ARN - Régulations naturelle et artificielle

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

RNA: Natural and Artificial Regulation

From the

University Bordeaux 2 Victor Segalen

INSERM

May 2010

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

Section des Unités de recherche

AERES report on the research unit

RNA: Natural and Artificial Regulation

From the

University Bordeaux 2 Victor Segalen

INSERM

Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	**Pierre Glorieux**

May 2010

Research Unit

Name of the research unit: RNA: Natural and Artificial Regulation (RNA:ANR)

Requested label

N° in the case of renewal: INSERM U869

Name of the director: Mr. Jean-Jacques TOULME (proposed new director: Mr. Jean-Louis MERGNY)

Members of the review committee

Committee chairman

Mr. Alain JACQUIER (CNRS - France)

Other committee members

Mrs.Mary O'CONNELL (UK)

Mr. Dr. Joachim ENGELS (Germany)

Mr.Javier MARTINEZ (Austria)

Mr. Stephen NEIDLE (UK)

Mr.Olivier BENSAUDE (INSERM - France)

Mr. Christophe LEN (CNU section 32 - France)

Mr. Patrick MIDOUX (INSERM - France)

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

Mr. Patrick MIDOUX (INSERM - France)

Mr. Christophe LEN (CNU section 32 - France)

Observers

AERES scientific advisor

Mrs. Michelle DEBATISSE (CNRS)

University, School and Research Organization representatives

Université Bordeaux 2:

Mr Antoine de DARUVAR (vice président du CA)

INSERM:

Mrs Liliane CHARTIER (AD Aquitaine)

Mrs Christine TUFFEREAU (CSS en remplacement de Catherine Labbe Jullie)

Report

1 • Introduction

- Date and execution of the visit

The committee visited the laboratory by October 19 to 20 (morning) 2009. October 19, the visit was at IECB (Pessac campus), October 20, at University Bordeaux 2 (Carreire campus). The visit was well prepared, with a concise, yet informative, well-presented document. On October 19, presentations were given the heads of each group (there are 4 teams with 2 groups each), with plenty of time for discussion. October 19, was devoted to a visit the Carreire campus, and to discussions with scientists, technical and administrative staff as well as technicians, students and postdocs. There were in addition a few poster presentations.

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

The Unit 869 ("RNA: Natural and Artificial Regulation) was created jointly, in January 2007, by Inserm and University of Bordeaux 2 on the basis of the former Inserm Unit 386. It was created for eight years. The initial Unit started with 11 researchers in three teams. At the end of the first period, the Unit hosted 13 scientists. Quite remarkably, the project presented for the second contract period will involve 18 scientists working into four teams, which points to the dynamism of the Unit. The Unit is located at Carreire (Bordeaux 2 main campus). In addition, three young researchers were appointed "group leaders" at the IECB ("Institut Européen de Chimie et Biologie", an Institute supported by CNRS, Inserm and the Universities of Bordeaux 1 and 2 to host young group leaders for a limited time - ~10 years). Therefore, these three groups are located on the IECB Pessac campus, about 4 km away from the Carriere campus. All teams of Unit U869 benefit from the infrastructure and technical platforms available at IECB. This is an interdisciplinary unit with strong biophysical chemistry and biology of nucleic acids, in particular RNA.

- Management team

During the first four years contract period (2007-2010), the Unit was directed by Jean-Jacques Toulmé. However, according to INSERM rules, which do no allow head of Units older than 65, Jean-Jacques Toulmé will not be able to head the Unit for its second contract period (2011-2014). Jean-Louis Mergny (DR1-Inserm) former head of INSERM Unit 565 – Muséum National d'Histoire Naturelle, Paris, joined the Unit 869 in August 2009 to head the Unit 869 during its second four-year contract period. During the past period, the Unit was composed of three teams. For the next period, a substantial reorganization is proposed to take into account the significant growth of the unit. Therefore, in the new organisation, the unit will be composed of four teams that only partially overlap with the previous teams. Each team has its own team leader, although the teams are each composed of two groups with their own group leader with scientific independence. Hence, overall, eight group leaders can be identified in the unit.

- 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)	6	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6	9
N3: Number of other researchers (Form 2.2 and 2.4 of the application file)	2	2
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6.9	7.9
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2.6	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	11	(4)
N7: Number of staff members with a HDR or a similar grade	7	10

2 • Overall appreciation on the research unit

- Summary

This is a dynamic Unit. When it was created, it comprised 11 scientists at the outset. The project for the second period involves 18 scientists, due to the recruitment of young investigators. This is an interdisciplinary Unit with strong chemistry and biology in particular areas. There are particular strengths in nucleic acid-associated studies, which have been most recently emphasised with the appointments of several talented young team leaders in biological fields. The new director, with a background and international reputation in the biophysical chemistry of nucleic acids, will emphasise new ways of integrating chemistry and biology. The Unit has produced 100 publications in good quality peer-reviewed journals during the 2005-2009 period, which, for a group of this size, can be considered to be very good. The Unit is also highly active in teaching activities, six of its scientists being faculty members attached to University Bordeaux 1 & 2 (2 Prs and 4 MdC). The present director should be congratulated for the way he managed to recruit a future director and to ensure a smooth transition.

- Strengths and opportunities

One of the strengths of the unit is its composition, combining teams expert in biophysical chemistry with teams expert in biology. This interdisciplinarity is obviously a plus, given that there is unifying theme around the study of nucleic acids, in particular RNAs. We were pleased to see that there is a clear willingness, witnessed by the choice of the new director, to reinforce this interdisciplinarity. Probably the most striking strength of the Unit to be noticed is its ability to attract very talented young group leaders. Of note, these are all in the biology field. The consequence of all this is that the Unit, as a whole, is globally young and extremely dynamic, with very high potential. The more established teams have a high reputation in their own fields as well and continue to have very good output. Notable as well is the excellent ability of the Unit to raise funds; they also have plans for technology transfer.

- Weaknesses and threats

Although there is a strong and obvious willingness to foster collaborations between chemists and biologists of the Unit, we felt that in some instances, the interdisciplinarity could be better optimised. In particular, the presence of biologists in the Unit should help establish even more collaborations between the Biophysicochemistry teams and biologists, not only within, but also outside of the Unit. Internal collaborations sometimes appear somewhat opportunistic rather than fully rational. This should also help strengthen technological transfer.

A rule of the PhD school at Bordeaux is to restrict students to an average of 1.3 per HDR (supervisor). Although we perfectly understand that this is done in order to maintain high quality supervision, we felt that it is much too restrictive and that the Unit, as a whole, could contribute more to the training of students. All the scientists stated that their administrative load is too high. One reason for that is the significant understaffing of administration, with only one permanent position to deal with all the administration of the Unit, including that of grants and fellowships.

- Recommendations to the head of the research unit

- Production results

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

A1: Number of lab members among permanent researchers with or without teaching duties who are active in research (recorded in N1 and N2)	12
A2: Number of lab members among permanent researchers with or without teaching duties who are active in research (recorded in N3, N4 and N5)	10.5
A3: Ratio of members who are active in research among staff members [A1/(N1+N2)]	1
A4: Number of HDR granted during the past 4 years	0
A5: Number of PhD granted during the past 4 years	7

3 • Specific comments

- Appreciation on the results

The Unit is working at the interface of biophysical chemistry and biology. The interdisciplinarity of the Unit is reflected in some quite original projects.

Of the major contributions of the Unit during the period, one can highlight the followings. On the biochemical side: new technologies based on nucleoside and oligonucleotide amphiphiles have been developed especially to facilitate nucleic acid cellular uptake. The 2D-SELEX method was developed for the selection of modified aptamers with good nucleic acid targeting properties, such as the characterization of hyper-stable kissing complexes and their use as regulators of prokaryotic and eukaryotic gene expression. On the biological side: discovery of a new form of RNA Pol III characterized by a novel subunit (RPC32beta), evidence for a yet undescribed RNAPIII regulator (Miz1). Several X-ray structures have been described: an RNA kissing complex and structures of proteins involved in RNA metabolisms, including a factor involved in mRNA 3'-end formation and a protein involved in Diamond-Blackfan anemia. Also, a key contribution was made to the genome-wide characterisation of non-coding RNAs in H. pylori, involving the characterisation of human miRNA expression in response to H. pylori infection.

The Unit has produced 100 publications in good quality peer-reviewed journals during the period 2005-2009, which, for a group of this size, can be considered to be very good. There have been 7 PhD theses defended during the period, which is the expected number for a group of this size. We note that the number of students per supervisor is limited by the PhD school, therefore, the number of PhD students could not be much higher.

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

The recent recruitment of several very talented young investigators is a strong indication of the attractiveness of the Unit. This is for a large part to the credit of former director who was one of the instigators of the creation of the IECB (Institut Europeen de Chimie et Biologie). This Institute plays a major role in the ability of the Unit and the University to attract high calibre young scientists.

Overall, the members of the unit show an excellent ability to raise funds, although there might be some variation from team to team.

Altogether, the senior scientists of the Unit have been invited to some 50 international conferences and have themselves organized 14 meetings during the past 4 years, which is excellent taking into account the size of the Unit, attesting to the international reputation of the team. This is especially true for the new director of the Unit, Jean-Louis Mergny. We noticed, however, that the younger scientists, with some exceptions, attend only a few meetings. Greater effort could be made to encourage young scientists to present their work abroad.

There is good socio-economic activity with the creation of a "cellule de transfert technologique", which task is to commercialise the SELEX expertise.

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

There seems to be a good spirit in the Unit. In particular, keeping the balance between biophysical chemistry and biology must be a delicate task. This has been achieved remarkably well and will no doubt continue under the leadership of the new director.

The Unit is very well integrated with Bordeaux University, with a good part of the Unit located on the University campus. Moreover, close to half of the permanent researchers are faculty members with major teaching duties (which is a lot in France).

The recruiting policy, with the creation of the IECB, is exceptional and allowed the emergence of cutting edge projects. This Unit is expanding with a very high quality of recruitment. This is an extremely positive point.

- Appreciation on the project

All teams of the Unit have good ongoing projects. In addition, the recently created young teams have very exciting, cutting edge projects.

4 • Appreciation team by team

Team 1: ChemBioMed (essentially corresponds to the CAST team during the first period)

Team leader: Philippe BARTHÉLÉMY

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

- Appreciation on the results

The research activity of this team is characterized by a high level of nucleic acid chemistry exploited in two domains, the design of supramolecular systems for nucleic acids delivery and new combinatorial methods for optimizing oligonucleotide ligands to nucleic acid targets.

New technologies based on nucleoside and oligonucleotide amphiphiles have been especially developed to facilitate nucleic acid cellular uptake. These hybrid molecules were found to form supramolecular structures, bioactive molecules or new vectorisation systems for drug and gene delivery. Biological applications involved the inhibition of hepatitis C virus mRNA translation with lipid-conjugated oligonucleotides. For this, "click" chemistry has been set up. The "antagomir" strategy taking advantage of 2'-lipid-modified oligonucleotides constitutes a new approach for the development of microRNA inhibitors. These investigations have led to the design of new delivery system based on the non-ionic recognition of nucleic acids via nucleotide-based lipids, which represents a promising approach in the nucleic acid (gene) delivery international field. NANOVA is an emerging project that will use the remarkable capacity of these hybrid molecules to form nanoparticles with low toxicity for the delivery of antitumor reagents.

The Dynamic Combinatorial Chemistry (DCC) method was found to be a good method for testing nucleotide modifications supposed to improve oligonucleotide properties. Modification of 2'-aldehyde group increased the stabilization of DNA-DNA and RNA-RNA duplexes or triple helix-forming oligonucleotides. The 2D- SELEX method was developed for the selection of modified aptamers with good nucleic acid targeting properties.

Overall, the research activities are of high scientific and biotechnological level. The scientific level that has been achieved is reflected by the excellent output in term of publications, patents and scientific communications. 48 publications: most of them are in the most cited Journals in this category: 2 x JACS IF 8.1 ; 3 x Chem Commun IF 5.34; 3 x J Med Chem IF 4.9; 6 x Bioconjug.Chem IF 4.58; 1 x Langmuir IF 4.1; 1 x J.Org.Chem IF 3.95; 4 x Tetrahedron Lett IF 2.54. 5 patents. 33 scientific communications (3 oral, 30 posters); 4 meeting organizations (1 international). 2 theses have been defended.

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

The team has major collaborations including 3 in France, 3 in the US, 1 in Latvia, and 1 in Spain.

The members of the team have been invited to 9 conferences including 4 international. There seems to be some difficulties in attracting post-docs and students more recently. It seems that this is, at least in part, one of the disadvantages of working at the interface between chemistry and biology.

The team has a very good ability to raise funds. The research activities received financial grants from Ligue contre le Cancer, AFM, Région Aquitaine, ANR. Several projects are already funded by national agencies such as ANR, Aquitaine region and international: Army research office (US).

The team is well aware of the obvious potentials for translational research associated with these projects, but biological validations are still required to reach this goal.

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

There seems to be a good spirit in the team. Of the four teams, this is the most heavily involved in teaching since four of its scientists are faculty members with full time teaching duties. The leader is a member of the faculty council and sits on committees for the recruitment of associate professors. He was a member of 15 PhD juries.

- Appreciation on the project

The staff composition will increase by the arrival of a MCU with HDR with expertise in biomaterial functionalization for drug delivery design. Numerous bio-inspired amphiphiles derived nucleosides, nucleotides and oligonucleotides have been synthesized, characterized and tested. These leads should be carefully selected and pursued, be it nucleoside amphiphiles: nucleoside amphiphiles; NANOVA for cisplatin delivery; anionic nucleolipoplexes for transfection; NADA nucleosides amphiphiles for delivery: neutral nanoparticles for delivery, hydrogels or oligonucleotide amphiphiles.

The projects concerning bioimaging are novel and have promise for practical use.

NANAN : Multifunctional oligonucleotide-based nanoplatform; Design of QD-based nanotools: understanding intracellular RNA trafficking; Aptabeacons, aptamer labelling and aptamers for imaging.

Once robust techniques will have emerged from the combinatorial approaches (DCC and 2D-SELEX), these methods may be exploited with inter-team collaborations for the discovery of novel ligands of biological targets including new generations of lipid-oligonucleotides for miRNA targeting or other targets.

Original investigations have led to the design of new delivery system based on the non-ionic recognition of nucleic acids via nucleotide-based lipids. This is a promising approach in the nucleic acid (gene) delivery field.

- Conclusion

Summary: Overall, the design of new delivery system based on the non-ionic recognition of nucleic acids via nucleotide-based lipids is a promising approach in the international gene delivery field. Dynamic Combinatorial Chemistry (DCC) combined with SELEX seems to be potentially a valuable technique to find the best set of substituents for a given RNA-target interaction such as the kissing complex.

Strengths and opportunities: The original background of the team relying on expertise in the nucleic acid chemistry and combinatorial methods should obviously be continued. Being in an interdisciplinary environment should help foster collaborations with biological partners, even outside of the Unit. The very good scientific and commercialisation levels that have been achieved are reflected in the excellent output in term of publications, patents and grants.

Weaknesses and threats: Cellular investigations should be undertaken of the various delivery systems in order to achieve better understanding of them and to improve them. There are a number of distinct projects and the risk of dissipation between them is real, in particular considering that most scientists have heavy teaching duties.

Recommendations: The focus of the team effort lacks some concerted direction with the Unit. Collaborations is advised with cell biologists to set up crosstalk between cell biology and chemistry. Young assistant professors are encouraged to increase their presentations of HDR.

Team 2: Olifans (involves part of the scientists from the former PAR group)

Team leader: Jean-Jacques TOULMÉ

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

- Appreciation on the results

The team is organized in two scientifically independent groups. Group 1 is headed by the former head of the unit, involves several of the scientists of the former PAR team. Group 2 is a new group headed by the new director of the unit who will join the Unit to take the function of director. Its past activities are that of its former group at the Muséum National d'Histoire Naturelle in Paris and will thus be only briefly discussed here.

Group 1: The team has an international reputation in the field of RNA aptamer SELEX. Its major contribution during the period has been the characterization of hyper-stable kissing complexes and their use as regulators of prokaryotic and eukaryotic gene expression. The originality of the approach has been to focus more specifically on RNA aptamers that target natural RNA hairpin loops by forming highly stable and specific loop-loop interactions. The strategy proved interesting as, on the one hand, RNA stem-loops are structures commonly found in RNA-protein interactions in biological systems, and thus constitute potential good biological targets, and on the other hand, RNA aptamers are expected (and proved themselves) to be particularly appropriate to target these types of structures. Group 1 has a good publication record, with 22 articles published during the period, including 1 "PNAS" (IF – 9.4), 3 "Nucleic Acids Research" (IF–6.9), 4 "Biochemistry" (IF-3.4), 1 FEBS Lett. (IF-3.3), etc. 2 theses have been defended. One patent obtained.

Group 2: The team has a major international reputation for their contributions to the field of quadruplex nucleic acids. In particular they have developed much of our current understanding of the underlying thermodynamics of quadruplexes and have devised some of the principal spectroscopic techniques that are now widely used in this field. The track record of group 2 is excellent: 42 high-quality publications including 1 "PNAS" (IF – 9.4), 2 "J Am Chem Soc " (IF – 8.1), 1 "EMBO Reports" (IF – 7.1) , 12 (!) "Nucleic Acids Research" (IF–6.9), 1 "J Med Chem" (IF–4.9), 1 "Mol Pharmacol" (IF-4.7), 5 "ChemBioChem" (IF-3.3), etc.

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

Group leaders of both groups were invited to a number of national and international meetings, witnessing their international recognition. Members of Group 1 were invited to 20 meetings, including 8 international. They were also, quite remarkably, involved in the organisation of six meetings, including one international (in Russia), which highlights their high international reputation.

Good ability to recruit post-docs and students, given the constraints.

The team has an excellent ability to raise funds. Group 1 received financial grants for ANR (3 grants), ANRS, and grants from Région Aquitaine.

Group 1 is involved in a number of collaborations, including the participation to three European networks (SMILE, SAFER, SAFE).

The team is strongly involved in technology transfer, with the creation of a "Cellule de Transfert Technologique", called "Novatech", which proposes providing services in selecting, using an in-house designed SELEX platform, aptamers against various targets of potential translational interest.

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

The team leader of group 1 (former Unit Director) must be strongly commended for its initiative to found the "Institut Europeen de Chimie et Biologie" (IECB), which was spectacularly successful in recruiting young investigators and teams, particularly from abroad. This must be recognized as a major achievement. It has a major impact on research in Biology at the regional level by its capacity to attract high profile young team leaders. This initiative must be credited to, for the large part, the team leader of group 1 (former Unit Director).

- Appreciation on the project

Group 1 proposes two main areas of research. The first one intends to exploit the understanding of the rules governing high affinity loop-loop "kissing" RNA interactions, knowledge gained during the first period, to design specific hairpin ligands to be used in several biological projects: i) inhibition of toxin synthesis in H. pylori, ii) inhibition of an RNA-protein interaction involved in the HCV life cycle, iii) inhibition of pre-miRNA maturation, iv) inhibition of an RNA maturation process involved in the unfolded protein response in the endoplasmic reticulum. The second project proposes to use SELEX expertise to develop various aptamer-based biotechnological tools. These

projects are original. They will all be performed with adequate partnerships with biologists directly interested in the respective themes, either internal to the unit or external, providing a good probability of success.

The six projects of group 2 explore a diversity of aspects of quadruplex nucleic acids, ranging from biology to nanotechnology. There is good evidence of coherence between the projects, and a central theme is the investigation and validation of the biological function of quadruplexes, especially RNA quadruplexes. The team has wisely selected this topic as being of likely high biological relevance. All the projects are highly collaborative, and a set of well-established collaborations is in place, with other appropriate ones being envisaged. The team will also extend its expertise to work closely with others in INSERM U869 on aptamers, recognising that aptamers often contain a quadruplex motif. This work, while being an obvious partnership, will benefit both the existing aptamer work and the new team.

- Conclusion

Summary: Bringing together two groups with complementary strong specific expertise in the field of biophysical studies of nucleic acids has resulted in the creation of an excellent team, internationally at the forefront in its field.

Strengths and opportunities: Strong synergy is expected by the gathering of these two groups. The evident willingness to take advantage of the interdisciplinary nature of the unit should be encouraged.

Weaknesses and threats: Although both groups are making valuable efforts to reduce the gap between biophysical in vitro studies and biology, this side of the work remains probably the weakest and we strongly encourage the members of the team to redouble on their efforts in this direction.

Recommendations: To further foster collaboration with biologists, in particular outside of the Unit. For example, we suggest that efforts be made to develop some of the aptamer technology into potential clinical candidates, by bringing in new collaborations with expertise in target selection and validation.

Team 3: TMS (Transcription, Maturation and Structure; essentially the same team as the former TMS team)

Team leader: Martin TEICHMANN

- 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)	1	2
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)	2	2
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)	3	1
N7: Number of staff members with a HDR or a similar grade	1	2

- Appreciation on the results

The team is organized in two scientifically independent recent groups, headed by young scientists. The major focus of group 1, led by the leader of the team, is the study of human Pol III regulation, in particular during cellular transformation. This is a very interesting subject, RNA Pol III regulation being poorly studied despite its anticipated

great importance during cellular transformation. The group has made very significant contributions to the field: identification of a subunit of TFIIIC, discovery of a new form of RNAPIII characterized by a novel subunit (RPC32beta), evidence for a yet undescribed RNAPIII regulator (Miz1). Some extremely promising results, not yet published, have been presented. The group is internationally well recognized.

Group 2 is quite new since its team leader joined the Unit at the end of year 2007. The group is performing extremely well. The aim of the group is to perform structural studies on factors or complexes in relation to RNA metabolism, in particular in collaboration with other teams of the unit, for example with group 1 on structural studies of a ternary complex involved in the RNA Pol III initiation. Other significant published results were also obtained on structural studies in relation to Diamond-Blackfan anemia.

Both groups have good publication records since each published during the period 6 articles in very good journals. Group 1: 3 Mol Cell Biol (IF – 5.9), 1 J Biol Chem (IF-5.5), 1 Trends Genet (IF-8.7), 1 BMC biochem. Group 2: 1 Nat Struct Mol Biol (IF-11.0), 1 Blood (IF-10.4), 1 Human Mol Gent (IF-6.2), 2 Nucleic Acids Res (IF-6.9). 2 theses have been defended.

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

The two groups have established very strong and productive collaboration, both nationally (in particular with the CEA, Saclay and the CNRS in Toulouse) and internationally (in USA, Germany, and Switzerland).

1 invited conference, 2 meeting organizations.

Good ability to recruit PhD students and PostDoc

Although group 1 mentioned some difficulties in adapting to the "French funding system", the committee felt that they were doing pretty well in that matter: group 1 obtained an "ANR blanche" and Group 2 is an INSERM "avenir" group and obtained an ANR grant as well!

Strong collaborations abroad (USA, Germany and Switzerland).

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

Group 1 is heavily involved in teaching: its head is a full professor and one of the scientists is an assistant professor, each with heavy teaching duties, as usual in France. The leader of group 1 is also quite heavily involved in the organization of the teaching at the University (member of the "Conseil Scientifique de l'UFR", member of the "Conseil scientifique et pédagogique de l'Ecole Doctorale, etc.).

- Appreciation on the project

Group 1 is developing its very interesting project on the regulation of Pol III in mammals, with very exciting unpublished results. In addition to the continuation of the ongoing projects, group 2 is taking advantage of the arrival in the team of an internationally recognized expert on the mechanism of mRNA 3'-end formation, to initiate detailed structure-function studies of the very large complex involved in this maturation step. This is a very good project given the expected synergy between the competences of this newly arrived investigator and and those of the leader of group 2.

- Conclusion

Summary: This team is composed of two highly dynamic and promising groups. In addition, major collaborations have been established between the two groups making the team very promising.

Strengths and opportunities: The leader of group 2 has only been in the TMS team a short period of time and has been very successful since he arrived both in terms of publications and in obtaining external funding. One of the main strengths of the TMS team is that they work closely together: one of the main projects of group 2 is the structural analysis of subunits of RNA Pol III that is in collaboration with group 1. The recent recruitment of a new researcher is ideal as he has previously published with the leader of group 2 on the structure of CstF-77, a component of the mammalian 3'end processing complex and in the future they want to continue this fruitful collaboration and look at other protein complexes involved in 3'end processing. This is of great benefit to the Fribourg group as it will

allow them to expand their work so not only will they solve the structure of the protein complexes but they can also analyse these complexes from a more biological perspective.

Weaknesses and threats : Both researchers in group 1 have a heavy teaching load and there is no full time researcher within this group. This may be the reason why they have many external collaborations and do not end up being senior authors on some subsequent publications. Therefore they do not have as many publications as principal investigators as some of the other groups; however their situation has to be taken into consideration. They have some exciting work that they are about to publish and considering the recent discovery of the role of RNA Pol III in the innate immune response, they should be able to attract new researchers and additional funding to their group.

Recommendations : One concern is that some of the protein complexes that the Fribourg group is endeavouring to crystallize are very large and maybe unstable and difficult to work with. However they are very aware of this and are already planning to perform cryo EM on these complexes if they encounter too many difficulties. This is also a direction the committee would recommend. If financially possible we would also recommend that more of the TMS group attend international conferences.

Team 4: sRNA PAR (involves part of the scientists from the former PAR group)

Team leader: Fabien DARFEUILLE

- 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)	2	3
N3: Number of other researchers (Form 2.2 and 2.4 of the application file)	1	1
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	1
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

Team 4 regroups two scientifically independent recent groups, headed by young scientists. Group 1, led by the team leader, studies the function of small non-coding RNAs in Helicobacter pylori and the involvement of microRNAs in human gastric cells upon infection by H. pylori. The first part of this program is performed in collaboration with laboratories in Germany and at the Institut Pasteur. In particular, the collaboration with the German group led to very important work, with the genome-wide characterization of the complete transcriptome of H. pylori by deep-cDNA sequencing. This work, currently under revision in a top-ranked journal, will be a landmark in the field. One main output of this work is the finding of the prevalence of antisense non-coding transcripts. This opens a very potentially fruitful area of research. The group have chosen a few of the most promising in term of potential implications for regulatory mechanisms, for detailed functional analyses. In particular, work on antisense RNAs targeting toxin-encoded genes is particularly promising, but there are many other research leads to follow. The research on microRNAs in H. pylori infected cells is also very promising, with the identification of miRNAs whose expression responds specifically to H. pylori infection. The group is thus very dynamic and has high potential.

Group 2 constitutes the "Avenir team" called "Genome Regulation and Evolution". It is led by a researcher who joined the Unit in September 2007. This small group has implemented a machine specifically designed by the group

leader during his post-doc and which allows high throughput sorting of C. elegans based on spatial reading of in vivo fluorescent reporters. The group leader wants to use this system to quantitatively analyse mRNA-UTR mediated regulation by miRNAs and post-transcriptional regulations, in particular at the splicing step. The committee was enthusiastic about the presentation, the work already accomplished and the project.

In conclusion, this team regroups two extremely promising young groups.

The publication record is excellent. Given the young age of the two groups, some of their publications are follow-ups of work performed when the group leaders were post-docs, but these underscore their high quality.

Group 1: 13 publications, including 2 Genes Dev (IF-13.6), 1 Mol Cell (IF-12.9), Angew Chem Int Ed (IF-10.9), Nucleic Acids Res (IF-6.9), J Med Chem (IF-4.9), etc. As mentioned above, the research of Group 1 is highly successful, in part thanks to very fruitful collaborations, in particular with a group in Berlin, collaborations in which Fabien Darfeuille is instrumental.

Group 2: publication record over the period is exceptional (1 Nature, 2 Nature biotech, 1 PLoS Biology, 1 Genome Res., etc). Note that, given he only very recently arrived to set-up his lab, these publications principally denote the work performed during the post-doc of the team leader.

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

The leader of group 1 was a member of the organizing committee of two French meetings or workshops. A CNRS researcher recently joined this team. The leader of group 2 received an FRM award and a Bettencourt-Schueller Fondation award. He was the main organizer of two international workshops (China) and was invited to give lectures, keynote addresses and oral presentations to more than 10 meetings. Altogether, he gave 26 seminars or oral presentations at meetings.

The ability to raise funds appears excellent. Group 1 obtained an "ANR jeune chercheur", two ARC and two "La Ligue" grants and is a partner of an "ANR blanc". Group 2 is an INSERM "Avenir" group and obtained the "Avenir" Award from the Bettencourt-Schueller Fondation.

- Appreciation on the project

As stated above, both groups in the team have very promising projects that are already at an advanced stage. Group 1, through its collaboration with the German group, is a key player in a project on the characterization of non-coding RNAs in H. pylori, which will undoubtedly give rise to a high profile publication. The project on miRNA expression in response to H. pylori infection is also very promising. Group 2's project is really a cutting-edge project that takes advantage of a unique experimental set-up. This is a truly exciting project.

- Conclusion

Summary: Team 4 regroups two independent groups headed by enthusiastic and talented young group leaders. This team has a high potential.

Strengths and opportunities : The two groups are young, well integrated in the Unit, and have exciting projects.

Weaknesses and threats: The committee was surprised that the granting of an Avenir group to the leader of group 2 was not paralleled by the granting of a Tenured INSERM position by the CS2 INSERM commission. The rational for joining these two groups in a common team is not obvious, scientifically speaking, although we understand that this allows reaching an adequate size, the two groups being small young groups."

Recommendation : Keep going.

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+	A

Nom de l'équipe :CHEMBIOMED (Groupe 1 – Barthélémy)

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

Nom de l'équipe : OLIFANS (Groupe 1 – TOULME)

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

Nom de l'équipe : OLIFANS (Groupe 2 – MERGNY)

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

Nom de l'équipe : TRANSCRIPTION, MATURATION, STRUCTURE (Groupe 1 – TEICHMANN)

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	Non noté	Non noté	A+

Nom de l'équipe : TRANSCRIPTION, MATURATION, STRUCTURE (Groupe 2 – FRIBOURG)

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	Non noté	Non noté	A

Nom de l'équipe : sRNA PAR (Groupe 1 – DARFEUILLE)

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	Non noté	Non noté	Non noté	A

Nom de l'équipe : sRNA PAR (Groupe 2 – DUPUIS)

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+	Non noté	Non noté	Non noté	A+

Monsieur Pierre GLORIEUX
Directeur de la section Unités de recherche
AERES

Bordeaux, le 25 février 2010

Monsieur le Directeur,

Je vous transmets les observations de Messieurs Jean-Jacques Toulmé, Directeur de l'Unité « Régulation naturelle et artificielle » et Jean-Louis MERGNY, Directeur du projet d'unité, faisant suite au rapport du Comité de visite de l'AERES.

Je vous prie de croire, Monsieur le Directeur, à l'assurance de mes sincères salutations.

Le Vice-Président du Conseil Scientifique,

Alain BLANCHARD

Université Victor Segalen Bordeaux 2 • *Sciences de la Vie, Sciences de la Santé, Sciences de l'Homme*
Affaires Scientifiques • Esplanade Jacques Latrille • 146, rue Léo-Saignat • 33076 Bordeaux cedex
Tél. 05 57 57 13 08 / 48 60 • Fax. 05 56 99 03 80 • e-mail : affaires.scientifiques@u-bordeaux2.fr • www.u-bordeaux2.fr

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

Unité 869 – ARN : Régulations Naturelle et Artificielle

Université Victor Segalen Bordeaux 2

Pessac, February 24, 2010

We are very grateful to the committee for their thorough evaluation and their supportive comments and recommendations. A few minor factual errors and typos are listed in an independent document. Concerning the evaluation of the unit and its teams, we would like to make a few comments and update some information:

General comments:

1) As the visit was held in October 2009 and the report sent by the AERES in February 2010, some of the elements are now outdated. In particular, some results listed as "*very exciting unpublished results*" "*not yet published*" (page 11) or "*currently under revision in a top-ranked journal*" (Page 12) are now in press in prestigious journals. Specifically, we are very pleased to mention the following articles:

- Sharma, C.M. *et al.* The primary transcriptome of the major human pathogen *Helicobacter pylori* **Nature** (2010) available online Feb 17; DOI 10.1038/nature08756
- Haurie V. *et al.* Two isoforms of human RNA polymerase III with specific functions in cell growth and transformation. **Proc. Natl. Acad. Sci USA** (2010) *in press*

Taking into account these recent additions, the staff of the laboratory has now published more than 20 articles in high impact (IF >8) journals since 2005. An updated list of publications will be sent to the trustees and the AERES before April 1st.

2) "*The team leader of group 1 (former Unit Director) must be strongly commended for its initiative to found the "Institut Europeen de Chimie et Biologie" (IECB), which was spectacularly successful in recruiting young investigators and teams, particularly from abroad. This must be recognized as a major achievement*"
We appreciate the recognition of the role played by the IECB in the attractivness of the lab. The institute is clearly an essential asset for the INSERM unit, allowing the recruitment of young and promising group leaders. This will continue to play a very positive role in the forthcoming years provided that new teams are offered an attractive package and teams leaving the IECB at the end of their 10-year contract are offered appropriate lab space in the Bordeaux campus. Specifically, two U869 groups are expected to leave the institute within the next quadrienal, in 2011 and 2013 and we cannot emphasize too much the need to prepare these moves with our trustees.

3) "*significant understaffing of administration, with only one permanent position to deal with all the administration of the Unit*"
We are pleased with the committee's recommendation to reinforce our administrative staff. Note that we regret that the current AERES recommendation for committee composition no longer implies the presence of an ITA/ IATOS representative.

4) "*The Unit is very well integrated with Bordeaux University*".
This becomes even more true as several members of the lab play an important role in the preparation of new local federative structures.

5) "*the interdisciplinarity could be better optimised*" & "*the presence of biologists in the Unit should help establish even more collaborations between the Biophysicochemistry teams and biologists, not only within, but also outside of the Unit. Internal collaborations sometimes appear somewhat opportunistic rather than fully rational*"
We fully agree with the recommendation that chemists should establish stronger links with biologists. Note however that many groups in the lab are recently installed (2007 or later) and that novel collaborations will emerge with time. Initial collaborations were indeed opportunistic, but efforts are being made to convert them into functional ones. It is worthy to note that the chemistry team is involved in 8 of the 9 inter-team publications.

6) "*We noticed, however, that the younger scientists, with some exceptions, attend only a few meetings. Greater effort could be made to encourage young scientists to present their work abroad*" (Page 6).
Acknowledged. Efforts are made to solve this issue.

Specific comments:

1) Team 1:

"*There seems to be some difficulties in attracting post-docs and students more recently*"
Note that Team 1 hosts currently 5 post and 3 PhD students. To overcome this problem of visibility (for PhD) a new option entitled: "Chemistry-Biology Interface" was recently created by the "Ecole doctorale des Sciences de la Vie et de la Santé".

"*biological validations are still required to reach this goal*" "*Cellular investigations should be undertaken of the various delivery systems in order to achieve better understanding of them and to improve them*"
We thank the reviewers for this remark. Biological validations are indeed an unavoidable dimension for the understanding of our delivery systems. Note however that most of the papers published by our chemistry groups within the last period feature biological studies demonstrating the cellular internalization of the novel systems. Our future investigations will include the determination of the internalization mechanism(s). Thanks to intra- and extra-Unit collaborations we expect to solve these puzzling questions. Importantly, current ANR projects include internalization studies, *in vitro* and *in vivo* studies.

"*There are a number of distinct projects and the risk of dissipation between them is real, in particular considering that most scientists have heavy teaching duties*"
We agree with this remark. In order to avoid a dissipation risk we will select projects according to the following criteria: *i)* encourage projects with high potential in terms of high impact publications, *ii)* favor projects with technology transfer possibilities *iii)* reinforce intra Unit collaborations

"*The focus of the team effort lacks some concerted direction with the Unit. Collaborations is advised with cell biologists to set up crosstalk between cell biology and chemistry*"
It is clear that the chemistry team will take advantage of collaborations with cell biologists and the chemistry team is working in that direction, as shown for example by a recent

publication involving members of teams 1 & 4: G. Godeau, C. Brun, H. Arnion, C. Staedel and P. Barthélémy, *Tetrahedron Letters* (2010) 51: 1012-1015

"*Young assistant professors are encouraged to increase their presentations of HDR*"
We thank the commitee for this message. Young assistant professors will be strongly encouraged to obtain this Habilitation.

2) Team 2:

"*The team has an excellent ability to raise funds. Group 1 received financial grants for ANR (3 grants)…*"'.
This is true also for Group 2, with 2 ANR grants, 1 FRM grant, support from the Conseil Régional, etc…

"*Although both groups are making valuable efforts to reduce the gap between biophysical in vitro studies and biology, this side of the work remains probably the weakest and we strongly encourage the members of the team to redouble on their efforts in this direction*"
Both groups are making efforts in that direction, establishing new links with biology laboratories (as shown by ANR proposals submitted recently). Some of the aptamer work could lead to potential candidates for clinical use (at least for diagnostic application). This is the case for aptamers targeted to MMPs.

3) Team 3:

First note that we kindly request the AERES committee to remove the name of a novel Pol III regulator from the document as these data have not been published and should be kept confidential.

" *Group 1 is heavily involved in teaching*"
Efforts are made by the group leader of team 1 to reduce the teaching load by applying to the 'Institut Universitaire de France'. Additional efforts will have to be made with the University administration for reducing the teaching load for the Assistant Professor in the laboratory.

" *One concern is that some of the protein complexes that the Fribourg group is endeavouring to crystallize are very large*"
The strategy adopted in order to tackle such large complexes has been used in the past on other large complexes such as TFIIH. It is based on identifying core structural elements of the various subunits as well as the identification of core sub-complexes. In a final step, one expects to obtain experimentally-based models of the whole complex either by X-ray crystallography and/or Electron Microscopy. In the case of CFI A, the structure of CstF-77/Rna14p (largest subunit) has been obtained as well as the Rna14p-Rna15p core heterodimer thus recapitulating almost the entire Rna14p protein. In parallel, efforts have been made to reconstitute a core CFI A complex (done) and obtain pure native CFI A from yeast cells. Altogether with previous data, we are able to start crystallization and EM studies of native and reconstituted CFI A. The risk associated with such a sample is equivalent to the risk of any other sample at the same stage.

"*If financially possible we would also recommend that more of the TMS group attend international conferences*"

Postdoc and students have been sent to an international meeting in UK and will attend the next RNA meeting in Seattle. They are also encouraged to participate to workshops in Europe. Further efforts will be made, and we will finance the attendance of junior members of the laboratory to international conferences.

4) Team 4:

(Group 2) "*Note that, given he only very recently arrived to set-up his lab, these publications principally denote the work performed during the post-doc of the team leader*"
Note that Group 2 recently submitted a MS to ***Nature Biotech***, currently under review. Group 1 published the very recent ***Nature*** paper on *H. pylori* transcriptome.

"*The committee was surprised that the granting of an Avenir group to the leader of group 2 was not paralleled by the granting of a Tenured INSERM position by the CS2 INSERM commission*"
We share that surprise and hope that this situation will be solved in 2010 !

"*The rational for joining these two groups in a common team is not obvious, scientifically speaking*"
The models may differ (group one is interested in *H. pylori* and group two in *C. elegans*) but both groups share a common interest in natural regulation with a particular focus on post transcriptional regulation programs involving miRNAs.

Jean-Louis Mergny
Candidate Director

Jean-Jacques Toulmé
Current U869 Director