industrial, national contracts.

This team efficiently transfers technological developments to industry through patenting, licensing or internal spin off (SPI-Bio company) in agreement with CEA goals and missions (3 patents, two licensed).

  - Weaknesses and threats

This group has a limited number of high impact factor articles and their efforts may be diluted given the large number and technological challenge of ongoing projects.

The project concerning the development of human monoclonal antibodies is very ambitious but does not provide guarantees of success or hope of true technological breakthroughs.

The decision to develop immunotherapeutic human antibodies might require significant developments and dedicated funds and persons to be competitive.

  - Recommendations

The team should clarify its strategic choice: technological developments and immunoassays versus immunotherapy, beyond the FIDGI project.

Title of the team : Metabolome, biomarkers and therapeutic proteins

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	4
N3: Number of other researchers (Form 2.2 and 2.4 of the application file)/ POSTDOCTORAL FELLOWS	4	3
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	1
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	7	2
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

Two axes of research were presented which fit well into the research unit strategy of providing and developing broad uptodate analytical expertise:

Development of ultra-high resolution mass spectrometry allowing new approaches in metabolomics

Sensitization of toxin and biomarker detection by combining immunodetection and mass spectrometry

In both projects, the laboratory has proven its potential to innovate and reach very high standards in term of MS analysis. The team also made excellent choices to update and focus on high end mass spectrometry equipment that can be used for both research axes.

19 papers (ACL) among which 13 originate from the LEMM team 19, 7 published in very good journals in the field of biochemistry (JBC, Anal Chem, J Proteome Res, Proteomics)

7 PhD students were coached since 2005 with publication outputs.

2 patents were filed.

The recognized expertise of this team in MS analysis generated several collaborative programs funded by ANR and European grants. Furthermore more than 50 studies were funded by 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 reputation of this team allow them to postulate for an IBISA platform in 2010. Furthermore, they obtained the “Good Laboratory Practice” label from french authorities.

This team trained 7 PhD during the last 4 years.

Numerous links with pharmaceutical companies, 5 ANR grants, one EU grant provided adequate funding to this team.

The team is a nationally recognized center of expertise in MS analysis.

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

The team is well organized and focused. However, they seem to have underestimated the need for the rapid development of a dedicated bioinformatic support to handle the massive mass spectral metabolomic and proteomic data sets and the need to establish and benefit from databases.

The activity of the team is devoted to technological innovation which should provide many scientists with a strong expertise in MS applied to both proteome and metabolome analysis. Numerous collaborations are already engaged in the Ile de France region.

Team members regularly contribute to teaching (Université Technologique de Compiègne, CEFIRA) both in academic and industrial set ups.

- Appreciation on the project

The project is centered on human health with a specific focus on toxicology.

Scientifically the goals are to extend the sensitivity of detection, to develop metabolite databases from biological fluids and new applications of MS for detection of novel metabolites through active collaboration with clinical teams providing biological fluids.

Another project connects LEMM to BioMerieux in the field of microbe detection with a very ambitious and maybe a bit optimistic goal to use MS as a way to simultaneously type species, strains but also parameters of drug resistance and virulence.

The bottlenecks may come from the delay in establishing a strong and dedicated bioinformatic platform and the risk of dispersion into too many collaborative projects.

The team obtains numerous project-based funds from public or industrial and can allocate part of them to technological investments. The team has also decided to apply to become a public IBISA platform and simultaneously create a start up SPI-MET. It will be important to clarify the respective missions of these two environments with distinct financial and scientific objectives. More specifically, the division of intellectual property and know-how between company propriatory and open academic access needs to be clarified.

There is a potential for significant discoveries in the field of MS based applied metabolomics and proteomics perhaps even more so in the integration of both expertises.

- Conclusion :

  – Summary

This team has a recognized high expertise in mass spectrometry analysis. It has made good technological choices and developed innovative detection methods by coupling immunodetection and MS analysis. There is an urgent need for development of adequate bioinformatic tools to meet the competitive challenge of extending metabolome approaches to several aspects of human health. Contacts with clinical teams have already been set up and the choice to request an IBISA label should further increase their national recognition.

  – Strengths and opportunities

Their strength rely on:

Good use of combined immunocapture and MS analysis

Good instrumentation choice for metabolomic and proteomic approaches at the appropriate timing (Orbitrap, FT/ICR)

Excellent analytical article

GLP (Good Laboratory Practices) environment to extend and facilitate contacts with pharmaceutical companies and clinical applications

Leading position in high resolution MS metabolomics

State of the art mass spectral technology platform in France

– Weaknesses and threats

This team should maybe focus on fewer high impact projects rather than disperse their efforts on more opportunistic applications which will lead to very good but not major articles in the field. Despite the revendicated objective for technological development and technology transfer, this team has the potential to develop more risky science-driven projects and develop an analytical expertise and research profile which will allow the team to excel among the competition of applied metabolomics and proteomics

Concerning all applications, it is essential to promote the development of a strong bioinformatic/mass spectrometry competence within the team.

– Recommendations

Develop bioinformatics and define the most needed applications towards efficient application of metabolomics and proteomic approaches

Clarify the split between academic and commercial (private) activities

Focuse rather than disperse their efforts towards higher impact applied projects and maybe a more targeted translational research (example: cetuximab detection in patients ?) in line with the research profile of the whole research unit

Identify a project (projects) in which one could set up a high throughput strategy for which dedicated funds could be fetched in to a spin-off company.

Better define the relative risk concerning the Microbial identification project which looks rather ambitious and might be competed out by other technological approaches.

Title of the team : Drug bioanalysis, pharmacokinetics, metabolism and neuropharmacology : LEMM

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers (Form 2.2 and 2.4 of the application file): POSTDOCTORAL FELLOWS	2	
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	8	3
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

This team contains in fact two group leaders with distinct projects in relation with pharmacology.

The first project relies on a well calibrated in vitro model of the human blood brain barrier. This team has efficiently set up experimental conditions to reconstitute this important brain/vessel interface and validated its use to study drug delivery in brain by a thorough comparison between in vivo (PET imaging) and in vitro assays. This approach is now proposed to clinicians and industrial interested in studying blood brain barrier permeability to different drugs.

The second project investigates the CYP450-mediated detoxification potential towards various drugs. The objective is to assess this potential for each individual by developing a tool-box which studies by LC-MS the fate of labeled representative metabolites in biological fluids. This team leader has a good expertise in MS application to pharmacology.

Number and quality of the publications, scientific communications, thesis and other outputs

34 papers (ACL) among which 14 are mainly originating from the LEMM team 20, 4 published in good journals in the field of biochemistry (J Mass Spectrometry, Anal Chem), cell biology (Cell Mol Neurobiol) and pharmacology (Eur J Pharmacol)

5 PhD theses

1 patent

This team of 3 researchers (including two group leaders) handles a large number of external collaborations with clinicians interested in their expertise. Nevertheless one has the feeling that this dispersion of efforts may prevent them from investigating further technological developments. This impression is reinforced by the fact that the total number of persons in the team will be reduced in the forthcoming period.

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

Regular participation to meetings

8 PhD students were trained during this period.

Their technological expertise is recognized and allow them to participate to several cooperative projects (ANRS grants, EU FP6, Nanotrans, Sidaction)

The expertise of the team members is valorized through external collaborations.

Appreciation on the strategy, management and life of the team

This team is composed of two group leaders developing distinct pharmacological projects.

Regular participation to teaching at CEPHIRA or University Paris 11.

- Appreciation on the project

The project aiming at developing predictive assays of neurodegenerative diseases based on culture models (project Add Med Brain : New Medicine for Brain Disorders). This relatively ambitious and risky project would be applied to Alzheimer and Rasmussen's diseases or deficiency in transporter activity (creatine). At this stage, there is no guarantee that these goals might be reached using these cell culture models.

A start up should be created to dedicate the Blood Brain Barrier culture model to more systematic and transferable procedures.

- Conclusion :

  - Summary

This team possesses a real expertise in applied pharmacology and has focused its activity on the development of predictive tools for the evaluation of drug pharmacology in vivo. The two projects presented have no real synergy at this stage and depend on experimental models that might not be applicable to all the situations envisaged.

– Strengths and opportunities

- Development of a successful technology to study human BBB function in vitro

- Many applications are envisaged concerning BBB permeability for drugs

- Good knowledge in pharmacology

- GLP (Good Laboratory Practices) environment to extend and facilitate contacts with pharmaceutical companies and clinical applications

– Weaknesses and threats

- Dependence on a single technology and model

- There are many projects for a limited number of researchers.

- No obvious coordination between the BBB and the cytochrome projects within the same team.

- The cytochrome project is in a very competitive field and depends on one researcher at this stage.

– Recommendations

- Enhance collaborations with cell biology teams for mechanistic issues

- Improve synergy between leading staff members

- Better define the collaborations with clinical departments

Title of the team : LIAS, Diagnostic and therapeutic antibody engineering

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6	6
N3: Number of other researchers (Form 2.2 and 2.4 of the application file) INDUSTRY AND POSTDOCTORAL FELLOWS	4	2
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	3
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	3
N7: Number of staff members with a HDR or a similar grade	5	5

- Appreciation on the results

Three themes of research were presented: the first one deals with the molecular engineering of antibodies and toxins, partly with private partners or through a EU fund (CONCO project). The second one focuses on the design of recombinant and therapeutic antibodies applied to the Prp protein in an an attempt to vaccinate against the pathogenic form. The third one focuses on engineering of protein immunogenicity. All three projects lead to

interesting results in term of publications but were reorganized to limit thematic dispersion and optimize outputs following AERES recommendations two years ago.

Two groups persist in the new scheme : Recombinant antibodies for therapy and imaging of cancers and Immunogenicity, vaccination and antibodies. The first team reoriented its research with success by focusing on endothelin receptors (members of the GPCR family) as putative targeting receptors for immunotherapy. A monoclonal antibody to endothelin receptor B with candidate antagonist potential was obtained and is currently calibrated to image and potentially target tumors in vivo. The second group focuses on the immunogenicity of the Tat protein as a candidate target for a HIV vaccine. Interesting results were obtained demonstrating the autoadjuvant potential of a fragment of the Tat protein and the interest of stabilizing Tat protein structure to enhance its immunogenicity. Vaccination trials in monkeys indicate that this strategy permits a significant improvement of anti-Tat immunoreactivity with a possible impact on HIV replication following in vivo challenge.

18 papers (ACL) among which 12 are originating from the LIAS team, 3 published in very good journals in the field of biochemistry (JBC, Prot Exp and Purif), molecular biology (J Mol Biol) and immunotechnology (J Immunol Meth, Vaccine, Mol Immunol, J Neuroimmunol)

1 PhD thesis

3 patents

This group has well-established collaborations with a number of academic and private institutions and is involved in numerous programs.

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

3 invitations to international congresses

3 national postdocs and 4 PhD students

Neuroprion, EU-FP6 (CONCO, toxin research), CEA, MESR, ANR

Numerous collaborations with institutional and private partners,

A CEA/ Biomerieux Joint Research Unit is being planned in this team

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

A significant reorganization occurred during the last 3 years which is accompanied by a refocusing of research activity with interesting preliminary results.

Several collaborations exist within the institute between the LERI, LEMM and LIAS teams

- Appreciation on the project

Two projects were presented on the endothelin receptors and the Tat protein. The first one should concentrate on endothelin repector as target for imaging and immunotherapy of cancers. New immunisation protocols based on combined genetic and cellular strategies should help obtaining excellent antibodies to such receptors. New staining techniques (Q-dots and carbon nanotubes) will be developed in collaboration with local partners for imaging and possibly immunotherapeutic potential.

The Tat project will continue in two directions: 1) exploring the biology of Tat adjuvant property and immunoprocessing. Collaboration with a immunocell biology laboratory is envisaged to achieve this goal. 2) Extending the exploration of Tat as a candidate anti-HIV vaccine target. This aspect will obvioulsy require the development of more extensive collaborations and appropriate sources of funding.

There is a potential for interesting new developments in both the endothelin receptor and Tat projects

- Conclusion :

– Summary

Based on its previous expertise in the optimization of immunogens, this team has reorganized its activity and reduced the number of projects to focus on two main directions: endothelin receptor as a new immunotherapeutic target in tumors and Tat as an target anti-HIV vaccines. The results are promising and will need dedicated sources of funding to reach optima results.

– Strengths and opportunities

- Many projects in the past (Prp, animal toxins, therapeutic Ab, anti-idiotypic Ab) were interrupted and focusing on two successful projects is appreciated
- Production of an antagonist anti endothelin receptor mAb is promising
- Development of a productive interface around the immunogenicity of the Tat protein combining protein engineering and immunological approaches:
- Opportunity for the development of Tat based anti HIV vaccination protocols

– Weaknesses and threats

This team has made significant efforts to limit thematic dispersion and focus on two projects under the responsability of different senior scientists. However, the role of other senior scientist within the LIAS team was not fully clarified.

– Recommendations

Increase the coordination and list the responsabilities

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	A	A	B

Equipe 1 : IMMUNOANALYSIS STUDIES AND RESEARCH LABORATORY

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	B

Equipe 2 : METABOLOME, BIOMARKERS AND THERAPEUTIC PROTEINS

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

Equipe 3 : DRUG BIOANALYSIS, PHARMACOKINETICS, METABOLISM AND NEUROPHARMACOLOGY

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	B

Equipe 3 : DIAGNOSTIC AND THERAPEUTIC ANTIBODY ENGINEERING

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	B

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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/2010-133

Objet : Observations du CEA sur le rapport d'évaluation du « Service de pharmacologie et d'immunoanalyse » (iBiTec-S/SPI)

Monsieur le Directeur, Cher Pierre,

Je remercie tout d'abord l'AERES pour la qualité du rapport d'évaluation sur l'activité du « Service de pharmacologie et d'immunoanalyse » 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

Commissariat à l'énergie atomique et aux énergies alternatives
Centre de Saclay – 91191 Gif-sur-Yvette Cedex
Tél. : 33 - 1 64 50 10 00 – Fax : 33 - 1 64 50 11 86 – bernard.bigot@cea.fr

Etablissement public à caractère industriel et commercial
R.C.S. PARIS B 775 685 019

DIRECTION DES SCIENCES DU VIVANT
INSTITUT DE BIOLOGIE ET DE TECHNOLOGIES DE SACLAY
SERVICE DE PHARMACOLOGIE ET D'IMMUNOANALYSE

Dear Professor Philippe Naquet, Président of the committee,

Please find enclosed our response to the Evaluation Report of the Service de Pharmacologie et d'Immunanalyse.

Best regards

Dr Christophe Créminon
Chef du Service de Pharamacologie et d'Immunoanalyse

Commissariat à l'énergie atomique et aux énergies alternatives
Centre d'Etude de Saclay – DSV/iBiTec-S/SPI – Bât. 136 – Point courrier n°18 - 91191 Gif-sur-Yvette Cedex
Tél. : 01 69 08 72 99 – Fax : 01 69 08 59 07

Etablissement public à caractère industriel et commercial
R.C.S. PARIS B 775 685 019

We would like first to thank the members of the committee for their in-depth analysis of the activities of the Unit. We will take into account all their constructive advices and comments to further improve the future evolution of the Unit. We would also like to comment on some of the weaknesses and related recommendations made by the committee.

Comments concerning the overall evaluation of the Unit:

Recommendations "better define the priorities for the different projects", "define a very few 'truly scientific program', resource them adequately" and **Weakness** "limit dispersion".

As clearly stated in the documents and during the presentations and underlined by the committee, the SPI Unit is "technology-driven" and "problem-solving oriented". The different evaluated groups are thus linked to a technological background more than to very long-lasting research programs. Moreover, as also clearly mentioned, financial supports for all the different programs undertaken come from external funding. We are thus applying to numerous grants and this contributes for sure to the corresponding impression of dispersion (**Comment** "disperse their efforts on more opportunistic applications"). However the different programs are clearly ranked in terms of priority inside the research teams, with, in first position biosafety and the FIDGI program for team 18 or metabolomics studies and the bioMérieux contract for team 19 for instance. To our point of view, these priorities correspond to 'truly scientific programs' and the corresponding resources are always identified since, as pointed out, the Unit is 'self-financing' all the different research programs.

It is also worth noting that the various 'dispersed' programs and the large set of technical expertise allowed the Unit to very rapidly move from one subject to another and thus to efficiently mobilize human resources to face important scientific problems. This reactivity was previously a strength to work on priority goals and this way of working was always validated by the CEA.

Weakness: "Better evaluate the risk when embarking new technological developments in highly competitive areas such as immunotherapy, human monoclonal antibody production or microbial diagnosis"
We are aware that these three areas are highly competitive and it must be emphasized that, to limit the risks, the works are clearly focused on defined and limited subjects linked to other programs and in collaboration with specialized groups. Indeed microbial diagnosis involves partnerships either with Pasteur Institute teams (in straight line with FIDGI confidential program) or world-leading diagnosis company (BioMérieux). On the other hand, immunotherapy and human mAb production is presently focused either in bioterrorism area or on selected specific receptors. These different subjects have been started recently and should be considered also as preliminary evaluating projects aiming at enlarging our scientific and technological background. This strategy of starting new projects with limited human and financial resources in a preliminary phase has previously proved to be successful in the Unit, in particular for implementing MS technologies or prospecting Bovine Spongiform Encephalopathy or bioterrorism areas.

Comments concerning the team Immunoanalysis and diagnosis

Weaknesses: "The project concerning the development of human monoclonal antibodies is very ambitious" and "the decision to develop immunotherapeutic human antibodies might require significant developments and dedicated funds and persons to be competitive"
The project on immunotherapy is presently clearly linked to the bioterrorism program and takes advantage of the previous production of efficient antibodies devoted to diagnosis to evaluate this field. As for human monoclonal antibodies production, we aimed at evaluating the feasibility of this kind of project to enrich our methodological and technological background. These studies

only involve very limited resources and we are not pretending to become specialist on these competitive areas but rather to collect scientific information. These limited surveys are more a proof of concept type of program.

Comments concerning the team Metabolome, biomarkers and therapeutic proteins

Weakness: "it is essential to promote the development of a strong bioinformatic/mass spectrometry competence within the team"

Although it was perhaps not enough highlighted in the report and presentation, the team has started this year a formal collaboration with a bioinformatics team at the Technological Research Division at the CEA Saclay (Dr. Olivier Gal). The collaboration is supported by two projects:
- The *Massdetec* program (2010-2012) financially supported by CEA to develop mathematical tools and bioinformatics for the analyses of MS data obtained from genomics and post genomics studies,
- The development of algorithms tools for rapid bacterial detection and characterisation using new MS methods (Industrial collaboration with BioMérieux, 2010-2013).

These two projects will be integrated within the Ibisa platform (project under application).

Furthermore in the frame of the National "*Reséau Français de Métabomique et de Fluxomique",* the team is associated with the *Centre de BioInformatique de Bordeaux* (CBiB) to develop a database (MetabDB project) dedicated to the storage of data in the field of metabolomic.

Comments concerning the team Drug bioanalysis, pharmacokinetics, metabolism and neuropharmacology

"*This team is composed of two group leaders developing distinct pharmacological projects*"; "*The two projects presented have no real synergy at this stage*"; "*No obvious coordination between the BBB and the cytochrome project within the same team*"

Such a partition (possibly resulting from the dual oral presentation of the team) is not felt as such by the team's members. Present work and publications highlight the true collaborative spirit in the team. For example:
1) The last submitted publication on the rat cell-based blood-brain barrier originated from complementarities between the 2 team leaders involved (BBB and validation using, among other, the cytochrome tool).
2) The 3 full time researchers are currently involved in the creation of the PreCeM spin-off in the fields of the blood-brain barrier pharmacology.

*"Many projects for a limited number of researchers**".***
The Add Med Brain Project (New Medicine for Brain Disorders) is involving both team leaders (one at nearly full time and the other at half time) and also 2 PhD students, 2 Postdoctoral fellows and 1 technician full-time. All of these projects revolve around the blood-brain barrier, share a common expertise, address cerebral pathologies and thus, to our point of view, cannot be considered as "*a dispersion of efforts*" linked to "*a large number of external collaborations with clinicians*".