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

Department for the evaluation of research units

AERES report on unit:

Chemistry, Modelling and Imaging for Biology

CMIB

Under the supervision of the following institutions and research bodies:

Paris-Sud University

Centre National de la Recherche Scientifique - CNRS

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

Curie Institute

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 Yves MELY, 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 independent and collegial deliberation of the committee.

Unit name:	Chemistry, Modelling and Imaging for Biology
Unit acronym:	CMIB
Label requested:	UMR CNRS and INSERM
Present no.:	
Name of Director (2013-2014):	
Name of Project Leader (2015-2019):	Ms Marie-Paule TEULADE-FICHOU

Expert committee members

Chair:	Mr Yves MELY, Strasbourg University
Experts:	Mr Erick DEFRANCQ, Joseph Fourier Grenoble University (CoNRS representative)
	Mr Philippe DERREMAUX, Paris 7 Diderot University
	Ms Isabelle GILLAIZEAU, Orléans University (CNU representative)
	Mr Sébastien LECOMMANDOUX, Bordeaux University
	Mr Andreas MARX, Konstanz University, Germany
	Ms Françoise PEYRIN, Lyon University (CSS INSERM representative)

Scientific delegate representing the AERES:

Mr Pierre VIERLING

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

Ms Geneviève ALMOUZNI, Curie Institute

Mr Etienne AUGE, Paris-Sud University

Mr Patrick BERTHET (Ecole doctorale N° 470 representative)

Ms Marie-Josèphe LEROY-ZAMIA, INSERM

Mr Jacques MADDALUNO, CNRS

1 • Introduction

History and geographical location of the unit

The new unit "Chemistry, Modelling and Imaging for Biology" (CMIB), proposed for creation is based on the merging of the Orsay part of the UMR 176 laboratory with the biophysics unit U759. These two groups are located in the same Curie Institute building in Orsay.

The UMR 176 CNRS-Curie Institute unit was created in 1996. Due to its dual location in Paris and Orsay, the unit was directed by a director (Mr. Jean-Claude FLORENT) and a deputy director (Ms Marie-Paule TEULADE-FICHOU) in charge respectively of the Paris and Orsay part of the laboratory. As a result of the inherent difficulties associated to the dual location, the UMR 176 was split into two independent units. The Paris laboratory has merged with an INSERM team from the Curie Institute in Paris to create, starting at January 2014, a Chemical Biology unit that has been evaluated by the AERES in 2012-13. Thus, the present assessment will only concern the Orsay Laboratory (UMR 176-Orsay) headed by the deputy director, who is proposed as the CMIB director for the next five-years contract.

The biophysics laboratory of the Curie Institute in Orsay presently headed by Mr Sergio MARCO was created in the seventies. NMR techniques under different forms played always a central role in this laboratory. Since 2006, the unit has been restructured in order to focus on biological imaging. The current unit director is proposed as the CMIB deputy director.

Management team

The CMIB will be leaded by Ms Marie-Paule TEULADE-FICHOU, CNRS research director and former deputy director of the UMR 176-Orsay, assisted by Mr Sergio MARCO, INSERM research director and current director of the INSERM U759 Unit, who will act as a deputy director.

AERES nomenclature

ST4 (principal) and SVE1_LS1 Biologie moléculaire et structurale, biochimie (secondary).

Unit workforce

Unit workforce	Number as at 30/06/2013 U759/UMR 176	Number as at 01/01/2015
N1: Permanent professors and similar positions	1/2	3
N2: Permanent researchers from Institutions and similar positions	6/6	11
N3: Other permanent staff (without research duties)	10/5	14
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	2/5	1
N6: Other contractual staff (without research duties)	1/1	
TOTAL N1 to N6	**20/19**	**29**

Unit workforce	Number as at 30/06/2013 U 759/UMR 176	Number as at 01/01/2015
Doctoral students	1/4	
Theses defended	9/11	
Postdoctoral students having spent at least 12 months in the unit*	4/8	
Number of Research Supervisor Qualifications (HDR) taken	1/3	
Qualified research supervisors (with an HDR) or similar positions	4/6	11

2 • Assessment of the unit

As the new laboratory results from the merging of two existing units, the following will be assessed separately, when applicable.

Global assessment of the unit

UMR 176-Orsay. The UMR 176-Orsay is of rather small size, composed, on June 30-2013, of 13 permanent staff,4 post-docs and 4 PhD students. Its overall goals are based on the development of chemical biology tools for studying mechanisms associated to cancer development and identifying anticancer drug candidates. The UMR 176-Orsay is structured in four teams working on different targets, but having a common expertise in heterocyclic and bioorganic chemistry. Team "Structure and fluorescent probes for nucleic acids" is specialized in the design of probes for targeting and sensing nucleic acid secondary structures. Team "Chemistry of Porphyrins, Photodynamic Therapy" is focused on the design of glycoconjugated porphyrinic photosensitizers for targeting retinoblastoma cell membranes. This team will be closed in the future unit, due to the retirement of its PI. Team "Design and Synthesis of Kinase inhibitors" develops purine and heterocyclic chemistry for selective targeting of kinases with a special focus on GSK3 and Tyro-3 inhibitors. Team "Medicinal Chemistry" works on the identification and optimization of inhibitors of HIV replication (that had led to the creation of the Splicos start-up) and inhibitors of phosphatase 1 and Lim-Kinase. All four teams are of rather small size with one and six permanent staff for the smallest and largest one, respectively. The unit projects appear quite diverse with limited connection between them, as shown by the small number of articles in co-authorship (< 10). Moreover, within each team, multiple projects are conducted in parallel, so that the total number of projects is high with respect to the size of the unit. The overall scientific activity in the 2008-13 period is globally good (see below for details), but with some variations from one team to another. An excellent international visibility is associated with the research of one team. The number of post-docs (8) and PhD students (8) in the unit within the 2008-13 period was reasonable, but again with some differences between the teams (from more than 10 in one team to only 0.5 in another one). A rather large number of competing grants (5 ANR, 3 INCa, 2 ARC, 1 LCC, 1 CNRS-PEP…) as well as of fellowships for PhD students and post-docs were obtained.

U759. The U759 is also of rather small size, composed on June 30-2013 of 14 permanent staff, 2 post-docs, 1 PhD student and 1 CDD. The number of researchers has dropped by half between 2010 and 2013. The major objective of U759 was to use multimodal imaging techniques to understand, at the molecular scale, the dynamic and functional/structural properties of normal and pathological biological systems. To reach this aim, the unit carried out fundamental and applied cancer research activities as well as methodological developments on data acquisition protocols and image analysis. The unit is structured in three teams working at different organization levels. At the molecular level, the team "Molecular bases of the cellular functions of proteins" is studying structures and molecular interactions by NMR spectroscopy and electron microscopy combined with molecular modelling and various biophysical methods. At the cellular level, the team "Structural bases of cellular processes/Treatment of the signal and image analysis in biology" observes complex molecular assemblies and organelles by transmission electron tomography and analyses data from electron energy-loss spectroscopy and secondary ion mass spectrometry (SIMS) to characterize the chemical composition of the observed structures. At the level of the whole animal, the team "In vivo functional and molecular MRI" uses magnetic resonance imaging (MRI) and localized magnetic resonance spectroscopy (MRS) to investigate the structure and physiology of normal and pathological tissues.

On the whole, the unit was able to generate good quality publications over the last 5 years in spite of its small size. The projects of the three teams differ significantly from each other and are poorly interconnected, as shown by the very small number of co-signed papers. The unit has been impacted by the death of one of its PI in 2009. This required refocusing the research projects of the corresponding team. Another prejudicial event was the recent shutdown of the in vivo MRI facility strongly impacting further development of in vivo imaging in animal models. The number of ANR (6) and INCa projects (4) in which the unit has been involved is quite impressive with respect to its small size.

Strengths and opportunities related to the context

UMR 176-Orsay. The UMR 176-Orsay shows unique expertise in organic and bioorganic chemistry with high potential value to the Curie Institute. Some projects have led to cutting-edge data in highly competitive areas. From these projects, lead series of inhibitors with clear potential in therapeutics are now available. An additional strength is its direct connection with the Curie Institute chemical library (with nearly 9000 compounds) managed as a platform by one member of the UMR 176-Orsay. This library is based on a large number of collaborative projects, publications, patents and ANR projects. A strong connection seems also to be established with the Splicos start-up, with two members of this start-up being in the organization chart of the UMR 176-Orsay. An additional key strength is its inclusion in the Curie Institute, so that it can benefit from the international visibility and attractiveness of this institute. Moreover, this institute provides a privileged access to biological resources and even of human nature, so that there is a strong potential for translational applications.

U759. The unit shows a unique expertise in highly specialized imaging techniques, both in electron microscopy and MRI. The unit is also recognized to some extent for its expertise in molecular modelling. Overall, the unit benefits from a very strong support of experienced technical staff. The electron microscopy facilities are included in a PICT-IBISA platform (2D/3D structural and chemical imaging platform), and are managed by two engineers. The unit benefits also from a platform of recombinant protein production run by an engineer. One of its teams recently obtained an "Institut Carnot" funding. More generally, the fundings of the whole unit are quite high, with a strong support from INSERM and Curie Institute.

Future CMIB unit. The future unit will benefit from the very rich scientific environment of Paris-Saclay and Paris-Saclay University, with the possibilities to access to a number of top-level facilities and to collaborate with high-level teams of similar or complementary expertise. Being also part of the Curie Institute, the unit can benefit from its international visibility and attractiveness. Through this institute, there is a strong potential for applications of the developed techniques. The unit will also have a significant involvement in teaching activities at the Paris Sud University.

Weaknesses and threats related to the context

UMR 176-Orsay. The international visibility and, to a lesser extent, the scientific productivity of several teams need to be improved. Part of these limitations may be related to the small size of the teams, with a too limited number of permanents and, in some cases, a small number of PhD students and post-docs. Thus, for several projects, the critical workforce for an effective research with complementary approaches could not be reached. Moreover, the large number of projects as well as the limited number of internal collaborations further contributes to weaken the competitivity of the teams. A decrease in the permanent staff is expected in the next years due to the retirement of several senior scientists.

U759. The number of patents (3 in 2008-12) of this unit specialized in imaging developments and applications is rather small. Its international visibility is also suboptimal. Several senior scientists retired during the five last years and were not replaced. As the total number of researchers was divided by a factor of two, there is mechanically a decrease in the research potential of this unit. Probably as a consequence of the decrease in the number of senior scientists, the number of PhD students decreased as well. The current small number of PhD students and postdocs is of concern and questions the ability of the unit to attract and recruit young scientists.

Recommendations

To take into account the decrease in the number of senior scientists, as well as the shutdown of the 4.7 T MRI, reorganization with a merging of teams will increase its critical workforce and gather all the expertise on a smaller number of projects. An obvious effort in this direction was done in the CMIB project, as the number of teams was decreased from 7 to 4.

A refocusing of the projects is needed to concentrate the human resources on the most challenging and promising questions. Again, this recommendation was partially anticipated in the project of the new unit, though some room for improvement still exists. There is a further need to attract young scientists to compensate for the retirement of senior scientists as well as to increase the number of PhD students and post-docs and increase the critical workforce on the most promising projects.

The unit should also initiate discussions with other chemical biology laboratories of Paris Sud University to federate the efforts. A clearly defined long-term plan for the development of the imaging facilities and expertise should be proposed, in coordination with the Curie Institute and the other imaging platforms of Paris Sud University. Clear plans are notably required for the future of in vivo MRI imaging.

Some unit members are encouraged to patent more systematically their methodological developments.

3 • Detailed assessments

Assessment of scientific quality and outputs

UMR-176 Orsay. The overall scientific activity in the 2008-13 period is very good, with 110 papers and 22 patent applications. A large part (70%) of these papers is directly related to the scientific projects of the teams. A significant part (20%) of the papers is published in journals of impact factor larger than 5, while the vast majority of papers are published in journals with impact factor between 3 and 5 (50%). The UMR-176 Orsay shows also a strong activity in patenting with a total of 22 drafted patents, mainly in the field of anticancer drugs, imaging probes and inhibitors of HIV splicing. The team associated with the Curie Institute chemical platform is especially active in this field, being involved in 75% of these patents.

One team exhibits an outstanding productivity (46 papers in the 2008-13 period), publishing regularly in high-level journals (Angew Chem, J Am Chem Soc, Nat Struct Mol Biol, Nucleic Acids Res), so that the percentage of high impact factor (> 5) for this team is above 40%. The situation for the other teams is more contrasted (see section Team-by-team analysis below for more details).

U759. The overall scientific activity in the 2008-13 period is good, with 91 papers and 3 patent applications. Close to 70% of these papers are however collaborative papers.This high percentage underlines that the instruments and expertise of this unit largely benefit to the community. The primary publications of the two imaging teams are mainly related to instrumental and methodological applications, as well as to specialized applications of the techniques, in which these teams are experts. These primary publications are mainly published in specialized journals (Eur Phys J Appl Phys, Microsc Res Tech, CR Chim, Contrast Media Mol Imag, Photodiagnosis Photodyn Ther, Magn Reson Med), underlining that the expertise of these teams in their respective fields is well recognized. The primary publications of the molecular team correspond for a large part to projects of the deceased PI. About 20% of the publications of the unit are in journals with impact factor > 5, while the vast majority (> 50%) was published in journals with impact factors between 3 and 5. The highest impact factor publications (3 PNAS, 1 Embo J and 1 JACS) were produced by the team “Structural bases of cellular processes”, which was also recently associated to a Nature paper in 2013 in collaboration with the Harvard Medical School. Thus, the expertise of this team is interesting enough to attract top-level scientists. A substantial decrease in the number of papers could be noted in the last two years (20-24 papers/year in 2008-10, but only 12-13 papers in 2011 and 2012). The number of patent applications for this unit with a strong focus on methodological developments is low (3 for 2008-12). However, one team has chosen to provide open source software such as the TomoJ Plugin for ImagJ, which is another way to valorise its production.

Assessment of the unit's academic reputation and appeal

UMR 176-Orsay. The unit is well visible in the chemical biology field. The research on the hot field of quadruplexes as well as the PI working on this research are highly visible on an international level, as evidenced by the numerous papers in first rank journals, the numerous international collaborations, the involvement in two EU-cost networks, the vice chairing of an international conference in Singapore, the invitation as a speaker in 20 conferences, and the coordination of the French network GDR 3431 on quadruplexes. The visibility associated to the projects on porphyrins and kinase inhibitors is more national. An excellent visibility is also associated to the Curie Institute chemical library, which is central in numerous collaborative projects either within the Curie Institute or with other French laboratories. Moreover, it is worth mentioning that a junior CNRS researcher was recruited in 2010.

U759. The overall visibility and recognition of the unit are rather good, but there is still some room for improvement. For instance, the invitations of the team members to conferences are mainly restricted to french conferences. Nevertheless, it is worth noting that one PI became honorary professor of the "Universidad Autonoma de Madrid". Another positive element is the rather large number of international groups collaborating with the unit, showing that its expertise and equipments are well recognised. This is also exemplified by numerous collaborations not only inside the Curie Institute, but also with a large number of French laboratories. Collaborations have also been established with industrials, further confirming the unit recognition in its field of expertise. A probably less positive sign is the absence of international grant or membership in international networks in 2008-13, but this should be improved soon through an application to a FET-OPEN H2020 coordinated by the unit director. Moreover, the apparent difficulty in recruiting PhD students may partly be related to the insufficient attractiveness of this unit.

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

UMR 176-Orsay. The links of the unit with the socio-economic world are very strong. This constitutes an obvious strength and is notably illustrated by the large number of patents drafted by the unit as well as by the strong links with the Splicos start-up company or by the inhibitors developed for two other start-up companies (Ecrins Therapeutics and Cellipse). Of course, the chemical platform plays a central role in this respect, being involved in a large fraction of the patents of the unit. One should notice also that team members have participated in large public conferences and science festival events for high school students. One PI has been member of the board of the non-profit French organization "Rétinostop". Unit members have been participating in the scientific council of Paris Sud University, and in expert committees.

U759. The links with the socio-economic world are illustrated mainly by the connections established with industrials. The unit has developed since 2008, important activities with industrials leading to software development for tomography (commercialized by Digisens) and publications (together with Sanofi-Pasteur). These connections will continue through a contract with L'Oreal. Moreover, negotiations were established with Celenys, Sanofi-Pasteur and Reactivip. In addition, one team has recently been funded by the "Institut Carnot"-Curie Cancer for five years, on projects of interest for industrials. Two PIs are involved in conferences and technique demonstrations in high schools.

Assessment of the unit's organisation and life

During the on-site visit, various discussions were held with the researchers, PhD students and post-docs, and then with the technical and administrative staff from both the UMR 176-Orsay and U759 units together. These discussions confirmed the full adhesion of the permanent staff to the fusion project of both units and his strong support to the management team. They have also provided a very positive perception of the organization and life of both units as well as that of the future unit. Decisions both for now and for the future have been taken in a transparent and concerted way and they are well justified. The tasks of the technical staff are well planned, so that technicians and engineers feel well integrated in the life of their unit.

Assessment of the unit's involvement in training through research

UMR 176-Orsay. Most of the members of the unit are CNRS researchers with moderate involvement in teaching. There are only two assistant-professors with standard involvement in teaching duties and responsibilities. Of note, one of these assistant-professors was involved in co-organizing the "Journées de l'école doctorale" of chemistry in 2010-12 and has been a member of the "Concours d'attribution des bourses de l'ED 470".

The UMR 176-Orsay is connected to two doctoral schools and shows a good training activity of PhD students. Eleven PhD students have defended their thesis from January 2008 to June 2013. Two of them have got an assistant professor position, one works in a company, three have positions unrelated to research, and five are in post-doctoral position. The reasonable number of PhD students shows that the unit is attractive enough, and that the moderate involvement of the unit members in teaching does not constitute a major limitation for attracting talented PhD students.

U759. Apart from one assistant-professor, all other members are INSERM researchers with little involvement in teaching for some of them. Nevertheless, two PIs are involved in teaching of imaging techniques at Paris Sud University and also in the "Universidad Autonoma de Madrid". One PI is responsible of "teaching units" in master 1 and master 2. In addition, team members are also involved in training by organizing or participating in courses for the CNRS-entreprises, INSERM or French Society for Microscopy.

Nine PhD students have defended their thesis in 2008-13, which is reasonable considering the size of this unit. A more negative point is that the number of PhD students tended to decrease during the last years, with only one PhD defence per year and the presence of a single PhD student in the group June 2013. Due to the involvement of the PIs in teaching, this difficulty in attracting PhD students is somewhat difficult to explain.

Assessment of the strategy and the five-year plan

The proposed unit entitled "Chemistry, Modelling and Imaging for Biology" (CMIB) results from a common will of the two units (UMR176-CNRS and U759-INSERM) to develop and promote an integrated and trans-disciplinary research spanning from chemistry of probes and anticancer drugs to analysis of biological activity in cells, tissues and animal models. This project originates also from a number of inter-unit collaborative projects (photodynamic therapy, protein kinase inhibitors…) and a common need of spectroscopy equipments and biophysical methods.

The new unit will be organized in three transverse research "poles": one in chemistry, one in molecular modelling, and one in imaging. It will also lean on four associated facilities: 1) the 2D/3D structural and chemical imaging platform (PICT-IBISA Orsay facility); 2) the chemical library; 3) the recombinant protein production and 4) the preclinical MRI. In addition, the unit already hosts a start-up and is associated to the "Institut Carnot" through the Global Care project of the Curie Institute.

The new unit will be further divided in four teams based on 1) multimodal and multiparametric imaging; 2) modelling and molecular dynamics; 3) structure and photoactivatable probes for DNA, and 4) chemistry of small molecules for proteins targeting. Its projects will focus i) on the study, at the atomic level using combined modelling, chemistry and biochemistry approaches, of the structural bases underlying the mechanisms of proteins and protein-nucleic acid interactions in systems identified by the biologists as key partners for cancer developments and treatment, and ii) on the identification of the best molecular systems (small molecules, light-activatable systems) for a targeted pharmacological action on cancer cells and tissues as well as for theranostic applications in the field of cancer. To this end, the unit will develop an integrative approach based on chemistry and multimodal imaging in cells, tissues and animal models.

By gathering recognized experts in bioorganic chemistry, molecular modelling and imaging, this unit has the potential to become central in the Curie Institute, by providing innovative tools to solve key biological questions. Obviously, the proposed organization of the new unit responds at least in part to a number of the concerns that were associated to the previous individual units. Indeed, the number of teams has been reduced from 7 to 4, so that each new team is composed from 4 to 10 permanent staff. This will definitively increase the critical workforce and efficiency of the research efforts on each project. However, in several teams, the number of described projects is still high, with no clear prioritization, so that a dispersion of the efforts could be expected. Moreover, the interconnection between the projects and the interaction between the teams could still be improved. Further collaborations among teams would be required to use optimally the complementary expertise on imaging and chemistry on the more challenging projects, and thus enhance the competitiveness and international visibility. The development of an integrated project, for instance on G-quadruplexes, with synergic efforts of all teams is recommended.

There is also a crucial need to increase the recruitment of young scientists (potential group leaders, post-docs and PhD students), through applications for external grants, in order to strengthen the research efforts on the most promising projects.

Moreover, a long-term vision should be elaborated to plan the needs in imaging techniques. Currently, this vision does not seem to be mature and needs to be optimized.

Overall, the project of the creation of this unit appears attractive and of interest for the Curie Institute. However, some progresses are still required to maturate further the project and propose more integrated and focused projects with stronger interactions between the teams and a clear prioritization of the most challenging projects.

4 • Team-by-team analysis

Team 1 : Multimodal and multiparametric imaging

Name of team leader: Mr Sergio MARCO

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	4
N3: Other permanent staff (without research duties)	6	6
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	**13**	**10**

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	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	4

• Detailed assessments

Assessment of scientific quality and outputs

The "Multimodal and Multiparametric Imaging" (MMI) team results from the merge of the "Structural bases of cellular processes" and "In vivo functional and molecular MRI" teams from the U759 INSERM unit.

The goal of the "Structural basis of cellular processes" team was to develop and evaluate tools for cellular imaging and chemical mapping applied to the understanding of intracellular communication and signalling mechanisms. Their studies were based on a number of cellular imaging techniques such as transmission electron tomography (ET), transmission electron microscopy (TEM), electron energy-loss spectroscopy and secondary ion mass spectrometry (SIMS), providing complementary information about the chemical composition of the observed structures. The ultimate goal of the team was to correlate all the data about an organelle or any other molecular assembly obtained from these different techniques into a single integrative structural model. The team has also a strong expertise in 3D chemical mapping and correlative multimodal imaging. Its members have done particularly innovative developments in EFTEM (Electron Energy Filtered Transmission Electron Microscopy). They have also developed various softwares, some being public. For instance, they have produced the PlugIn TomoJ in ImageJ, which is a well-known and visible imaging tool. The team has a strong collaboration with the Synchrotron SOLEIL for the development of imaging tools at the Nanoscopium beam line.

This team has produced 42 publications in peer-reviewed journals and had 17 invited conferences (11 national meetings). More than 90% of these papers are collaborative papers, underlining the mainly service oriented nature of this team. Of note, the team has signed 3 collaborative publications in PNAS and one in Nature in 2013. In the two last years, there was a significant drop in the number of papers (5 per year, compared to 12/year in 2008 and 2009). The team published mainly in microscopy journals but not in image processing journals although it has activities related to algorithm developments.

The team "In vivo functional and molecular MRI" was mainly developing, evaluating and optimizing MRI and magnetic resonance spectroscopy (MRS) in small animals to investigate the structure and physiology of normal and pathological tissues, to characterize tumour and to follow-up therapy. Its research has been conducted on three interconnected long-term axes. The first axis is the development of contrast agent based functional and molecular high field MRI approaches and multi-parametric association of complementary MRI techniques. The group has a strong expertise in DCE-MRI (Dynamic Contrast-Enhanced) methods. In particular, they have developed a method to model the pharmacokinetics of tumour blood flow and/or capillary permeability. Its latest achievement is a technique called RETIA (Radial Entire Tumour with Individual Arterial input function) DCE-MRI. The team has proved its ability to extract relevant perfusion parameters in the field of cancer. The second axis is the characterization of various experimental tumour models and response to new anticancer therapy protocols assessed by in vivo small animal imaging. Its expertise in MRI has particularly been used in i) MRI guided preclinical therapy trial in a transgenic mouse model of colorectal cancer, ii) multi-parametric MRI characterization of new meningioma models in mice, and iii) follow-up of a treatment in models of breast cancer using RETIA DCE-MRI. The third axis is sodium MRI for which they have developed dedicated MRI RF-probes. The method has been used to assess photodynamic therapy (PDT) on grafted mice bearing different types of human tumours (colorectal and retinoblastoma).

This team has produced 19 publications in peer-reviewed journals and given 5 invited conferences (3 in national meetings). Almost 50 % of these papers are primary papers from the team. The team members regularly publish in good magnetic resonance journals (MRM, MRI). They also publish as co-authors in more biologically oriented journals.

Globally, the two teams have a strong expertise in a large range of imaging methods at different scales. Its methodological developments are closely related to biological studies. The scientific production is rather good.

Assessment of the team's academic reputation and appeal

The academic reputation and attractive force of this new team is rather good as highlighted by i) the number of its collaborations at the local (Curie Institute), national and, to some extent, international level (Spain and Algeria), and ii) its successful fund raising (3 ANR, 4 INCa, 2 FRM).

Though the general visibility of the new team could still be improved, one member has a rather good notoriety (56 papers in peer reviewed journals, H-index 20). He is also honorary professor of the Condensed Matter Physics Department of the Universidad Autonoma de Madrid. The team leader also plans to coordinate a FET-OPEN H2020 project.

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

According to their self-evaluation, the two teams spend between 5 and 25% of their time in non-academic research. Since 2008, one of the teams had important activities with industrial partners such as Digisens, Sanofi-Pasteur and L'Oréal. The collaboration with Sanofi is expected to increase in the next years. They collaborate also with the synchrotron SOLEIL. From a financial point of view, the input of industrial contracts is moderate. The two teams have produced 3 patents. One team has also provided several ImageJ Plugins, which is a good way to valorise research in computing science.

Assessment of the team's organisation and life

NA

Assessment of the team's involvement in training through research

NA; see above comments related to U759.

Assessment of the strategy and the five-year plan

The new MMI team will be led by the PI of one the two former teams that have merged. Its permanent staff is currently composed of 3 permanent researchers and 6 engineers and technicians. In comparison with the two merged teams, two CR-CNRS will no more participate in the new team. The team members gather expertise in different complementary imaging techniques.

The goal of the MMI team will be to contribute, via integrated imaging approaches, to the understanding of the effects and action mechanisms of diagnostic, therapeutic, and theranostic agents on cells, tissues and organisms essentially in the field of oncology. To this aim, the team will develop and optimize multimodal and multiscale imaging approaches. The methods on which the team is working include nano-SIMS, TEM- STEM-EFTEM, MRI. Its developments will include softwares, image acquisition procedures, preparation techniques for biological samples and methods to improve sensitivity and resolution of imaging equipments. The team plans to focus on four questions:

1) How to perform, in a therapy follow-up context, multiparametric/multiscale imaging to assess heterogeneity of the characteristics of healthy and cancer tissues?

2) How to track the effects of photon irradiation of photosensitizing molecules?

3) How to characterize and track radiosensitizing nanoparticles and drugs within cells?

4) How to study the bio-distribution and pharmacokinetics of drugs and chemical elements in normal or pathogenic tissues and cells?

Although the main field of the team is the development in imaging methodologies, this project is organized in biological projects, which do not highlight what are the real technical challenges to be solved from an imaging point of view. However, it gathers different entities working on different aspects, develops interesting ideas in the context of the unit, and has established close links with other teams of the unit.

Since the overall goals of the CMIB are to develop chemical biology tools for studying mechanisms associated to cancer development and to identify potential anticancer drug candidates, this team has a major role to play in the unit to develop and maintain state of the art imaging facilities at various scales. In this respect, the methodological developments planned by the team are important and need to be pursued.

The project looks ambitious compared to the limited human resources of the team in terms of researchers. This team has a very large support in engineers and technicians (which represent the 2/3 of the team workforce). This is a force to develop and maintain the instruments as well as to apply these instruments in biological applications, but it is important that the group increases its number of researchers to be able to maintain its research activities.

Conclusion

- **Strengths and opportunities:**

The new team gathers expertise in various specific imaging methods at different scales (SIMS, TEM, EFTEM, DCE MRI). It has a good link to university and has established connections with other teams of the unit. The environment of Curie Institute will provide competitive biological projects that will benefit from the instruments of the team. It also possesses sufficient engineer and technician resources to further develop the techniques and apply the sophisticated instruments to competitive biological projects. Concerning the developments of imaging algorithms, the team has some links with the Signal and Image Processing community, which could be reinforced.

- **Weaknesses and threats:**

The number of researchers and of PhD students is small compared to the number of projects, since there is basically only one researcher on each project. The risk for the team would be to be limited to a technical platform while methodological developments in imaging are necessary to answer biological questions. A major threat for the MRI based developments is the availability of MRI machines: the 4.7T required to be fixed and developments have to be made to transfer some of the applications on the 9.4T MRI system. Moreover, a solution has to be found to enable the team to do its research in good conditions.

- **Recommendations:**

The team has the ambitious project to develop imaging at different scales, but due to the limited resources it has to carefully select the projects on which it is the most efficient and recognized. A clear strategy should be defined in order to plan the future developments in imaging, within the context of the Curie Institute and Paris-Sud University. There is an urgent need to improve the team attractiveness in terms of the permanent researchers, post-docs, and PhD students. The later would be easier to find if the level of funding would be increased.

Team 2 : Modelling and molecular dynamics

Name of team leader: Ms Liliane MOUAWAD

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	2
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)	1	
TOTAL N1 to N6	**4**	**4**

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	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The team "Modelling and molecular dynamics" stems from the team "Molecular Basis of the Cellular Functions of Proteins" of the U759 INSERM unit. Due to the retirement of several researchers and to the death of its former team leader, the number of researchers dropped to 2 and the number of technical staff dropped to one.

From 2008 to 2013, the general objective of this team has been to get a better knowledge of the relationships between the structure, dynamics and function of proteins mainly involved in cell proliferation. For this purpose, different techniques including biochemical, molecular biology and biophysical techniques, and computational approaches (normal mode analysis, drug design) have been used. In total, the team has been working on five different projects. The main project concerned centrins and calcium binding proteins. The team notably solved the structures in solution of two centrins by using NMR and X-ray crystallography. It also studied the conformational flexibility of the C-terminal domain of the human centrin2 in complex with an XPC-derivative peptide by solid state NMR. The team has also developed a bioinformatic method based on the inter-domain Linker Average Hydrophilicity (LAH) for predicting the form of calcium binding proteins. Another project concerned microtubules (MT), which are dynamic constituents of the cytoskeleton. Its functions depend on its intrinsic dynamics modulated by several proteins and the presence of GDP or GTP. To determine the dynamics of such a large system, the team used all-atom normal mode analysis (NMA) and found how GTP stabilizes MT. To go beyond all-atom NMA, the team developed a new method allowing NMA with a coarse-grained method (DIMB-ENM). The last three projects with external collaborations involved protein kinases (with the finding of several potent inhibitors with good affinities), NAD kinase (with the determination of 8 X-ray structures of NAD kinase complexed by various inhibitors, and a patent deposited for novel antibacterial compounds), and galactosyltransferase.

The scientific production for the considered period is of 33 articles in journals recognized in their disciplines (Structure, FASEB J, J Mol Biol, Crystal Growth & Design, Biochemistry, J Biol Chem). Noticeably, a large number of them have been signed by team members who will no more be present in the future unit and most of them (2/3) correspond to collaborative papers in which the unit members are not first or last authors.

Assessment of the team's academic reputation and appeal

The team has a good academic reputation as shown by a number of fruitful collaborations (local and national). In particular, the team collaborates with another team of the Curie Institute concerning the docking and virtual screening of protein kinases inhibitors. Another collaboration with the Pasteur Institute concerns new antibacterial compounds targeting NAD kinase. The last collaboration with the CERMAV group in Grenoble concerns galactosytransferase. The centrin and NAD kinase projects have been funded by one and three ANR grants supervised by the team, respectively, the last one ending in December 2013.

It is to be noted that the team lacks a network of international collaborations, which may preclude obtainting european grants, among others. The average attraction of the team is also measured by the low number of postdocs (1), PhD students (3,5 but 3 of them were supervised by members who left the team), M2 students (2), invited conferences (1), and organization of conferences.

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

There are only limited facts to assess the interaction with the social, economic and cultural environment. The links with the socio-economic world are illustrated mainly by one patent during the 2008-13 period. Moreover, the PI of the new team has recently been funded by the "Institut Carnot" for five years, on projects being of interest for industrials.

Assessment of the team's organisation and life

NA

Assessment of the team's involvement in training through research

NA; see above comments related to U759.

Assessment of the strategy and the five-year plan

The project for the next five-year contract is very ambitious, combining theory and applications, and attempts to foster collaborations with other teams of the laboratory. Even though there is a continuity in several projects (study of microtubule and associated proteins, protein kinases, and development of a NMA method with restraints provided by cryo-electron microscopy, application of NMA, molecular dynamics, docking and chemoinformatics), new projects are also proposed. These projects concern i) the design of new G-quadruplex ligands, which could be selective for one topology of G-quadruplex DNA (this is a real challenge and the contribution of modelling is certainly crucial), ii) the understanding of the interactions between the carbohydrate moiety of the photosensitizer molecule and its lectine target to propose new drugs for the photodynamic therapy, iii) the RecQ DNA-helicases and mutants, and iv) the Institut Carnot-Global Care projects with a focus on two target proteins, i.e. calcineurin (whose inhibition is expected to avoid relapse after chemotherapy treatment) and the Anti-silencing function protein 1 homolog B (Asf1b) (which is associated to an important risk of metastasis when present in high-level), in order to conceive new anticancer drugs.

Several of these projects (G-quadruplexes, RecQ DNA-helicases, Asf1b and calcineurin, protein kinases) are in close collaboration with the chemists of the CMIB unit and will really benefit from the expertise of this molecular modelling team.

Conclusion

- **Strengths and opportunities:**

The main strength of the new team is its unique expertise in molecular modelling and dynamics, which is of key importance for several projects of the new CMIB unit, notably those connected with drug design. The arrival of a new assistant-professor with complementary expertise will improve the critical workforce of the team. The "Institut Carnot" will provide important funding for several years to this team. The team benefits from a permanent technical support for computers. The existence of local and national networks in modelling, in which the team members are involved is a good opportunity to exchange information and know-how, and establish collaborations.

- **Weaknesses and threats:**

This team has clearly suffered from the decease of the team leader in 2009 and the retirement of other researchers. The arrival of an assistant-professor still teaching in Caen will not be easy to manage and clearly his mutation to Paris Sud University should be envisioned. The number of projects (7) is clearly much too high for 3 permanent researchers plus one engineer. The visibility of the team is essentially national. Its reputation and appeal is further average. Since there is some uncertainty in the duration of the "Institut Carnot" funding, and since the team apparently does not benefit from funds from other sources, there will be a real challenge to support all the planed projects.

- **Recommendations:**

The team should focus its efforts to a smaller number of projects. Obviously the projects involving close collaborations with the chemical biology teams of the future unit as well as with highly visible teams from the Curie Institute are promising and should be prioritized. The involvement of the team in these cutting-edge projects will certainly improve its network of international collaborations and its international recognition. The new team should have an active policy for recruiting permanent researchers, PhD students and post-docs.

Team 3 : Structure and photoactivatable probes for DNA

Name of team leader: Ms Marie-Paule TEULADE-FICHOU

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	0,5	
N2: Permanent EPST or EPIC researchers and similar positions	3	4
N3: Other permanent staff (without research duties)	2	3
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	**8,5**	**7**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	6	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

From 2008 to 2013, the team was part of the UMR 176 unit and named "Molecular Recognition of Nucleic acid: Structure and Fluorescence Probes". The team was relatively small and its size increased somewhat during this period (from 2 to 3.6 Full Time Equivalents (FTE)). Its research is based on the recognition of unusual DNA structures by small molecules (i.e. probes) able to bind specifically the target DNA structures through non-covalent interactions. The goal of this research is to design molecular tools for studying and controlling the formation of the target DNA structures with the ultimate aim of designing novel anticancer agents. The research is achieved mainly through the design of i) G-quadruplex DNA ligands, ii) ligands of mismatched DNA, and iii) two-photon fluorescent probes for DNA. In the context of G-quadruplex DNA ligands, the team has developed a series of ligands based on phenanthroline dicarboxamide bisquinolinium scaffold, which showed very interesting binding properties. Indeed, the PhenDC3 molecule is considered as one of the best G-quadruplex ligands and represents a product leader in this field. An analogue of PhenDC3 bearing a pyrididicarboxamide moiety instead of a phenanthroline motif has also been developed as a selective fluorescent probe for G-quadruplexes. The team is also involved in the development of metallic complexes for targeting G-quadruplexes found in the human telomeric region. Interestingly, some platinum complexes showed radiosensitization properties. Another family of G-quadruplex ligands is based on neutral polyheteroaryle scaffolds with the major objective to discriminate between different G-quadruplex topologies, which represent a major challenge in this field. The team has also beeen working since several years on a family of macrocyclic compounds (cyclo-bis-intercalators) that are able to efficiently bind to mismatched DNA and thus represent promising tools for investigating DNA repair processes. Finally, the team launched more recently a program for designing new fluorescent DNA probes excitable in the NIR region. The team designed original probes based on a well-studied triphenylamine scaffold. Optimization of these dyes led to very interesting IR excitable-red emitting fluorescent molecules for probing DNA in cells (more efficient than common DNA stainers).

Over the 2008-13 period, the team constantly published in the best journals of chemistry. It has published 48 publications (44 articles, 3 reviews and 1 book chapter), 20 of them having an impact factor higher than 4, including 1 Nat Struct Mol Biol, 3 Angew Chem, 2 J Am Chem Soc, 7 Chem Eur J, 4 Nucleic Acid Res. Most of these publications concern the G-quadruplex project. 50 % of these publications are signed as first/last author by a team member. Considering the ever-increasing demands of the editors and reviewers in the field of chemical biology for manuscript acceptance, this is a great achievement. Furthermore, these results are obtained by a relatively small group in comparison to other main “players” in the field. Thus, the publication outputs of this team are indicators for a constant excellent scientific quality and originality.

Assessment of the team’s academic reputation and appeal

The team leader is a worldwide-recognized scientist. The quality of her research is very well perceived in the community of nucleic acid chemists as indicated by numerous invitations to international conferences (16), coordination and/or membership of/in scientific networks, organization of international conferences, and competitive national fundings (2 ANR, 1 INCa, 1 ARC). In the international context, she has co-organized the IVth International Conference on quadruplex nucleic acids held in Singapore on July 2013. She is also member of two EU-COST actions. In the national context, she is the coordinator of the GDR-CNRS (12 teams) also dedicated to quadruplex nucleic acids. It should be noted that this GDR aims at increasing the collaboration and visibility of teams working from chemistry to biology of G-quadruplexes.

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

The team is engaged in many activities along these lines. For instance, the team leader was and still is a committee member at the “Muséum National d’Histoire Naturelle” and at the Paris Sud University. The team has addressed the urgent need of bringing more talented women into science by organizing a public conference “Women in Science - Facts and Figures”. This is more than one can expect from a team of the depicted size. The team is also active in the field of valorisation with 4 international patents.

Assessment of the team's organisation and life

NA

Assessment of the team's involvement in training through research

See above comments related to UMR 176. Of note, this team has a strong training activity, as 7 PhD and 4 master students have been trained during the period. In contrast, the team involvement in teaching is limited with only some teaching in a master course, but it should be noted that the team is essentially composed of researchers.

Assessment of the strategy and the five-year plan

The team in the new CMIB unit derives from the former team "Molecular Recognition of Nucleic acid: Structure and Fluorescence Probes", will be named "Structure and photoactivatable probes for DNA", and will be directed by the same PI. Two additional senior CR1 researchers (from CNRS and INSERM) will join the new team, one of them is coming from the U759 Unit. Thus, the size of the team will increase from 3.6 to 5.3 FTE.

The research plan for the next five years is structured in four projects that are built in most parts on the precedent achievements and focused on the targeting and imaging of unusual structures of nucleic acids. The guideline of the projects consists in providing novel molecular tools to probe nucleic acid polymorphism and in identifying chemical hits for anticancer drug development. The following projects will thus be developed :

i) small molecules for probing G-quadruplex DNA and in particular able to discriminate between different topologies of G-quadruplexes. Different approaches will be used including structure-based design from PhenDC3, screening of chemical libraries by using high-throughput G-quadruplex assay, and G-quadruplex directed reactions,

ii) macrocyclic small molecules as potential inhibitors of DNA repair. This research is based on macrocyclic compounds recently identified in the team for their specific recognition of abasic sites and mismatched base pairs,

iii) IR-photoactivatable targeted molecular tools. The development of IR-NIR probes based on triphenyl scaffolds will aim to identify biocompatible probes and find IR excitable agents for PDT. It should be mentioned that a diversity oriented synthesis will be developed to generate a library of fluorescent triphenylamine probes,

iv) Pt-complexes and telomere targeting. This project takes benefit from the arrival of a new researcher and is based on previous platinum complexes, which show radiosensitive effects on cancer glioblastoma.

Several lines of collaborations (e.g., screening, imaging) are depicted that are scientifically reasonable and of added value. The plan is straightforward, scientifically compelling and well balanced in terms of feasibility, risks and gain. The topics are of very high novelty and of broad interest for the chemical biology community.

Conclusion

- **Strengths and opportunities:**

The team is internationally visible, highly successful (especially when considering its size), following trans-disciplinary approaches in a highly timely topic of chemical biology, with strong potential for translational applications. It has also the unique opportunity to expand its activities to cellular and animal studies in collaboration with biologist partners from Curie Institute, as well as from other laboratories in France or abroad. Moreover, a federation of the chemical biology laboratories of Paris Sud may be developed in a close future. This will add to the prosperous future development of the group.

- **Weaknesses and threats:**

The group size is at an edge where competitive research (e.g., publication in the very best journals of the field, translational research) is threatened. For frontier research in the field targeted herein, a single group has to hold a broad expertise in several highly specialized areas (i.e. RNA and DNA synthesis, preparative organic chemistry, photochemistry, biochemical assays, etc…) for which a sizable number of personal is absolutely essential. Thus, any reduction in human resources or funding would constitute a significant threat to the research outputs of the team in terms of quality, originality and quantity. Surprisingly with respect to its international visibility, the team has not benefited from European fundings.

- **Recommendations:**

It should be essential for the team to keep its excellence by recruiting junior researchers. In a longer term, the transmission of knowledge and expertise as well as the international visibility of the group leader should be taken into account. To boost the research of this team and its international reputation, application to competitive international funding with high budget should be a priority.

Team 4 : Chemistry of small molecules for protein targeting

Name of team leader: Ms Sandrine PIGUEL

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1,5	1
N2: Permanent EPST or EPIC researchers and similar positions	3	2
N3: Other permanent staff (without research duties)	3	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	1
N6: Other contractual staff (without research duties)	1	
TOTAL N1 to N6	**10,5**	**6**

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	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

The "Chemistry of small molecules for protein targeting" team results from the merge of the "Design and chemistry of kinase inhibitors" and "Medicinal chemistry" teams from the UMR 176-Orsay unit.

The team "Design and synthesis of kinase inhibitors" was directed by a INSERM CR1 and included two assistant professors, one being present at 30% of his time. Its main achievements concerned the development of new "small molecules" that target proteins in order to impede their function for therapeutic reasons. The approaches were mostly derived from classical medicinal chemistry comprising identification of lead structures and their optimization through iterative derivatization of heterocycles and evaluation to obtain structure activity relationships. In total, three projects were subjected to analysis. The main project concerned the synthesis of protein kinase inhibitors and the development of new methodologies around heterocyclic scaffolds. Potent inhibitors of GSK-3 were thus synthesized and were shown to be of potential interest in Alzheimer disease and other neurodegenerative diseases. During these investigations, original methodologies in organic synthesis and functionalization of the purine ring were developed. In collaboration with biologist partners of the Curie Institute, the team launched a new research program on the design and synthesis of inhibitors of the tyrosine kinase Tyro3, which was demonstrated to be a new therapeutic target in bladder cancer. Their specific approach was to design type II inhibitors of Tyro3, which target the so-called DFG-out conformation of kinase and are expected to be more specific than classical type I inhibitors. About 60 compounds were synthesized and tested. Molecular modelling studies suggested that it was possible to modify the selectivity profile against a panel of close protein kinases, by small structural changes. This project is funded by INCa (2011-2014). Another project was devoted to the development of new methodologies based on the metal catalyzed (Pd, Cu) direct C-H bond functionalization of heterocycles including oxazoles and purines. This area of metal-catalyzed direct alkynyl-, alkenyl- or arylation through cleavage of C-H bonds has recently emerged as an attractive alternative to the traditional cross-coupling of organometallic species with a halide partner. Such an approach provides unprecedented avenues for the streamlined synthesis of biologically important bis(hetero)aryls.

The scientific production for the considered period is of 12 articles in very good journals of organic chemistry and more specialized journals (with IF>4: 1 Angew Chem, 1 OrgLett, 2 JOrgChem). Almost all of them, including the one published in Angew Chem, are primary papers from the team. Considering the small team's size, the output of the team appears very good.

The team "Medicinal Chemistry" was directed by a CNRS CR1 and included another CNRS CR1, as well as two technicians. The team has mainly a service character providing expert knowledge in screening of small molecules to discover molecules that could constitute tools in chemical biology or potential drugs. The team manages the chemical library of the Curie Institute/CNRS. The library is managed as a Curie Institute platform and is open for testing to all the teams of the Curie Institute, and to external groups upon request. The activities of the team are focused on two main research areas, i) the discovery of splicing inhibitors, and ii) heterocyclic medicinal chemistry with the design and synthesis of inhibitors of LIM kinase and phosphatase 1 by the screening of the chemical library. Within these areas, the team has contributed to findings that lead to the creation of a start-up company (SPLICOS) in biotechnology, in 2008. The work was focused on HIV applications as well as on metastatic migration. This project dealing with the modification of alternative splicing mechanisms paves the way to novel therapeutic solutions in virology and oncology. The team has collaborations on inhibitors of phosphatase 1 and on microtubule-associated proteins. The establishment of a start-up "Cellipse" is now in progress.

The team has contributed to 14 publications (8 with IF>4: 1 JACS, 1 OrgLett, 2 Canc Res, 1 J Med Chem). Nine of these publications are made with collaborative partners (including from other teams of UMR 176) who are the corresponding authors. Furthermore, the team has filed many patent applications (17 patents including 8 PCT and 4 european patents). The output is globally good and above what can be expected from a mostly service-oriented group.

Assessment of the team's academic reputation and appeal

The team "Design and synthesis of kinase inhibitors" has a limited number of local and national collaborations. Among them, a collaboration with biologists from Curie Institute on tyrosine kinase Tyro3 inhibitors was funded by INCa. The future PI of the team has been invited to 5 oral presentations in France and one international conference (6th Indian-French COS in 2010). Thus, it appears that the team might be better known in the French than in the international organic chemistry community.

The team "Medicinal Chemistry" shows a large number of local and national collaborations. Some international collaborations (Canada, Italy) could also be noted. Moreover, the team seems to have been well supported through one ANR and several other contracts. From these figures, it appears that the team is networking very well. However, the team is better known in the French than in the international community. The limited visibility of the team is illustrated by the limited number of invited conferences in international conferences (1), and the lack of international networking or conference organization. However, the participation in the network EU Open Screen is an excellent recent development that will increase the visibility of the team.

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

Through the chemical platform, the links of this team with the socio-economic world are strong. This is notably illustrated by the large number (17) of patents drafted by this team, as well as by the strong links with the Splicos start-up company (the team PI is responsible of the chemistry program for the Splicos start-up) or the inhibitors developed for two other start-up companies (Ecrins therapeutics and Cellipse). The PI of this team gave an interview on "Radio Curie" in October 2012 entitled "New therapies". This radio is designed for patients and their families and aims to popularize the research conducted at the Curie Institute.

Assessment of the team's organisation and life

NA

Assessment of the team's involvement in training through research

See above comments related to UMR 176. Of note, the two former groups forming this new team were reasonably involved in training, having 5 PhD students, 3 post-docs and 3 master students during the period.

Assessment of the strategy and the five-year plan

For the next five-year period, the team "Chemistry of small molecules for protein targeting" will merge the forces of the two aforementioned teams, and will be leaded by a previous member of the "Design and synthesis of kinase inhibitors" team. The new team will consist of three researchers (1 Associate Professor, 1 CR1 CNRS who is going to retire in 2017, 1 CR1 CNRS (30%)), 1 CNRS technician and one PhD student. The combination of both teams is considered to be an excellent action which will lead to added value and increased research strength in future.

The research plan for the next five years consists of two projects mainly built on the achievements of the past years and focused on the development of small molecules targeting kinases. The first project "Design and synthesis of selective type II inhibitors of Tyro3" constitutes a significant challenge and will benefit from the contribution of the molecular modelling team. The second project "Design and evaluation of CDK2/cyclin A inhibitors" consists into the development of small molecule combinatorial libraries of dianiline or bisquinoline systems using modern and highly versatile transition metal based methodologies and automated parallel synthesis facilities, which exist at the Curie Institute.

Noteworthy, the two projects will be performed in close collaboration with experts from other disciplines either within the new unit, or with collaborators from the Curie Institute or from a laboratory in Montpellier. In addition, innovation in organic chemistry will be achieved by the development of regioselective transition metal-catalyzed C-C bond formation via C-H bond functionalization methodologies, which recently became one of the most attractive research fields in organic synthesis. The development of efficient methodologies to generate biologically relevant molecules constitutes indeed an essential area to create libraries by varying functional groups, building blocks, and molecular frameworks in order to obtain molecular diversity.

The plan is scientifically compelling and well balanced in terms of feasibility, risks and gain. It is positively seen that considering the past achievements of the PI and the small size of the team, the team focuses on two projects, otherwise it needs to be re-enforced.

Conclusion

- **Strengths and opportunities:**

The team shows a good expertise in organic and medicinal chemistry, which is of key importance in chemical biology approaches. The chemical library and the links with the Splicos start-up are an obvious asset. While the development of drugs is most often "wishful thinking", the development of tools for "discovery biology" is much more in the "frame" of academic research and of great asset for biological science. Moreover, the team has the opportunity to expand its activities to biology through collaborations with biologists from the Curie Institute and elsewhere.

- **Weaknesses and threats:**

The group size is at an edge where competitive research (e.g., publication in the very best journals of the field, translational research) is threatened. For frontier research, a single group has to hold a significantly broad expertise in several highly specialized areas for which a sizable number of personal is absolutely essential. Thus, the reduction in workforce that will occur as a result of the move of one technician and the retirement of a CR1 is a significant threat to the research outputs of the team in terms of quality, originality and quantity.

- **Recommendations:**

Due to the small size of the team, it might be essential to focus its activities on the most promising projects in order to achieve highly visible science. The recruitment of an engineer for the chemical platform will be critical. An active policy for the recruitment of permanent researchers in this team will be a key issue for its success and visibility.

5 • Conduct of the visit

Visit date :

Start : Monday, December 16, 2013 at 8 am

End : Monday, December 16, 2013 at 6 pm

Visit site :

Institution : Paris Sud University/Curie Institute

Address : Campus Universitaire Bat 110, 91405 Orsay

Conduct or programme of visit :

8h00-8h15	Presentation of the AERES by the AERES delegate to the committee (intra se)
8h15-8h30	Presentation of the AERES by the AERES delegate to the unit (intra-se)
8h30-9h30	General presentation of the unit (results/project) by the unit director then discussion
10h-10h30	Audition of Team Multimodal and multiparametric imaging
10h30-10h50	Audition of Team Modelling and molecular dynamics
11h10-11h40	Audition of Team Structure and photoactivatable probes for DNA
11h40-12h	Audition of Team Chemistry of small molecules for protein targeting
12h-12h30	Meeting with the representatives of the unit's supervising institutions and bodies (Université Paris Sud, CNRS, INSERM, Curie Institute)
	Auditoire : committee members, AERES delegate
12h30-13h30	Lunch (around posters)
13h30-13h50	Meeting with permanent and contractual staff (without research duties)
	Auditoire : committee members, AERES delegate
13h50-14h10	Meeting with the PhD students, post-docs and contractual researchers
	Auditoire : committee members, AERES delegate
14h10-14h30	Meeting with the permanent professors, reserachers from institutions and similar positions (without the unit direction)

	Auditoire : committee members, AERES delegate
14h30-14h45	Meeting with the director of the "Ecole doctorale"
	Auditoire : committee members, AERES delegate
14h45-15h	Debriefing
	Presence : committee members, AERES delegate
15h-15h20	Meeting with the unit management team
	Auditoire : committee members, AERES delegate
15h20-17h30	Meeting of the committee (intra-se)
	Presence : committee members, AERES delegate

Specific points to be mentioned:

Ms Laurence PARMENTIER, regional INSERM delegate, and Mr Marius REGLIER, chargé de mission INC CNRS, participated to all presentations and to the meeting of the committee with the supervising institutions.

Mr Eric SIMONI, vice-dean of the Faculty of Sciences, Paris-Sud University, participated to the meeting of the committee with the supervising institutions.

Ms Isabelle REMY-JOUET, representing the technical/administrative staff of the CSS 8 INSERM participated to all presentations and to the meeting of the committee with the technical and administrative staff.

6 • Supervising bodies' general comments

Centre de Recherche

institutCurie

AERES
Section des Unités
20, rue Vivienne
75002 Paris

Paris, le 18 mars 2014

Concerne : Rapport S2PUR150008249-Chimie, modélisation et Imagerie pour la biologie-0753172R

Chers collègues,

En tant qu'organisme hébergeur et déposant unique des rapports des unités de recherche du site d'Orsay vague E, je vous informe avoir bien reçu le rapport en date du 25 février 2014, le rapport d'évaluation de l'AERES sur l'unité indiquée en rubrique.
Nous tenons tout d'abord à remercier les experts pour le temps consacré à la visite et le travail réalisé pour leur rapport.
Les constats et recommandations qui sont formulés dans ce document sont extrêmement précieux.

L'association de compétences en Chimie et Imagerie moléculaire présente une forte valeur ajoutée qui a été reconnue. Néanmoins, à ce jour, un certain nombre de limitations ont été relevées, également constatées en d'autres occasions, telles que la productivité suboptimale de certaines équipes et leur faible visibilité internationale. Par ailleurs, plusieurs équipes proposent un nombre important de projets par rapport à leur taille, sans que les priorités n'apparaissent clairement, ce qui risque de conduire à une dispersion des forces.
De fait, j'ai bien noté les recommandations de ce comité pour concentrer les ressources actuelles sur les questions les plus pertinentes et prometteuses dans des approches plus collaboratives. En parallèle, il est crucial d'inciter cette unité à adopter une démarche active pour attirer des étudiants, post-doctorants…de haut niveau en s'appuyant sur les partenaires environnants et les programmes existants à l'institut Curie. Il sera également important pour l'avenir de cette unité, de poursuivre des discussions avec d'autres laboratoires de chimie pour fédérer les efforts avec les projets de Paris Sud et tirer un bénéfice maximal du site d'Orsay dans ses spécificités.

Ce point sera particulièrement critique pour définir un plan de développement viable à plus long terme pour la plateforme d'imagerie de cette unité en lien avec celle de l'Université Paris Sud.

Une discussion active est en cours avec l'ensemble des tutelles de l'unité pour encourager des efforts de mutualisation garantissant le futur de l'imagerie in vivo pour les projets de cette unité et aider dans la maturation à la fois du projet et de son organisation. Un objectif important sera d'adresser les défis de la chimie sur le site d'Orsay en cohérence avec les autres sites de l'Institut Curie en bénéficiant de l'environnement scientifique riche de Paris Saclay et bien sûr de l'Institut Curie dans sa nouvelle politique de recrutement global sur le site afin de favoriser les collaborations.

Je vous prie d'accepter, Chers collègues, mes plus sincères salutations.

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