



Différenciation Cellulaire et Croissance

Rapport Hcéres

► To cite this version:

Rapport d'évaluation d'une entité de recherche. Différenciation Cellulaire et Croissance. 2010, Université Montpellier 1 - UM1, Université Montpellier 2, Institut national de la recherche agronomique - INRA. hceres-02032345

HAL Id: hceres-02032345

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Submitted on 20 Feb 2019

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

Section des unités de recherche

AERES report on the research unit

Cell Differentiation and Growth

From the

University of Montpellier 1

INRA

Mai 2010



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et de l'enseignement supérieur

Section des Unités de recherche

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Cell Differentiation and Growth

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University of Montpellier 1

INRA

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

Mai 2010



Research Unit

Name of the research unit: Cell differentiation and growth

New proposed name : Muscular Dynamics and Metabolism

Requested label : UMR

N° in the case of renewal : 866

Name of the director: M. Arnaud CHATONNET

Members of the review committee

Chairperson

Mrs Josiane FONTAINE-PERUS, University of Nantes, France

Other committee members

Mrs Carole CHARLIER, University of Liège, Belgium

Mrs Véronique COXAM, INRA, France

M. Fernando GOGLIA, Università degli Studi del Sannio, Italy

M. Pascal MAIRE, University of Paris-Descartes, France

Mrs Anna POLESSKAYA, Institut André Lwoff, France

Committee members nominated by staff evaluation committees

Mrs Eve DEVINOY, INRA CSS member

M. Daniel COURTEIX, CNU member

Observers

AERES scientific advisor

M. Jean-Antoine LEPESANT

University representatives

M. Jacques MERCIER, Université Montpellier 1

INRA representatives

M. Patrick ETIEVANT

M. Benoit MALPAUX



Report

1 • Introduction

- Date and conduct of the visit :

Visit took place in the INRA buildings on the day of January 26th, 2010. After a 1st meeting in closed hearing of the members of the committee, a debate took place with the University and INRA representatives in the presence of the unit Director. He then undertook the presentation of the unit. Afterwards, the three team leaders gave reviews of their past results and future plans. Both sessions were helped by booklets containing the slides. The works, milestones and projects of each of the teams were presented in front of all the unit members (lasted for each: 20 min, debate: 15/20 min). The organization of the visit provided time for separate discussions with the researchers, the technicians and the students out of the presence of the director. The last meeting of the members of the committee has allowed drawing up the report of the day. The visit was efficiently organized and carried out in relaxed but critical atmosphere.

- Geographical location and history of the unit and brief description of its field of study :

The unit is installed in the INRA buildings at Montpellier on a surface of 2307m². The unit was previously structured in 4 teams: Mitochondrial endocrinology and Nutrition (EMN); Functional genomics and myogenesis (GFM); Skeletal muscle remodeling and signaling (RMS); Adult stem cells (CSA). In the next contract, the number of teams will merely consist of 3 with the abolition of the team CSA associated with the incorporation of its ex-members in the team GMS and RMS. It is a logical evolution, which does not bring radical modifications in the research developed in the previous contract. The research is integrated into "Myology" domain and keeps as objective to understand the regulation of the muscle growth. The research orientation towards studies of remodeling of muscle, muscle growth and development and metabolism in association with nutrition justify changing the unit name. The proposed one is Muscular Dynamics and Metabolism that better summarizes the team activities.



- **Management Team and Staff :**

The management team is composed of a director (he will begin his 2nd mandate in 2011) and an assistant-director. On January 30th 2010, 41 statutory members except CDD and PhD students participate in the Unit life, the staff has moved in the following way:

	In the report	In the project
N1: Number of professors (see Form 2.1 of the unit's dossier)	3	4
N2: Number of EPST, (Public scientific and technological institution) or EPIC, (Public industrial and commercial institution) researchers (see Form 2.3 of the unit's dossier)	15	15
N3: Number of other professors and researchers (see Form 2.2 and 2.4 of the unit's dossier)	7	1
N4: Number of engineers, technicians and tenured administrative staff members (see Form 2.5 of the unit's dossier)	21	21
N5: Number of engineers, technicians and non-tenured administrative staff members (see Form 2.6 of the unit's dossier)	1	1
N6: Number of doctoral students (see Form 2.8 of the unit's report dossier and 2.7 of the unit's project dossier)	8	8
N7: Number of persons accredited to supervise research and similar	8	8

2 • Overall assessment of the unit

- **Overall opinion :**

In a general way, the committee appreciated the relevance and the interest of the research made in the Unit. It creates good tools and models for the development of its activity. Its scientific production shows, for period 2005-2009, 131publications with an average index of quotation of 5,04, the most representative spreading out from 8,29 to 2,59. In at least 55 publications, a unit member appears as a last author and in 19 as a first author.

The publications authenticate a monothematic research, almost exclusively concentrated on skeletal muscle, what establishes a perfect coherence. No patent registration was made during the last four years, but the Unit accommodates a Start-up DIALPHA.

The Unit is well inserted into the university of Montpellier, it participates in the pole Biologie-Santé and is a constituent team of the IFR 122. The list of its national and international collaborations is very satisfactory, and testifies of excellent scientific quality. Consequently, the Unit has national (AFM, ARC, 4 ANR) and international (WADA project) fundings.

In equipment, the Unit benefits from a favorable environment. It has for the management of its animals a conventional animal house integrated into the platform RAM. It hosts the platform of imaging MRI. It shares common services (secretary, laundry, workshop of mechanics).



- **Strengths and opportunities :**

The unit is composed of teams of good quality. The projects are coherent. Several activities have direct agronomic applications, an important goal in the INRA units.

The major strength of the unit is that its activities are entirely devoted to studying the skeletal muscle, with special attention to very interesting research fields: the mitochondrial endocrinology, the processes controlling the hypertrophy/atrophy of muscle fibers. The researches of the unit have good experimental tools and models at their disposal, and have significantly contributed to identification of regulatory mechanisms that control the skeletal muscular mass. Consequently, the unit activities have an impact in agronomy and medicine.

The unit benefits from the technical platforms available particularly for animal housing, imagery and histology. The technical staff in charge of each platform is installed in the unit.

- **Weaknesses and threats :**

- The unit has a too low international profile. A better external development of the unit should be encouraged in the coming years, with more post-docs assigned to the projects developed in the unit;

- Collaborative efforts between the three teams must be better planned;

- Scientific communication inside the unit should be improved: Weekly work-in-progress meetings where students and researchers present their results and ongoing projects must be organized. External speakers must be invited;

- Scientific communication outside the unit: The unit must assert its authority in the INRA regional scheme that is rather orientated to the vegetal field;

- Recruitment of both permanent and temporary scientific staff (researchers and post-doctoral fellows) should be more active in the Unit;

- Lack of patent applications does not do justice to scientific excellence of the studies carried out in the Unit.

- **Recommendations for the unit director :**

- The unit director must be more assertive as a leader of the Unit.

- He must think about the future direction of the unit and encourage a researcher to succeed him. Arrival of new researchers must be planned.

- The director must better use the statutory unit council comprising representatives of all personnel categories to take decisions.

- A strong recommendation is aimed at reinforcing collaborations between the teams. A probable evolution could be to have 2 teams rather than 3, that is not considered to be a priority, the important goals remaining to organize active contacts between the present teams.



- Data on work produced:

A1: Number of produisants (professors and researchers whose names appear in a minimum number of “publications” over a 4-year period) listed in N1 and N2 in the project column	19
A2: Number of produisants among the other staff listed in N3, N4 and N5 in the project column	23
A3: Proportion of produisants in the unit [A1/(N1+N2)]	1
A4: Number of theses for accreditation to supervise research defended	1
A5: Number of theses defended	7

3 • Specific comments on the research unit

- Assessment of work produced and scientific quality :

The unit has an authentic expertise in myology and has made major contributions to this domain.

The scientific production of the unit is good and is associated to several publications of a high quality.

- Assessment of the influence, appeal and integration of the research unit in its environment :

The unit collaborates with some renowned groups. During the past 4 years, 7 theses were defended and 7 PhD students are currently present in the unit. No post docs were and are currently present in the unit. The unit activity is funded by national sources including ANR, AFM and one international source. The unit members are implicated into very competitive topics but are in a less favorable position at the international level.

- Assessment of the strategy, governance and life of the unit :

The director maintains good relations with the three team leaders. The working conditions are satisfactory. The friendly atmosphere that resides in the unit reflects the quality of the management. No conflicts were reported. The team leaders and staff in charge of common facilities meet the director to discuss the general running of the unit. Each team leader is in charge of the running of her/his staff.

The unit teams work in a pleasant and functional space. A good atmosphere exists inside each of them. The quality of exchanges between the technicians, the students and researchers was well appreciated by the committee members. They have however the feeling that the director must be encouraged to impose himself on his role.

A better distribution of the PhD students between the teams is suggested.

The communication strategy merits to be improved. Several recurrent events are to be organized to favor the exchanges.

Suggestions:

- once a year a lab meeting (outside the unit) in which scientific objectives, recruitment policy, financial supports are discussed.



- once a month, a meeting including the director and the team leaders in which science, resource and recruitment management are debated.
- twice a month a work-in-progress meeting in which data, results, ongoing projects or techniques are presented.
- more national and international invited lectures.

These initiatives might highly contribute to the dynamics of the unit.

The unit members participate to training courses. Several members are responsible of the channels of teaching. The contribution of the researchers is appreciated notably at Master degree level.

- **Project assessment :**

From a theoretical stand point the projects proposed by the three teams are important and were satisfactorily presented and discussed.

However, at the end of its internal private deliberation the review committee needed to discuss with the director in order to clarify his attitude in relation to the three teams: their respective leaders (in terms of joint or autonomous decision) their respective supports (in terms of recruitment and grants), their scientific exchanges, their intra-unit collaborations, the imbalance of the teams (their number could be reduced to 2 from 3), the extent of their projects.

An effort to participate to a national, or better still, European consortium should be appreciated.

20% of the allowance from INRA and University and 10% from team grants are devoted to the unit functioning. 12% are specifically allocated to the animal housing and 3% to the IFR. The rest is divided between the researchers (1 to C; 0.5 to EC). Each team is respectively allowed 90% of the grants. ANR, AFM, ARC and WADA illustrate the major financial partners.

The project appears coherent and is based on a recognized expertise of the three teams.



4 • Specific appreciation team by team

Team 1: Mitochondrial endocrinology and nutrition (EMN)

Team leader: G. CABELLO

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	8	8
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file) (non permanent position)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	4
N7: Number of staff members with a HDR or a similar grade	5	5

- **Appreciation on the results :**

The team 1 has a longstanding experience of the effects of the thyroid hormones (T3) on muscle development and has a strong scientific leadership in this field. Its members made efforts to elucidate several aspects of hitherto not very well understood mechanisms of a direct mitochondrial pathway of T3 at cellular level. In this light, their work is pioneering and has substantially improved the understanding of this mechanism. Both during the last years and presently, they have expanded their range of action and followed several lines:

- the involvement of the nuclear receptors for T3 in the effects that this hormone exerts on myoblasts.
- the direct mitochondrial pathway of T3 in muscle development (*in vivo* and *in vitro* studies).
- the nutritional status and mitochondrial activity.

Of particular relevance, are the results they obtained in proliferating and differentiating myoblasts. Their data on interacting factors of p43 (the truncated form of the T3 nuclear receptor discovered in the mitochondria by the team members) probably involved in its internalization, are of outstanding importance. The direct T3 mitochondrial pathway demonstrated in myoblast differentiation is particularly interesting, it merits deep investigations. Recently they started to investigate on another issue high on the agenda of the current debate on the nutritional prevention of metabolic syndrome and obesity, in order to avoid or delay functional impairments, i.e. the role of mitochondria in such pathophysiological impairments. The role of antioxidants is also of particular relevance. Finally, a wide spectrum of up-to date and adequate to the research objectives methods have been developed.

The committee appreciated the good scientific production of the team with 77 publications. 33 publications are original articles among which in 30 a team member appears as last or first author. 44 publications are collaborative articles among which in 12 a team member appears as last or first author. Indeed, the team displays a sum of good papers (8 with an IF>7 and 4 in PlosOne). The researchers are used to attend to international scientific events of high level.



- **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 developed key collaborations with research groups. As far as international links are concerned, it has contact with 5 countries and belongs to 2 European networks. The researchers and especially the team leader have been invited to give 7 lectures during the last 4 years. They participated in 3 ANR (and coordinated one). The members are teaching in Master 2 level. The team leader is an Associate professor at ENSAM School.

- **Appreciation on the project :**

The project is of a great scientific relevance and noteworthy. It is scheduled for long term. Nevertheless, with regards to the nutrition target, it is not completely clear to the committee what the scientific priorities of the team will be. Therefore, the team is encouraged to focus on defined scientific objectives.

- **Conclusion :**

Overall excellent quality of the science produced in this team. As a whole, the activity of the team is of a great scientific relevance and noteworthy.

- **Strengths:**

- The team conducts research that is of basic scientific relevance.
- The team has a good publication record.

- **Weaknesses and threats:**

- Lack of communication with the other teams.
- Team1 is a member of the MitEuro network and is a present member of the MitoFood COST. More emphasis should be given to research projects with the industry to improve the budget.

- **Recommendations:**

- Collaborative efforts and/or scientific exchanges with the unit teams must be planned.
- The team should try to focus on a more limited number of projects.



Team 2: Functional genomics and myogenesis (GFM)

Team leader: S. LEIBOVITCH

	In the report	In the project
N1: Number of professors (see Form 2.1 of the unit's dossier)	0	0
N2: Number of EPST, Établissement public à caractère scientifique et technologique (Public scientific and technological institution) or EPIC, Établissement public à caractère industriel et commercial (Public industrial and commercial institution) researchers (see Form 2.3 of the unit's dossier)	3	4
N3: Number of other professors and researchers (see Form 2.2 and 2.4 of the unit's dossier)	1	0
N4: Number of engineers, technicians and tenured administrative staff members (see Form 2.5 of the unit's dossier)	1	1
N5: Number of engineers, technicians and non-tenured administrative staff members (see Form 2.6 of the unit's dossier)	0	0
N6: Number of doctoral students (see Form 2.8 of the report unit's dossier and 2.7 of the project unit's dossier)	1	0
N7: Number of persons accredited to supervise research and similar	2	2

- Appreciation on the results :**

The team 2 has joined the unit in 2004, and has since developed strong interest in molecular mechanisms of atrophy/hypertrophy of skeletal muscle. The team has recently made a number of major contributions to the field, notably by identifying two key targets of MAFbx/Atrogin-1 in atrophied muscle: the transcription factor MyoD and the traduction factor eIF3f. It has demonstrated the pivotal role played by eIF3F in anabolic and catabolic pathways regulating the skeletal muscle mass (1 EMBO J IF: 8,9).

The team has a good publication record over the last 4 years, with 12 papers that were accepted in high impact journals (IF between 8,9 and 5,6). In 6 publications all the authors are team members. In the other four ones, the first author is a team member.

The team leader has secured external funding that will allow the team members to continue their work and even to increase their activity.

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

The team leader had attracted and trained outstanding PhD students who left the laboratory with two-three excellent publications, and finished their PhDs after three years work. These young scientists have gone on with their careers in research as post-docs in very good laboratories. The current members of the team are enthusiastic about the projects, the working atmosphere and environment. They have the opportunity to present their research within the unit, national and occasionally international conferences.

- Appreciation on the project :**

External development of the team should be encouraged in the coming years, with more PhD students and post-docs assigned to the projects developed in the team. Indeed, its current size does not do justice to the quality



and the potential of past, present and future research projects presented by the team leader. National and international collaborations could help to attract post-doctoral fellows and PhD students and ensure the rapid progress of the research projects proposed for the next four years.

- Conclusion :

- Strengths:

- The scientific production is at a good level.
 - The originality and the impact of the work performed in the field which is very competitive; the projects are ambitious.
 - The team has a secure financial situation due to numerous contracts and grants.

- Weakness:

- The major weakness is the small size of the team. Its projects require a suitable mass to be developed at the level needed to reach international visibility. The team is encouraged to recruit.

- Recommendations:

- The team should further develop international collaborations and participation in international scientific events and increase the collaborations with the other teams of the laboratory.

Team 3: Skeletal muscle remodeling and signaling

Team leader : A. BONNIEU

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file) (non permanent position)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	3
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results :

The team 3 aims at identifying the networks of genes involved in the regulation of adult skeletal muscle growth during hypertrophy and repair. It relies upon two different strategies. The first one is to study the effects of drugs on myostatin transduction pathways (Notch and calcineurin/NFAT) during muscle differentiation. The second one is to describe the effects of hypoxia. The team demonstrates that the application of a potent inhibitor of Notch (DAPT) downregulates myostatin and induces myotube hypertrophy. It also demonstrates that the atrophy of hypoxic muscles is attenuated by myostatin downregulation. These findings could have interesting applications in muscle health.



The team results have been published in journals with reasonable impact factors (ranging from 1.0 to 5.5 during last year). The team has little published in 2006/2007 but better published in 2008/2009. Several publications are mentioned in preparation in 2010. It has 41 papers, among which 30 are focused on the research field : in 3 papers the team member is the first author and in 11, the last author. The results are presented by the team leader during international meetings or by students during the international meetings taking place in France. The team members collaborate with INRA researchers as shown by some common communications at international conferences.

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

The team is tightly connected to the university. It has been training several students for the last four years. Among the three PhD students, two spent an unusually long time before defending their PhD. They revealed that this was not a major problem for them and the unit.

The team has obtained funding from INRA, ANR as well as the World Anti doping Agency (WADA). The funded projects are in close relation with the main project.

The team has developed several key collaborations at national level with several INRA, INSERM and University teams as well as at international level with 3 countries (United States, Italy and Sweden). It is now planning a new collaboration with a Polish scientist.

The studies related to drug treatment could potentially lead to interesting medical applications.

The team leader has an obvious sense of management. Half of the team is composed of scientists that belongs to the university and therefore deeply involved in teaching.

- **Appreciation on the project :**

The project is in line with the previous one and targets some candidate pathways involved in muscle hypertrophy. It almost exclusively relies on its expertise and partly based on the areas of expertise of the other unit teams. The project has advantage to use in vitro and in vivo models and to extent the in vivo studies to species and breeds selected for their agronomical interest. The approach will target candidate pathways such as PI(3)K/Akt and its downstream targets (mTOR, S6K and the factor eIF3f) in two genetic models: the KO myostatin mouse and the hypermuscular cattle. The phenotypes of the satellite cells isolated from normal and hypertrophic cattle will be compared in in vitro culture. Their global RNA profiles might be also studied. The impact of exercise, drug nutrition and oxidative stress on muscle hypertrophy will be explored. This program can offer new insights into the muscle growth.

- **Conclusion :**

The committee has a very good opinion of the team.

- **Strengths:**

The team has a correct publication record, is able to train PhD students and to rise funding to support its project. The team leader is open to collaborate with the other 2 teams of the unit what could create a new dynamics for the research unit. The committee must underline the tight interactions between researchers and teachers.

- **Weaknesses and threats:**

The team should try to use bovine and mouse original models to switch from a candidate pathway point of view to a more global (genome-wide) analysis of the skeletal remodeling and signaling.



— Recommendations:

The project is considered good but it needs to incorporate higher risks of failure to adhere to international competitive research.

The publication level could be in higher ranking journals.

Collaborations with the other teams (notably team 2) need to be reinforced.

The team must get on quickly to achieve new recruitments.



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

Nom de l'équipe : *MITOCHONDRIAL ENDOCRINOLOGY AND NUTRITION (EMN)*

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
<i>A</i>	<i>A</i>	<i>A</i>	<i>A</i>	<i>B</i>

Nom de l'équipe : *FUNCTIONAL GENOMICS AND MYOGENESIS (GFM)*

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
<i>A</i>	<i>A</i>	<i>B</i>	<i>A</i>	<i>B</i>

Nom de l'équipe : *SKELETAL MUSCLE REMODELING AND SIGNALING*

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
<i>B</i>	<i>B</i>	<i>A</i>	<i>A</i>	<i>B</i>



Montpellier, le 12 mars 2010

Le Président

Ph A/ NG
Départ n° 2010 - 86

Monsieur Pierre GLORIEUX
Directeur de la section des unités
de recherche
Agence d'Evaluation de la Recherche et de
l'Enseignement Supérieur (AERES)
20, rue Vivienne
75002 PARIS

Monsieur le Directeur,

Je m'associe aux remerciements formulés par l'ensemble de la direction de l'unité de recherche «**UMR866 : Différenciation cellulaire et croissance**» pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise.

Vous trouverez ci-joint les réponses du Directeur de l'unité auxquelles le Vice Président du Conseil Scientifique et moi-même n'avons aucune remarque particulière à rajouter.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma considération distinguée.



A handwritten signature in blue ink, appearing to read "Philippe AUGE".

Philippe AUGE



CENTRE DE
MONTPELLIER

UMR 866 DIFFERENCIATION
CELLULAIRE ET CROISSANCE
(INRA, Université Montpellier I & II)

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REPUBLIQUE FRANCAISE
MINISTERE DE L'AGRICULTURE

Ministère chargé de la Recherche
Et de l'enseignement supérieur

Montpellier le 11 mars 2010

Objet : Réponse à l'AERES

Dear Colleagues,

On behalf of my colleagues I would like to thank the AERES committee for their effort and their review. We are especially pleased that the committee found our teams and our project to be of good scientific quality.

Their suggestions are in line with the auto-evaluation we had made and the report pointed out very clearly the major items on which we have to focus our efforts.

In agreement with the comments of the committee we will enhance our efforts in order to open our unit to external scientists, as we have done during the past 6 years, greeting 6 post-docs and integrating a team from INSERM, three researchers from AlimH division of INRA, four scientists with teaching duties from University Montpellier 1, thus demonstrating significant attractivity. In addition three young scientists where recruited during this period. As suggested we will enhance thoroughly our internal communication in order to strengthen the ties between teams, and for this purpose, we will implement all the recommended items of which some were already in use.

The unit is involved in several important international networks (2 European and one international WADA networks as well as involvement in EGIDE, ERASMUS, AVEROES and POLONIUM exchanges programs). We agree that our project should focus on an even stronger integration at the international level and increase our external communication.

We hope the recommendations made to reinforce two of the teams with permanent staff researchers will be followed by INRA and University.

The full staff (including students and technicians) appreciated the recognition by the committee of the good atmosphere in favor of dedicated work they all contribute to build.

I personally appreciate the encouragements made by the committee to prepare the evolution of the unit in the years to come.

Arnaud CHATONNET Director UMR-DCC

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