



Dynamyc

Rapport Hcéres

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

Department for the evaluation of
research units

AERES report on interdisciplinary unit:
Dynamics of colonisation and infection by *Aspergillus
fumigatus* in the respiratory tract in humans and
animals

DYNAMYC

Under the supervision of the following
institutions and research bodies:

Université Paris-Est Créteil Val de Marne - UPEC

École Nationale Vétérinaire d'Alfort

January 2014



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 2006¹,*

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

On behalf of the expert committee,

- Mr. Jean-Pierre GANGNEUX, 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 experts committee, the composition of which is specified below.

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

Unit name:	Dynamics of colonisation and infection by <i>Aspergillus fumigatus</i> in the respiratory tract in humans and animals
Unit acronym:	DYNAMYC
Label requested:	EA
Present no.:	
Name of Director (2013-2014):	Mr Jacques GUILLOT
Name of Project Leader (2015-2019):	Mr Jacques GUILLOT

Expert committee members

Chair:	Mr Jean-Pierre GANGNEUX, Université Rennes 1
Experts:	Mr Dominique CHABASSE, Université d'Angers (representative of CNU) Mr Manuel CUENCA-ESTRELLA, Centro Nacional de Microbiología Spanish National Center for Microbiology, Spain Mr Frédéric DALLE, CHU de Dijon Ms Ilse JACOBSEN, Leibniz Institute for Natural Product Research and Infection Biology, Germany

Scientific delegate representing the AERES:

Ms Catherine SCHUSTER

Representatives of the unit's supervising institutions and bodies:

Mr Alain BERDEAUX (Doctoral school n° 402)
Mr Jorge BOCZKOWSKI, Université Paris-Est Créteil
Mr Georges GUELLAEN, Faculté de Médecine de l'Université Paris-Est Créteil
Mr Renaud TISSIER, École Nationale Vétérinaire d'Alfort

1 • Introduction

History and geographical location of the unit

The research team DYNAMYC was formed from the previously existing group Ecopham, part of the Joint Research Unit BIPAR (Molecular Biology and Immunology of PARasitic and fungal diseases) created in 1999 and located at ANSES (French Agency for Food, Environmental and Occupational Health & Safety). However, some structural and human resources modifications during the last years have led to the individualization of an independent group dedicated to the study of mycology in human and animal health. In order to reinforce the scientific and educational collaboration between veterinarians and physicians, DYNAMYC is now located at the Faculty of Medicine of the Université Paris Est Créteil and aims at integrating in the future the IMRB (Institut Mondor de Recherche Biomédicale) at the Henri Mondor Hospital in Créteil.

Management team

Head: Mr Jacques GUILLOT - Deputy head: Ms Françoise BOTTEREL

AERES nomenclature

SVE1_LS4; SVE1_LS6; SVE1_LS7

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	5 (4 EFT)	5 (4 EFT)
N2: Permanent researchers from Institutions and similar positions		
N3: Other permanent staff (without research duties)	6 (5.2 EFT)	6 (5.2 EFT)
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	2	2
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	14 (12.2 EFT)	14 (12.2 EFT)

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

2 • Overall assessment of the interdisciplinary unit

Global assessment of the unit

The research team DYNAMYC is currently composed of 14 members that are well established scientists and renowned in the field. The research topics addressed by DYNAMYC are very original. Focusing on the fungus *Aspergillus fumigatus*, epidemiological issues will be addressed, backed up with *in vitro/in vivo* models, aiming at clarifying the cellular consequences of these epidemiological observations. In addition, this team which involves experts in the veterinary and medical fields is unique in France, enabling projects and trans-disciplinary research with strong national and international impact to be achieved. In particular, the team leader has developed competitive networks in the field of research and teaching on veterinary mycology. The team is well organized, with easy access to pooled resources. Members share lab space and have a joined office area at the Créteil Faculty of Medicine. The head of the parasitology-mycology lab at Henri Mondor University Hospital is the deputy head of the DYNAMYC research entity. The atmosphere amongst the researchers is very good. Overall, the high scientific potential of the group and the unique combination of veterinarians and physicians is quite innovative and original in the field. The structure and logistics support strongly the team members as well as the research program.

Strengths and opportunities related to the context

The research developed by the research team DYNAMYC is original and the approach innovative and unique. There are opportunities for partnering in networks, platforms, associations, as well as for joint productions with non-academic partners. The expected impact of the research program is high at an international level. In the context of veterinary mycology, the academic reputation and appeal of the head of the unit has to be considered as outstanding. He is internationally known and very active in the veterinary mycology community, e.g. he founded the ISHAM (International Society for Human and animal mycology) working group on veterinary mycology and he is one of the organizers of the first workshop on veterinary mycology. In the context of interdisciplinarity, the organization of the unit is outstanding, in that it combines researchers from both veterinary and medical background sharing lab and resources. The group is actively involved in teaching at the master level, at the National Veterinary School d'Alfort, at the Faculty of Medicine of the Université Paris Est Créteil (UPEC) and at the Paris Descartes University, as well as in human and veterinary clinics. The atmosphere is very good and positive, they appear to see themselves really as one team with a common goal and a well-developed "team spirit". Innovative tools such as new generation sequencing and a unique mix of animal and human *in vitro/in vivo* models will warrant interesting and original manuscripts in high impact factor journals.

Weaknesses and threats related to the context

The DYNAMYC team is a newly created team with the technical and scientific prerequisites required for obtaining national and international grants. In general, the project is highly original and could lead to outstanding results, but the planned work exposed during the visit appears too descriptive. The experts committee suggests to develop hypotheses (based on previous work or data collected during the initial phases of the projects) to address mechanisms of pathogenesis/infection. This would also help to potentially increase the number of high impact publications of the group.



The experts committee felt that the reinforcement of the unit with a full time researcher and a full time technician (only 2.2 EFT technician in the team, one will retire soon) would improve the research capacity of the team.

Recommendations

DYNAMYC is a young team with a strong potential and a unique interdisciplinarity combination of veterinarians and physicians working on mycology. The structure and local logistics support provided by the institutions warrant the feasibility of the research program, and the team might rapidly integrate the INSERM Institute IMRB (Institut Mondor de Recherche Biomédicale, Créteil). A good level of scientific involvement in international and national projects and an outstanding contribution of well known experts incite the experts committee to express a highly positive assessment for this unit. The group should however refine its research strategy and aims going beyond descriptive studies to address mechanistical questions. The group will also have to be followed regarding its capacity to attract full-time scientists and post-docs and to apply for national and international research grants.

3 • Detailed assessments

Assessment of scientific quality and outputs

DYNAMYC involves experts in the veterinary and medical fields in a unique combination in France, enabling trans-disciplinary research to be promoted and developed. The research is original, focusing on *Aspergillus fumigatus*, either as an environmental microorganism that may colonize the respiratory tract in humans and animals, or as a pathogenic organism for respiratory epithelial cells. These scientific questions are high spots of research in the mycology field. Furthermore, *Aspergillus fumigatus* is a potential azole-resistant organism as shown in Northern Europe, but only limited data are available from France. Innovative tools, such as new generation sequencing, and a unique mix of animal and human *in vitro/in vivo* models will warrant important manuscripts in high impact factor journals. The track record (publications, talks) in the field is considered as excellent, taking into account that veterinary research topics generally do not reach the level of impact factors expected for human microbiology. In its previous configuration with 2 more scientists that are no more included in the DYNAMYC team, the group published 72 scientific publications, among them 41 original research articles (mean IF 3.57), 19 papers about clinical cases (mean IF 2.89) and 12 reviews (mean IF 5.29) over the period 2008 to June 2013. Papers were published in generalist and specialty journals considered as exceptional to excellent (based on Thomson Reuters IF): 1 Am J Transpl (IF 6.4), 3 Clin Infect Dis (IF 9.1), 2 Clin Microbiol Rev (IF 16.1), 1 AIDS (IF 6.2), 1 Emerg Inf Dis (IF 6.2), 1 in Haematol (IF 6.4) and 29 articles with IF between 2.5 and 6. Furthermore, the scientist who joined the group in September 2012 published 16 research articles and 8 clinical cases. Among them 8 as major contributor (1 Emerg Infect Dis. (IF 6.2), 4 Antimicrob Agents Chem. (IF 5.1), 3 J Clin Microbiol (IF 4.1) from January 2008 to June 2013. Members of the group gave 42 lectures as invited speakers, and a total number of 40 oral communications were presented during international (n=19) or national (n=24) conferences.

Assessment of the unit's academic reputation and appeal

The head of the research team as well as the leaders of work packages are used to contribute to projects with strong national and international impact. Particularly in the context of veterinary mycology, the academic reputation and appeal of the head of the unit has to be considered as outstanding. He is internationally known and very active in the veterinary mycology community, e.g. he founded, in 2012, the ISHAM (International society for human and animal mycology) working group on veterinary mycology and is one of the organizers of the first workshop on veterinary mycology. Furthermore, the DYNAMYC team, mainly composed by members from the Université Paris Est Créteil (UPEC) and the National Alfort Veterinarinary School (ENVA), has attracted a well established scientist from university Paris V with national and international expertise in the field of antimicrobial resistance. Some team members are already engaged in national and international funding programs and are regularly invited to oral lectures at national and international conferences. Team members are included in Editorial Boards (e.g., ISRN Veterinary Science, Cellular and Molecular Probe, Journal of Medical Mycology) and are regularly referee in journals in the field of medical or environmental Microbiology, Mycology and Veterinary Sciences.

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

Members of the DYNAMYC team have developed collaborations with pharmaceutical and veterinary industries that reflect the innovative nature of their research and potential for technology transfer. In particular, PhD funding from private companies (CIFRE convention) has been obtained recently. The work carried out has already contributed to the establishment of recommendations for the survey and control of fungal infections in humans and animals. The experts committee feels that new applications with pre-normative or prescriptive purpose could be obtained in a mid-term. A large number of articles in journals targeted to practitioners (veterinary and medical) as well as book chapters demonstrate an excellent to outstanding level of communication of the team members with non-researchers.

Assessment of the unit's organization and life

The DYNAMYC team is well organized. Team members share lab space and have a joined office area in the Créteil Faculty of Medicine. A weekly meeting is scheduled including scientific presentations by external members, reports of new data and logistics problems. An easy access to different platforms and pooled resources necessary for carrying out their research activities is supported by UPEC and ENVA. The DYNAMYC team may join the IMRB to ease the access to technical platforms but also to participate in research meetings.



The atmosphere amongst the researchers is very good and positive, they appear to see themselves really as one team with a common goal and a well-developed “team spirit”. This is quite remarkable and can be considered as an attractive feature. A website is available and regularly updated. The research team is well-balanced, including PhD students, post-docs and clinicians and tenured position research staff. However the unit should be strengthened by the addition of a full-time researcher and a full-time technician, since all the researchers have quite significant duties in patient and animal care as well as teaching. Reinforcement of scientific and technical staff would also increase the scientific output through full commitment to sustainability of technical knowledge.

Assessment of the unit's involvement in training through research

From 2008 to 2013, the research team was part of the ABIES (Agriculture, Biologie, Environnement, Santé, ED 435) doctoral school. The head of the research team has been a member of the executive committee of the doctoral school ABIES from 2003 to 2010. In 2014, the group will be part of the doctoral school SVS (Sciences de la Vie et de la Santé) from UPEC (Université Paris Est Créteil, ED n°402) and will probably be involved more and more in this structure. From 2008 to 2013, 5 students defended their PhD thesis. Within the DYNAMYC team, 2 students are preparing their thesis, a grant was obtained from a private company (bourse CIFRE) and an other from the China Scholarship Council. Besides, the team DYNAMYC hosts 1 post-doc and 2 Master students. Supervision of research activities is very well appreciated by students. Members of the DYNAMYC team are involved in teaching programs for bachelor and master students from Université Paris-Est Créteil (UPEC), Université Pierre et Marie Curie (UPMC) and Université Versailles Saint-Quentin (UVSQ). The head of the unit created a specific master (M2) course “Circulation des agents pathogènes dans les populations animales” (Master A2I, UVSQ). The deputy head recently created a specific M1 course “Interactions entre agents infectieux” with the Département Hospitalo-Universitaire (DHU) “Virus Immunité et Cancers at UPEC.

Since 2002, the head of the unit is an invited speaker for the Medical Mycology course from Pasteur Institute and for a course about Epidemiology and Public Health (“Circulation des agents infectieux”) from Pasteur Institute, UPMC and UVSQ. Other Members of DYNAMYC give presentations during the M2 courses “Lutte contre les pathogènes; aspects fondamentaux et économiques” (Paris 7) (since 2007) and “Réponses Immunitaires anti-fongiques et anti-parasitaires” (UPMC) (since 2009).

Assessment of the strategy and the five-year plan

The project aiming at the analysis of the role of *Aspergillus fumigatus* as an environmental microorganism that may colonise or be a pathogenic organism for the human and animal respiratory tract, and of growing importance as a resistant micro-organism, is very interesting and ambitious, but competitive with other international research groups. In this context, some comments are provided below in order to help improve the project, because the present proposal does not include a detailed description of that issue:

- specific objectives of working packages should be included;
- chronogram and division of tasks for team members should be described;
- the five-year plan should include a strategy for cooption of future partners, a broadening of the subject, and a strategic plan for funding;
- limitations and weaknesses are not well-described;
- a more detailed description of procedures used should be provided and a strategy of bioinformatics analysis could help to evaluate the feasibility of the plan.

In general, the planned work appears too descriptive and the experts committee suggests to develop hypotheses (based on former data collected initially in previous work in connection with the project) to address mechanisms of pathogenesis/infection. This would also help to potentially increase the number of high impact publications from the group.

In the first working package, it seems legitimate, after the discussion with the team, to include the study on bamboo rats (as a continuation of an existing collaboration that brings external funding in the form of PhD stipends to the group), but the rest of the package does not seem to be planned in detail and could be discarded in favor of more promising studies using specific skills of the group. For example, the group could focus and develop previous work that has been already published on the human respiratory microbiome and develop a strategy on how their work could add clinical significance. One of the strengths in this work package is the idea to investigate the microbiome in animals.



This field is clearly understudied and because there will likely be little competition, the group is set up very well to address this topic. If done in farm animals, the results could be of economic interest as they may lead to hypotheses on how to improve performance and/or management, e.g. in poultry. However, the strategy for such a study needs to be clearly defined in order to be more than just descriptive and lead to pathophysiological hypotheses. For example, the group could build upon their previous observation that different chicken lines have different susceptibility to aspergillosis. This could be extended by comparing the microbiome in both lineages to test the hypothesis that the specific difference in susceptibility to *Aspergillus* is inferred by the microbiome.

Similarly, the idea for the second work package is very good: interaction of *Aspergillus* with epithelial cells is understudied and the technical basis for sound experiments is given. However, a clear definition of concise projects is missing. There are many options on how to design scientifically sound and innovative projects: for example, based on the hypothesis that differences in the epithelial response between mammals and birds contribute to the higher susceptibility of birds to aspergillosis, a comprehensive comparison of porcine and avian primary epithelial cell cultures challenged with *Aspergillus* could be performed.

Overall, the project is highly original. The main positive point of this team is the original and cross-cutting nature of this project, which brings together researchers from veterinary and medical fields with specific skills, with the support of pooled technical resources and of their institution. This is a young team with scientific prerequisites that are required to obtain national and international grants. The investment in the various work packages should be cautiously adapted to the availability of funding, technical resources and scientists, after having clearly defined some priorities within this ambitious program.



4 • Conduct of the visit

Visit date:

Start: Thursday January 23rd 2014 at 08:00 a.m.

End: Thursday January 23rd 2014 at 15:30 p.m.

Visit site: Faculté de Médecine

Institution: Université Paris-Est Créteil

Address: 8 rue du Général Sarraill, 94000 Créteil

Conduct or program of visit:

Welcome

Closed door expert committee members meeting

Key achievements and project presentation (presentation - discussion)

Meeting with institution representatives

Meeting with the Doctoral School ED n° 402 representative

Meeting with scientists

Meeting with technical staff

Meeting with PhDs and post-docs

Meeting with head of the team

Experts committee closed-door meeting



5 • Supervising bodies' general comments

Réponse au rapport du comité d'experts AERES suite à l'évaluation Dynamics of colonisation and infection by *Aspergillus fumigatus* in the respiratory tract in humans and animals

Titre de l'unité : **DynaMyc**

Label demandé : **EA**

Nom du Directeur : **Professeur Jacques GUILLOT**

We first would like to thank the review committee for what we perceive as a strong encouragement to continue our research activity and further optimize our original approach combining medical and veterinary mycology. Furthermore, the review committee considered that the research topics addressed by our group are relevant. This positive evaluation should facilitate the recruitment of a permanent scientist and/or technician as lack of manpower remains, as wisely stated by the members of the review committee, a major threat to the achievement of our three working packages. In particular, the reinforcement of the scientific and technical staff would increase the scientific output through full commitment to sustainability of technical knowledge.

These are our responses to the main concerns raised by the review committee:

"Specific objectives of working packages should be included" and "A more detailed description of procedures used should be provided".

Our response for working package 1: the general objective is to characterize airway microbial species (microbiota), especially *A. fumigatus*, following colonisation or infection respiratory processes. Our goal, in the first two years (2015-2016) will be to explore the microbiota in humans with cystic fibrosis (CF). Given the polymicrobial nature of this condition and the complex interactions between microorganisms, characterising the microbial community (in terms of diversity and abundance) became a strong evidence to improve our knowledge of CF physiopathology and to optimize therapeutic management. The aim of our project will be to analyse bacterial and fungal microbiota before and after antibiotherapy and compare the population in terms of clinical and microbiological concordance or unconformity. The fungal and bacterial communities will be analysed in terms of diversity and dynamics. The modifications but also changes in the microbiota (emergence / extinction of a bacterial or fungal population), the impact of mixed bacterial and fungal colonization and impact of treatments associated will be analysed. For this study, we have access to the cystic fibrosis patients cohort (120 adult patients and children) of the Intercommunal Hospital of Créteil (Pr Ralph Epaud, Dr Laurence Bassinet) and the Hospital of Lille (150 adult patients and children) (Dr Laurence Delhaes, who has an expertise in pyrosequencing and cystic fibrosis). For this work, Françoise Botterel obtained a grant from the association "*Vaincre la mucoviscidose*" (2013-2015). In a second step (2016-2018), we propose to apply the same strategy for a better understanding of the role of microbial communities in the physiopathology of chronic obstructive pulmonary disease or ventilated patients. A similar approach is planned for the analysis of the respiratory microbiota in animals (birds and rodents). Specific objectives will be to obtain original data about the physiopathology of animal mycoses (aspergillosis in birds and penicilliosis in bamboo rats) but also to

use or develop animal models for a better understanding of the physiopathology of human diseases (in connection with working package 2). As suggested by the review committee, we plan to compare the respiratory microbiota in different lineages of chicken (and in a second step, in different avian species) to test the hypothesis that the specific difference in susceptibility to *A. fumigatus* could be inferred by the microbiota.

Our response for working package 2: the general objective is to understand the interactions of *A. fumigatus* (alone or associated with opportunistic bacteria) with airway epithelium cells leading to colonisation or infection. For the next three years, our specific objective will be to analyse differential transcriptomic approaches of epithelial respiratory cells exposed to *A. fumigatus*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* (either in a planktonic form or in a biofilm conformation). In line with the committee's recommendations, our team will focus increasing efforts into investigating mechanistic aspects. The access to the next generation sequencing platform of IMRB will allow us to work on differential transcriptomic using RNA-seq. Transcriptomic data will be confronted in order to identify candidate pathways involved in the interaction between the microorganisms and human epithelial cells. Cellular and molecular biology approaches will then be used to dissect the relevant pathways and unravel the mechanisms underlying the roles played by fungi, bacteria and epithelial cells. For this work, a grant has been submitted in February 2014 by Françoise Botterel (Leg Poix Foundation). In a second step, a similar approach will be applied to identify pathways involved in the interaction between the microorganisms and animal epithelial cells. Based on the hypothesis that differences in the epithelial response between mammals and birds contribute to the higher susceptibility of birds to aspergillosis, a comprehensive comparison of porcine and avian primary epithelial cell cultures challenged with *A. fumigatus* and bacteria will be performed.

Our response for working package 3: the general objective is to study the prevalence of azole-resistance in *A. fumigatus* in different patient populations and also in hatcheries, avian farms and the environment. For the detection of resistant isolates in hospitals in France, retrospective as well as prospective surveys have already been initiated. These studies are including: (i) the screening of collections of *A. fumigatus* isolates from collaborative centers; (ii) the confirmation of resistance by reference AFST methods; (iii) the molecular identification to the species level (ITS/beta-tubulin sequencing) for resistant isolates; (iv) the molecular analysis of *Cyp51* gene; (v) the molecular typing of sequential isolates from the same patient using the MLVA technique recently described by our group. For this work coordinated by Eric Dannaoui, several grants have been obtained from pharmaceutical companies (2013-2014) and we have the project to submit a national PHRC in 2015.

"a strategy of bioinformatics analysis could help to evaluate the feasibility of the plan"

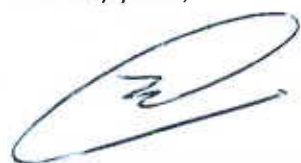
Our response: our group has an access to the new next generation sequencing platform of IMRB with the specific expertise of Dr Christophe Rodriguez, who is a member of VIC DHU. The fully automated new platform integrates classical Sanger sequencing and 4 next-generation sequencing devices, including one HiSeq and one MiSeq (Illumina) and two GS devices, including GS FLX and GS Junior (Roche). Our group collaborates with Genoscreen for the metagenomic approach, especially for the bacteria (Metabiote kit). Targeted sequences for bacteria will be V3-V4 and V5-V6 of 16S RNA using 454 FLX+, available in IMRB teams, to obtain long sequences. For fungi, the ITS region will be targeted to obtain long sequence with 454 FLX+ technology. Data generated with the ultra deep pyrosequencing method will be analysed with in-house Perl software programs PyroClass© and PyroMyc©. At the end of the process, only sequences ≥ 100 bp, with $\geq 98\%$ homology with reference sequences and 0.0 e-value will be included. The IMRB is the process of recruiting a Professor of Bioinformatics in charge of setting up a bioinformatics platform. Given our future interaction with IMRB, we will be able to take advantage of this facility.

"Chronogram and division of tasks for team members should be described"

Key steps (scientific leader)	2015- 2016	2016- 2017	2017- 2018	2018- 2019	2019- 2020
WP1. Explore the microbiota in humans with cystic fibrosis (F. Botterel)					
WP1. Explore the microbiota in humans with other chronic pulmonary diseases (F. Botterel)					
WP1. Explore the microbiota in rodents (J. Guillot)					
WP1. Explore the microbiota in birds (different lineages of chicken and different avian species) (P. Arné)					
WP2. Analyse differential transcriptomic approaches of human epithelial cells exposed to <i>A. fumigatus</i> and bacteria (F. Botterel)					
WP2. Compare the response of epithelial respiratory cells from mammals and birds (P. Arné)					
WP2. Analyse differential transcriptomic approaches of epithelial cells exposed to <i>A. fumigatus</i> and bacteria in different lineages of chicken (P. Arné)					
WP3. Detect and characterize <i>A. fumigatus</i> resistant isolates from the environment and avian farms (J. Guillot)					
WP3. Detect and characterize <i>A. fumigatus</i> resistant isolates from hospitals in France (E. Dannaoui)					
WP3. Evaluate the clinical relevance of the resistance in original mini-host animal models and to characterize the mechanisms of resistance (E. Dannaoui)					

We would like to thank again the review committee for his advice allowing us to shape a better research project and we hope that the members of the committee will be satisfied with our responses.

Sincerely yours,



Pr Jacques Guillot
Head of the research group Dynamyc



Luc Hittiger
President of UPEC



Marc Gogny
Director of ENVA