DHPI - Dynamique des interactions hôte pathogène

Rapport Hcéres

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

Research Units Department

AERES report on unit:

Dynamic of Host Pathogen Interaction

DHPI

Under the supervision of the following institutions and research bodies:

University of Strasbourg

February 2012

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

Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head

Pierre Glaudes

Unit

Name of unit:	Dynamic of Host Pathogen Interaction
Acronym of unit:	DHPI
Label requested:	EA
Present no.:	EA 4438
Name of Director (2009-2012):	Mr Bertrand LUDES
Name of project leaders (2013-2017):	Mr Ermanno CANDOLFI and Mr Olivier ROHR

Members of the committee of experts

Chair:	Mr Michel SIMONET, Lille
Experts:	Mr Alain BONNIN, Dijon (CNU representative)
	Ms Dominique BUZONI-GATEL, Nouzilly
	Mr Eric OSWALD, Toulouse
	Mr Bernhart RYFFEL, Orleans Center
	Mr Dirk SCHLÜTER, Magdeburg, Germany
	Mr Marco VIGNUZZI, Paris

Representatives present during the visit

Scientific Delegate representing AERES:

Mr Joost VAN MEERWIJK

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

Mr Eric WESTHOF, University of Strasbourg

Report

1 • Introduction

Date and conduct of visit:

The visit of the full evaluation committee took place on February 1st 2012 (1 to 5 pm) at the Faculty of Medicine. First, the unit's director presented its global activities followed by presentations by the two project leaders. In a closed-door session, the committee then discussed with the unit's directors. Finally, the representatives of the University exposed its scientific policy and discussed with the committee members. The visit ended with a closed-door meeting of the committee. PhD students and postdoctoral fellows; engineers, technicians and administrative assistants; and staff scientists had met in the morning with the committee members in three parallel meetings.

History and geographical location of the unit, and overall description of its field and activities:

The team, termed DHPI (for Dynamic Host Pathogen Interaction), results from the recent fusion (2010) of a research-group originated from a Strasburger Inserm unit with a research-group affiliated with the university. DHPI is located within the Institute of Parasitology and Tropical Pathology (IPTP), which hosts the National Reference Center for *Toxoplasma i*mmunology. The team also includes some clinicians (ophtalmologists).

DHPI proposes an innovative research project on epigenetic regulation of pathogen latency following intracellular infection by two medically-important infectious agents, the human immunodeficiency virus type 1 (HIV-1) and the Apicomplexa parasite *Toxoplasma gondii*. Both groups aim at deciphering the molecular and cellular mechanisms supporting the persistence of both microorganisms in infected hosts to develop new therapeutic strategies aimed at purging the microbe reservoir.

Management team:

DHPI is co-directed by two Professors who are internationally-recognized experts in their field of research. One of them has been recently appointed junior member of the «Institut Universitaire de France»; the other is also director of hospital parasitology and mycology laboratory and head of IPTP.

Unit workforce:

Workforce	Number on 06/30/2011*	Number on 01/01/2013*	2013-2017 Number of producers**
N1: Professors or assistant professors	7	9	8
N2: EPST or EPIC researchers	3	0	0
N3: Other professors and researchers	1	4	1
N4: Engineers, technicians and administrative staff *on a permanent position	9	7	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	1		
N7: Doctoral students	12		
N8: PhD defended	8		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	3	5	
TOTAL N1 to N7	**34**	**20**	**9**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

2 • Assessment of the unit

Overall opinion on the unit:

From oral presentations of the team by the two co-directors and discussions with permanent researchers, students, engineers, technicians and administrative assistants, it clearly appeared to the committee that fusion of the «HIV-1» and «*Toxoplasma*» groups, that occurred almost two years ago, is not artificial but a reality. For example, lab meetings are common, and people from the two original groups interact with each other. The groups have complementary areas of expertise (epigenetics and immunology, respectively) both at the scientific and technological levels, which are very beneficial to the team's development. Besides, the general objective of the unit, i.e. identifying molecular and cellular mechanisms of intracellular persistence in two distinct infection models, viral and protozoan, has already shown that common mechanisms may be involved, paving the way to the basic understanding of intracellular infection. Discussions with the Dean of the Faculty of Medicine and the Vice-President of the University Scientific Council revealed that DHPI is strongly supported by local authorities.

Strengths and opportunities:

The team proposes an innovative, focused scientific project, developed by a significant workforce and with a substantial financial support: comparing mechanisms of persistence in two distinct models of intracellular infection may identify basic features of manipulation of host cells by micro-organisms. The complementary expertise of the two groups leads to strong synergism. Lastly, the team, which successfully valorizes its research, is relatively "young" (notably, with a significant number of PhD students and post-docs), contributing to its dynamism

Weaknesses and risks:

Despite active international scientific collaborations, the team is still poorly attractive for post-docs from abroad (EU or North America). A decreasing rate of funding for fundamental research, needing to develop applied projects (with industrial partners) with short-term potential for valorization, and a high level of international competition for the "HIV-1" group are the two main incurred risks.

Recommendations:

The committee recommends to (i) integrate European networks to reply to calls for proposals from the EU commission's funding program, (ii) limit (wherever possible) scattering the focus of research, particularly in the case of the *Toxoplasma* group, for a better competitiveness, and (iii) balance (wherever possible) technicians in the two groups (0 vs 4 for the "HIV-1 group" and the "*Toxoplasma* group", respectively)

3 • Detailed assessments

Assessment of scientific quality and production:

DHPI highlighted that HIV-1 and *Toxoplasma* latency in the host is controlled by epigenetic events. The team identified host CTIP2 as a key cellular factor involved in HIV-1 transcriptional silencing: CTIP2 cooperates with LSD1 and silences the p21 gene promoter. Another important discovery is that *Toxoplasma* exploits UHFR1 and induces host cell cycle arrest at G2 to enable parasite-proliferation; *T. gondii* triggers UHRF1 phosphorylation, and a secreted rhoptrial kinase might be involved in this modification. Another finding, relevant to *Toxoplasma*-induced uveitis (due to parasite latency in retinal cells), is an enhancement of inflammatory cytokine IL-17 level in aqueous humor of infected hosts, an observation paving the way to therapeutic intervention.

Research mostly conducted by the team (i.e. with a team member as a first or co-first, last or co-last, or corresponding author) led to 51 original articles in peer-reviewed journals, the five most important (IF > 5) of them having been published in EMBO Journal, Oncogene, Nucleic Acids Research, Cellular Microbiology and Journal of Infectious Diseases, and 8 PhD-theses were defended. Additionally, it is worth noting that the number of citations of papers produced by the team increased over the past five years.

Overall, the team produced high quality, basic research during the past four years, contributing to a better knowledge of HIV-1 and *Toxoplasma* pathogenesis.

Assessment of the unit's integration into its environment:

The team obtained substantial grants (1800 k€) from French funding agencies (ANRS, Fondation pour la Recherche Médicale, ECOS-Nord, PHRC, Ligue contre le Cancer).

DHPI aims to develop new diagnostic tools and valorizes its research (contracts with companies) by the production of biological materials (recombinant proteins, monoclonal antibodies, native microbial antigens) intended for industrials. One patent (with international extension), concerning an anti-HIV-1 agent, was deposited. The team also brings out its research by transferring its knowledge to the general public (Téléthon, Jardin des Sciences…).

Valorization of its research is a constant concern of the team, and the committee noticed that the DHPI team satisfied this objective during the past four years.

Assessment of the research unit's reputation and drawing power:

One co-director was, in 2011, appointed "junior member" to the "Institut Universitaire de France". Members of the team were invited for conferences (13), for writing reviews (9) or book chapters (2), and were asked by editors of outstanding journals (e.g. EMBO Journal, Oncogene, Nucleic Acids Research) to review scientific original papers. The team organized, in 2007, the first joint meeting of French, German and Swiss Societies of Parasitology, and, in 2011, the annual meeting of the French societies of Parasitology and Medical Mycology.

During the past four years, the team recruited (in 2008) a permanent researcher (MCU-PH) and (for a 2-year period) 3 post-docs from France and Hungary. It collaborates, not only locally and nationally, but also with several groups throughout the world, half from the US.

The team has a good reputation; however it needs to reinforce its international visibility for a better attractivity of scientists from abroad.

Assessment of the unit's governance and life:

Team governance is satisfactory with a weekly lab meeting, journal club, and student follow-up, and a yearly evaluation of PhD students by external committees. Technical management (e.g. animal facility, strain or antibody storage) is under the responsibility of a specific permanent member. Two-thirds of the team members are teacher/researchers and therefore, the team is largely involved in educational activities (see below). The committee judged as excellent the unit's governance and life.

Assessment of the strategy and 5-year project:

The project, in continuity with the past, is well-focused: this feature confers international competitiveness to the team. However, four US research groups work on the same topic as the «HIV-1 group», and although there is no competition for studying UHFR1-*Toxoplasma* interactions, it is worth noting that this parasite is one of the most investigated by parasitologists throughout the world, in particular the immune response of infected host. The team has skills and has access to local facilities that render project-implementation during the next five years credible. It is worth noting that, in supplement to two non-permanent teacher/researchers (ATER and University Hospital assistant), two postdocs will be recruited soon. The main risk is a decrease of institutional financial support and to limit this risk, the team needs to develop more applied projects with short-term potential for valorization: the team is aware of the danger of such dispersal but « side projects » will allow a financial support (through industrials) for the DHPI fundamental project.

Assessment of the unit's involvement in training:

The team is largely involved in teaching with, almost 1,000 annual hours of lectures and practical courses in physiology and parasitology/mycology. It also participates to three Master's programs at the University of Strasbourg (Physiopathology and Translational Medicine; Neuroimmunology; Climate Change) and to the Pasteur Institute course "Arthropod Vectors and Human Health". Fourteen PhD students were hosted in the team from 2008 until today (5 by the "HIV-1 group" and 9 by the "*Toxoplasma* group"), and they were (are) funded by the state (Ministry of Research) or through charitable associations (SIDAction, The Medical Research Foundation) and in the case of foreign students, by their own governments. A follow-up by the co-directors of their experiments is scheduled every week. All but one doctors who defended their PhD during the past four years (8) are employed either as assistant-Professors at the University, engineers in private companies, or have a post-doctoral position.

4 ● Project-by-project analysis

Project 1: Molecular interactions with HIV

Name of project leader: Mr Olivier ROHR

Workforce

Workforce in Full-time Equivalents	06/30/2011	01/01/2013
FTE for professors or assistant professors	2	2
FTE for EPST and EPIC researchers	0	0
FTE for engineers, technicians and administrative staff on a permanent position	1	0
FTE for engineers, technicians and administrative staff on a non-permanent position	1	
FTE for postdocs having spent at least 12 months in the unity	1	
FTE for doctoral students	2	
TOTAL	**7**	**2**

● Detailed assessments

Understanding the mechanisms underlying HIV latency and reservoirs in the infected host is a primary goal of research in the field. Despite two changes of host laboratory during this period, which undoubtedly impeded the research program and limited recruitment or retention of personnel, the group has not shown a negative impact of scientific production. On the contrary, this small group has increased its production and took advantage of collaborations wisely, publishing 10 papers in broad scientific journals: e.g., EMBO J 2007 (80+ citations), Nucleic Acids Research, Oncogene 2009 (30+ citations), PloS One, with every junior member appearing on at least one article (average 3 per member).

During this period the group has made significant contributions to the identification of the cellular factors involved in HIV-1 transcriptional silencing required for the establishment of latency. Juxtaposing the small size of the group against the large international competition in the field, it is evident that this group has made intelligent, strategic choices to initially focus on the less studied, but very relevant, microglial latency reservoir. The research project proposed is well detailed and thought out, with a high likelihood of succeeding in terms of productivity. If more laboratory members can be secured, the proposal could also extend in breadth and take more exploratory, scientific risks.

In terms of funding, the group has successfully obtained grants at the national level to cover the near totality of its research. Given the new proposed structure merging virology and parasitology on a common, original theme, the committee would encourage the team to also seek funding from more general sources (ANR, EU, etc.). This will be particularly helpful to the "HIV group", to increase its size and scope of research.

The group's international visibility is good, as its research has been covered by several review articles, and senior team members have presented at international meetings. It should continue to increase its presence at international meetings with an effort to draw in students or postdocs from abroad, such as from competitive labs within the field or other teams of the HIV cure international working group in which they are involved.

Conclusion:

The “HIV group” has a very good track-record of scientific productivity that has continued over this period, despite having to shift administrative affiliation twice. The strategy set forth for the upcoming five years is solid and intelligently planned. The group has strength and expertise in epigenetics and viral latency and has a new opportunity to thrive within the proposed new structure. The group is encouraged to seize this opportunity to expand in terms of personnel, projects and international involvement. As acknowledged by the group itself, the field is highly competitive and the group is small; thus, it should continue to strike a balance between strategically focusing its central projects while attempting to broaden its horizons.

Project 2: Molecular interactions with *Toxoplasma*

Name of project leader: Mr Ermanno CANDOLFI

Workforce

Workforce in Full-time Equivalents	06/30/2011	01/01/2013
FTE for professors or assistant professors	5	7
FTE for EPST and EPIC researchers	3	0
FTE for engineers, technicians and administrative staff on a permanent position	8	7
FTE for engineers, technicians and administrative staff on a non-permanent position	0	
FTE for postdocs having spent at least 12 months in the unity	0	
FTE for doctoral students	10	
TOTAL	**26**	**14**

- Detailed assessments

The research achievements on host-parasite cellular and molecular interactions are mostly focused around *T. gondii*, one of the most common parasitic infections in France. After the previous AERES visit and recommendations in 2008, the team has turned to the studies of latency mechanisms focusing on the eye, a major target organ of the parasite, and one of the leading causes of blindness worldwide. The team has studied latency in toxoplasmosis in two *in vitro* and *in vivo* approaches: the initiation of the latency through cellular mechanisms such as regulation of transcription factors involved in cell proliferation and parasite reactivation in the eye, leading to inflammatory damage to this organ. Importantly, research of the group covers and connects both clinical and experimental aspects of toxoplasmosis.

The resulting scientific production is good, with publication quality increasing during the past 10 years (e.g. Cellular Microbiology in 2008; Journal of Infectious Diseases in 2009; Cellular and Molecular Life Science in 2010). The group and its leader are nationally and internationally well recognized in the field of toxoplasmosis.

The group is dynamic as attested by the supervision of numerous PhD students and the fact that it has obtained two new positions for hiring in 2012, underscoring strong institutional support. The team has brought together complementary skills from physicians, pharmacists, scientists that should favor the initiation of original scientific proposals and increase its visibility and its success in terms of funded grant-applications.

The project to associate with the “HIV group” should bring together two driving forces to pull up the scientific level by supporting discussions, sharing tools and mentoring excellent students. Beyond the common posted goal of the team about latency, which is not completely analogous when seen from the side of the parasite or the virus, the complementary approaches in cell biology should be a source of reciprocal enrichment. The immunological approaches about ocular inflammation include clinical and experimental murine studies. The clinical work includes studies in France and South America and should be extended. The experimental *in vivo* model should be better adapted to the research on human ocular toxoplasmosis with a clinically more relevant design, maybe less ambitious but with more accurate questions to be addressed.

The main threat of the group is the time-consuming involvement of some members in medical activities. However, this is at the same time an opportunity to get medical samples, strains and clinical cases, and create an

original scientific *continuum* from clinico-epidemiological to basic research, including laboratory diagnosis and industrial partnerships.

Conclusion:

Ocular toxoplasmosis is a real health problem worldwide. Emergence and reinforcement of a group capable of encompassing all aspects of this disease from clinical to physiopathological and basic science should undoubtedly be supported. In this context, the "*Toxoplasma* group" is very dynamic, with a real leader having recognized expertise in the field of toxoplasmosis, and performs good science in a context of medical, scientific and teaching requests. To do so, the group does not hesitate to open its doors to a young talented scientist who will bring complementary skills to the unit and the opportunity to have interesting scientific exchanges. However, the team should be careful to better define the addressed questions especially those regarding inflammation and ocular toxoplasmosis. This should be a chance to use efficiently the available tools and models and lead to publications with a higher impact factors.

5 • Grading

Once the visits for the 2011-2012 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the four criteria defined by the AERES and was given along with an overall assessment.

With respect to this score, the research unit concerned by this report (and, when necessary, its in-house teams) received the overall assessment and the following grades:

Overall assessment of the unit "Dynamic of Host Pathogen Interaction DHPI":

Unité dont la production, le rayonnement et le projet sont très bons. L'organisation et l'animation sont excellentes.

Grading table:

C1 Scientific quality and production.	**C2** Reputation and drawing power, integration into the environment.	**C3** Laboratory life and governance.	**C4** Strategy and scientific project.
A	A	A+	A

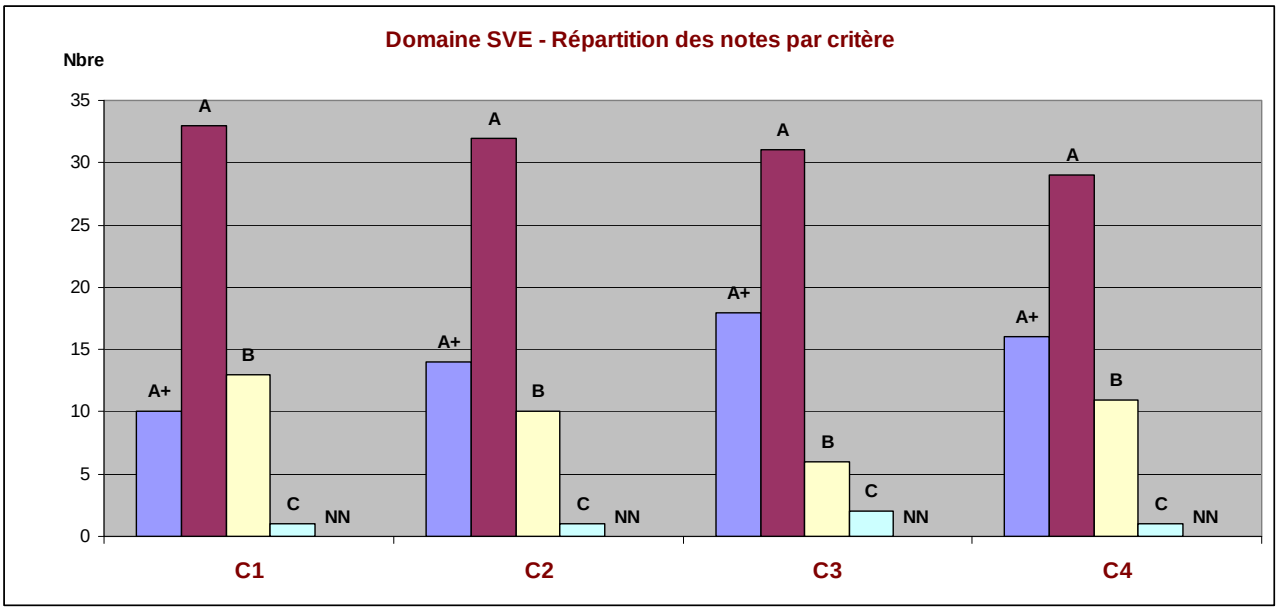
6 • Statistics per field

Notes

Critères	C1	C2	C3	C4
	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Gouvernance et vie du laboratoire	Stratégie et projet scientifique
A+	10	14	18	16
A	33	32	31	29
B	13	10	6	11
C	1	1	2	1
Non noté	-	-	-	-

Pourcentages

Critères	C1	C2	C3	C4
	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Gouvernance et vie du laboratoire	Stratégie et projet scientifique
A+	18%	25%	32%	28%
A	58%	56%	54%	51%
B	23%	18%	11%	19%
C	2%	2%	4%	2%
Non noté	-	-	-	-



7 • Supervising bodies' general comments

UNIVERSITÉ DE STRASBOURG

Monsieur Pierre GLORIEUX
Directeur de la Section des Unités de recherche
Agence d'évaluation de la recherche et de l'enseignement supérieur (AERES)
20 rue Vivienne
75002 PARIS

Alain BERETZ
Président

Strasbourg, le 5 avril 2012

Objet : Rapport d'évaluation du projet d'EA « dynamique des interactions hôte pathogène » (réf. S2PUR130004545-RT)
Réf. : AB/EW/N° 2012-168

Affaire suivie par
Eric WESTHOF
Vice-président Recherche
et formation doctorale
Tél : +33 (0)3 68 85 15 80
eric.westhof@unistra.fr

Direction de la recherche

Cher collègue,

Je vous remercie pour l'évaluation du projet d'équipe d'accueil « Dynamique des interactions hôte pathogène » porté par Monsieur Ermanno Candolfi.

Vous trouverez ci-joint les réponses du porteur de projet concernant les erreurs factuelles et les remarques et appréciations du comité d'experts.

Je n'ai pas de remarque particulière à ajouter au nom de l'Université.

Je vous prie d'agréer, Cher Collègue, l'expression de mes sentiments distingués.

Alain BERETZ

P.J. :

- **Une première partie corrigeant les erreurs factuelles**
- **Une seconde partie comprenant les observations de portée générale**

4 rue Blaise Pascal
CS 90032
F-67081 STRASBOURG cedex
Tél. : +33 (0)3 68 85 15 80
Fax : +33 (0)3 68 85 12 62
www.unistra.fr

Strasbourg March the 23th

COMMENTS ON THE AERES REPORT CONCERNING THE DHPI RESEARCH UNIT.

Pr Ermanno Candolfi
Faculty of Medecine
University of Strasbourg
Hôpitaux Universitaires de Strasbourg

Pr. Olivier Rohr
IUT Louis Pasteur
University of Strasbourg
Institut Universitaire de France

Olivier.rohr@unistra.fr

The DHPI unit members are very satisfied of the overall evaluation of their new research unit. The AERES report recognizes their investments in the past and supports our propositions for the future. We are specifically satisfied that the committee recognized that our DHPI unit is "not artificial but a reality" resulting from the fusion between the HIV and the Toxo groups. The quantity and the quality of our productions have been noticed and our future projects have been recognized as "innovative and focused". In the same line the double governance of the unit by Ermanno Candolfi and Olivier Rohr has been judged as "excellent".

Two recommendations have been made by the committee to further strengthen the DHPI competitiveness.

The first recommendation suggests to further **focus the Toxo projects for a better competitiveness.**

We would like to remind that huge efforts have already been done in the past decade to focus the all Toxo working forces on only two projects: the epigenetic and the ocular Toxo projects. However, we will develop the technical, the managerial and the scientific interactions between the working forces to further favor the development and the focalization of our goals toward the epigenetic regulation of immune gene essential in ocular pathogenesis.

The second recommendation concerns the HIV group. The AERES committee suggests **increasing the size of the HIV group in the DHPI unit.**

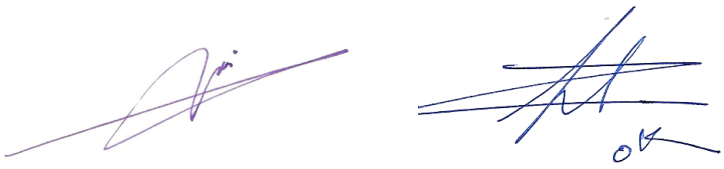
We fully agree that new recruitments are more than necessary. We will need to increase our working forces with the support of our institutions. It's the key point of our future competitiveness and a prerequisite to the perennial of the HIV latency thematic in Strasbourg. This AERES report confirms the high productivity of the HIV

Shipping adress:

Institut de Parasitologie et dePathologie Tropicale
3 rue Koeberlé
67000 Strasbourg
Tél. : +33 (0)3 68 85 37 00

group that is composed ***of only two permanent teaching researchers*** *(1 PR and 1 MC) and* ***no technical support****. The responsibilities and the teaching activities (IUT) of Olivier Rohr (president CNU 66) and Christian Schwartz (CNU member) are time consuming and thereby further contribute to the need of new young and talented recruitments. The very high investment of the managers made the good reputation of this team but the lack of new recruitments and the lost of the technician support two years ago (move from INSERM unit) may be very detrimental. We believe that weakening the Toxo group to reinforce the HIV-1 group is not a way to ensure the development of the DHPI unit.*

The competitiveness of the DHPI unit will need the development of both groups. As noticed by the AERES committee, the DHPI unit is strongly supported by the University and the Medicine Faculty. We are confident that this support will be confirmed by targeting permanent researchers (MC), ingenieur and technician positions in the HIV group. This is the prerequisite to ensure the perennial of its internationally recognized activity but also to the development of the entire DHPI unit.



Pr Ermanno Candolfi
Université de Strasbourg

Pr. Olivier ROHR
Université de Strasbourg
Membre de l'*Institut Universitaire de France*