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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
Unité de Génétique Moléculaire Animale
From the
Université de Limoges
INRA

December 2010



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

Section des Unités de recherche

AERES report on the research unit
Unité de Génétique Moléculaire Animale
From the
Université de Limoges
INRA

Le Président de l'AERES

Didier Houssin

Section des unités
de recherche

Le Directeur

Pierre Glorieux

December 2010



Research Unit

Name of the research unit : Unité de Génétique Moléculaire Animale

Requested label : UMR-A INRA

N° in the case of renewal : UMR1061 INRA

Name of the director : Abderrahman MAFTAH

Members of the review committee

Committee chairman

M. Edmond CRIBIU, INRA, Jouy-en -Josas, France

Other committee members

M. Serge LEIBOVITCH, University of Montpellier, France

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

M. Laurent TIRET, University of Paris-Est, Maisons-Alfort, France

Observers

AERES scientific advisor

M. Pierre LEGRAIN

University, School and Research Organization representatives

M. Serge VERDEYNE, Université de Limoges

M. Denis MILAN, INRA

M. Michel BECKERT, INRA



Report

1 • Introduction

- Date and execution of the visit

The visit took place on December 16th, 2010. The morning was devoted to oral communications. A general presentation of the Unit by the head of the lab was followed by scientific presentations by the different project leaders in the three fields: i) Glycosylation and myogenesis, ii) muscular development and animal models and iii) functional analysis of genes involved in valuable traits in bovines. The discussions with the leaders and the scientific staff enabled to evaluate the subjects in depth in an interactive manner. In the beginning of the afternoon, members of the committee received, separately, 3 groups of employees: researchers, postdocs and Ph.D students, the technical staff. The end of the afternoon was dedicated to a discussion between the different partners (President of the INRA center, The Head of INRA Animal Genetic department, the president of the University and the head of the IFR). At last, we met the head of the unit to clarify few points about the scientific production of the Unit.

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

The Animal Molecular Genetics Unit belongs to the University of Limoges and the Animal Genetics department of INRA. The Unit is located at the Sciences and Technology Faculty (surface of 1,321m²). The partnership between the University and INRA, launched ten years ago, led to the development of research activities devoted to the knowledge of the bovine genome. The objectives were to better understand how genetic variability regulates complex phenotypes in this species. During the 4 past years, the research unit was organized into two main research topics: "Glycogenome" (subdivided into functional and evolutionary study of glycosyltransferase genes and contribution of glycogenome in muscle cell differentiation and in bovine diseases) and "Skeletal muscle genomics" (subdivided into the study of muscle development, the analysis of the protease/anti-protease system and the identification of the genetic determinants of bovine muscle characteristics and coat color).

- Management team

The unit has a director (A. Maftah), and a deputy director (H. Levéziel) and two group leaders: A. Maftah for the glycogenome activity (responsibility of the glycosyltransferase genes in the physiological and pathological process) and V. Blanquet for the genomics and skeletal muscle (muscular development, meat quality and epigenic analysis of genes involved in bovin coat color). The management team is helped by a lab council which meets 4 times a year.



- Staff members (on the basis of the application file submitted to the AERES)

In December 2010, the Unit was composed of 35 persons including 17 researchers, 11 PhD students, 4 ETP engineers, technicians and administrative staff.

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	14	15
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2,5	4
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	0,5
N6: Number of Ph.D. students (Form 2.7 of the application file)	7	11
N7: Number of staff members with a HDR or a similar grade		7

2 • Overall appreciation on the research unit

- Summary

The main research objectives of the Animal Molecular Genetics Unit consist in the better understanding of cattle genomics and the study of genetic determinants of quantitative traits in bovine species in synergy with the INRA and University projects. The Unit's implication has been determining in the creation of the Federative Institute for Research (IFR n°145), which constitutes an efficient support to the research projects developed on the campus of Limoges.

During the last four years, the Unit produced 80 publications, among which 35 were directly related its scientific field, with an average impact factor of 3.86, and 1 patent. Twenty-one articles were published as first or last author with impact factors ranging from 1,5 to 6,2. The most significant publications resulting from the Unit's projects are a J. Biol. Chem of 2010 (IF 6,2), a Pigment Cell & Melanoma Research of 2006 (IF 4,6 - 12 times cited) and a BMC Genomics of 2006 (IF 3,8 - 4 times cited).

For the next period (2012-2017), the UMR1061 will focus on muscle tissue studies by combining academic and finalized research projects. This decision is favourably supported by the committee. Projects will concern identification and functional analysis of genes that regulate the early stages of muscle differentiation and development, as well as genes that control beef quality. The Unit will contribute to genome screening approaches based on high-throughput genotyping, transcriptomic and proteomic analyses with the dual aims to identify i) genome regions or genes which could be targeted for functional genomics and ii) genetic markers for animal selection. These scientific activities will be developed in individualized groups following three research axes: i) Glycosylation and myogenesis, ii) Muscle development and model animals and iii) Functional analysis of genes involved in some cattle phenotypes.

- Strengths and opportunities

The strengths of the unit may be summed up as follows:

- the originality and the impact of the work performed in the field, and the ambitious projects; the strength and complementarity of the three groups, that show a good scientific coherence;



- the expertise in glycogenomics which brings knowledge and opportunities for application to the animals studied by INRA;
- the large range of approaches used (molecular genetics, biochemistry, cell biology and physiology);
- the collaborations with Jouy-en-Josas INRA teams (GA and SA departments) and Clermont-Theix (PHASE and CEPIA units);
- the good quality of the management and the Unit organization;
- the upmost administrative and financial support expressed to the Unit by the Université de Limoges and INRA, both providing an overall satisfactory level of funding;
- the national attractiveness of this young Unit that helped recruit a high number of dynamic researchers and training students; students and post docs are enthusiastic about their projects and the working atmosphere of the lab seems very positive.

- **Weaknesses and threats:**

- the Unit does not have the international visibility that it deserves, in particular in terms of publications and participation in international networks. Also, the attractiveness of the Unit for foreigner scientists, especially international invited visitors, PhD and postdocs, is currently limited;
- isolation of the campus, which does not favour interactions and the organization of seminars;
- the committee feels that there is a clear need for technicians to assist a majority of researchers in the Staff who have important teaching duties. The committee, in particular, noted an obvious weakness in technical help provided by INRA (0 technician).

- **Recommendations**

- encourage researchers to publish in journals with higher impact factors and citation indexes;
- increase the visibility of the Unit, especially at the international level. Researchers should be encouraged to participate in more networks and students should be encouraged to present their work at least once or twice during their PhD training in national or international muscle congresses;
- focus on the specificity of the Unit to avoid overdiversification of the research projects;
- inside the Unit, improve the number of transversal projects; this should optimize the multidisciplinary skills present in the Unit.

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	15
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	2
A3: Ratio of members who are active in research among staff members $[(A1 + A2)/(N1 + N2)]$	1
A4: Number of HDR granted during the past 4 years	1
A5: Number of PhD granted during the past 4 years	9



3 • Comments about results and appreciation of projects

Inside the Unit, research projects have been recently re-organized following 3 axes, each associating 4 to 7 researchers. The two projects "Genetics of coat color" and "Pathogenic glycosylation of the prion protein" will be withdrawn. All researchers seemed happy with the new organization. Since the three axes are in the continuity of some results obtained, comments about results and appreciation of projects by the visiting Committee have been merged into a single section.

The first axis will focus on glycosylation and myogenesis, the second one will focus on muscular development and animal models and the third one will focus on the functional analysis of genes involved in valuable traits in bovines.

Axe 1: Glycosylation and myogenesis

This research is original, solid, and future directions are clear. This group animated by 7 researchers is engaged in the study of the glycogenome in mouse and satellite cells of cattle during differentiation. By screening approaches (glyco-genomics and glycoproteins) during the differentiation of C2C12 cell lines or primary mouse myoblasts (from GDF8-/- mice), this group has shown a differential regulation of genes involved in glycosylation of proteins. Most of these genes code for enzymes involved in the synthesis of glycosphingolipides (about 37 genes). Presently, 10 of these genes are under investigation.

The group is also focused on the establishment of the bovine glycogenome, exploring genes involved in the construction of O-glucosyl and O-fucosyl glycans during myogenesis. Polymorphism in the bovine genes of glycosylation is also investigated. One of the targets of this glycosylation is the Notch receptor. Notch signalling pathway has been shown to play several key roles during myogenesis in the embryo and during adult muscle regeneration. In particular, the Notch pathway activation is essential for the maintenance of the proliferation status of myoblasts and the quiescence status of satellite cells. The studies of main interest concern two families of genes (Pofut1 and Poglut), and a model proposed by this group is that their loss-of-function would inhibit Notch activity and thus promote muscular differentiation. Loss and gain-of-functions studies are planned for these genes, tools have been obtained (stable cell lines overexpressing Pofut1) or in the process of being characterized (stable cell lines for Pofut1 RNAi) and Notch activity and muscle growth will be investigated in these models.

The new direction of the projects is original, solid, well designed, relevant and realisable on a short, medium, and long-term. This group has acquired through the years the know-how, so the feasibility of the proposed projects on the medium and long-term is high.

It would be more beneficial to the lab to produce fewer small descriptive articles but more articles showing how post-translational modifications are accompanied by new functions. These approaches may be done in collaboration with other labs (from other INRA departments or foreign laboratories.)

Axe 2: Muscular development and animal models

This is an original research that is of a general scientific interest.

To identify genes involved in adult muscle growth, the authors have performed an ENU screen, and backcrossed their mice on a GDF8-/+ background. This ambitious project led to the identification of 49 variants and 7 lines showing a musculoskeletal phenotype. This project has been slowed down because of the fire of their animal facilities. Fortunately, four lines have been saved that will be further characterized. The group also investigated the role of Gasp-1 and Gasp-2 proteins, encoded respectively by the Wfikkn2 and Wfikkn1 genes, which are known inhibitors of myostatin. Tools to analyze loss and gain-of-function of these two genes in mouse models have been obtained or are in the process of being obtained. In particular, transgenic mice overexpressing Gasp-1 in muscles allowed to confirm a role of Wfikkn2 in muscle growth; and overexpression of Gasp-1 in Gdf8-deficient L6E9 cells allowed to demonstrate that Wfikkn2 also plays a role in proliferation and differentiation of muscle cells independently of Gdf8, which is a novel and interesting finding. Last, this group has an ambitious project aiming at revealing the epigenetic mechanisms controlling muscle growth. With a similar approach to the one used and recently published for the Texel sheep, the group will try to identify miRNAs involved in the regulation of gene transcription, more specifically GDF8. This project might lead in the long term to innovative applications but is also of outstanding scientific relevance, and thus could certainly benefit from a close relationship with national and international groups developing systems biology approaches and making new hypotheses on epigenetics inheritance.



The group acquired a real competence in the study of growth in skeletal muscles, and projects in this direction are of major interests. Particularly, the group has recently made major findings in the field of myostatin signalisation modulation in mouse models.

The Committee urges this group to fully characterize the *Wfikn2*-KO at the cDNA sequence level before any additional functional experiment are performed; also, the Committee strongly recommends that future knock-out/knock-in projects include conditional targeting strategies so that gene KO can be finely and timely controlled (see for example the International KOMP project).

Axe 3: Functional analysis of genes involved in valuable traits in bovines

This research is scientifically well-conducted and of high interest for the beef industry. Directions are clearly presented, original and well-positioned at the interface between academic and industrial expectations. Meat quality is a complex trait determined by environmental effects and genetics and this group, animated by six researchers, has a known competence in digging the gap between genomic polymorphisms and the quality of meat in ruminants. The long-term involvement of the leader of the group in beef cattle research programs has allowed efficient collaborations with French and international laboratories, among which a well-recognized leader in the field (Belgium). In the last 4 years, this group produced 17 articles (7 as first or last authors) and 4 PhD students defended their University thesis.

This research is dependent upon a relevant time- and money-consuming precise phenotyping of animals. This step has been successfully achieved and a database with results from 3,450 animals has been fully implemented in 2008, showing heritability of some traits. With the noticeable exception of few established correlations between muscle growth or meat quality and mutations (*GDF8*) or haplotype association (*CAST*, *CAPN1*), the candidate genes' approach has been disappointing. QTL detection in 3 French breeds will be used in the future by using the recently developed high density SNPs array. This should help to identify major genetic determinants of meat quality variation.

Another part of the project relies on comparative genomics and aims at determining some regulatory SNPs associated with traits of interest. The international ANR/NKTH programme was launched in June 2010 and ~3,000 rSNPs have been identified. They will be analyzed at the functional level and animals with confirmed phenotypes will be genotyped for those that will have been finally selected. This is a very original project which should give a high number of informative clues. It is expected that translation of these results to the beef industry, will be facilitated as functional consequences of rSNPs is already known.

Finally, the group has identified a unique cluster of 8 genes encoding proteins with anti-protease activities (*SERPINA3*) and involved in meat maturation. Biochemical characterization of members of the family has been initiated and will be continued. Association between genomic polymorphism in the cluster or protein levels and meat tenderness is also investigated and is presently under progress.

• General conclusion

It appears that the ratio between fundamental and mission-oriented research is well balanced. During the evaluated period, the team has performed very well and has good publication records which however, could be improved in publishing in higher IF journals. The members of the committee were impressed by the quality of the presentations and the project for the coming years which appeared highly pertinent and coherent. Finally, the surroundings and the mood of this unit are excellent and all the staff agrees with the objectives and the strategies of the manager.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
UNITÉ DE GÉNÉTIQUE MOLÉCULAIRE ANIMALE	A	B	A	A	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique



Statistiques de notes globales par domaines scientifiques (État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2_LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	42	5	20	26	36	59	5	17	29	239
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

* les résultats SVE2 ne sont pas définitifs au 06/05/2011.

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- SVE1 Biologie, santé
 - SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie
 - SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes
 - SVE1_LS3 Biologie cellulaire, Biologie du développement animal
 - SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie
 - SVE1_LS5 Neurosciences
 - SVE1_LS6 Immunologie, Infectiologie
 - SVE1_LS7 Recherche clinique, Santé publique
- SVE2 Ecologie, environnement
 - SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement
 - SVE2_LS9 Sciences et technologies du vivant, Biotechnologie
 - SVE2_LS3 Biologie cellulaire, Biologie du développement végétal

Limoges, le 5 Avril 2011

Le Président de l'Université

A

Monsieur le Président de l'AERES

*Unité de Génétique
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Objet : Réponse au Rapport du comité de visite,

**S2UR120001483 – Unité de Génétique Moléculaire Animale – 0870669E
(UMR1061, Université de Limoges-INRA)**

Monsieur le Président,

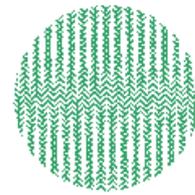
Les membres de l'unité de Génétique Moléculaire Animale, l'INRA et l'Université, remercient le Comité de Visite pour le travail accompli dans l'analyse du bilan et des projets de l'UMR1061. Le rapport d'évaluation porte des éléments importants que l'unité ne manquera pas de prendre en compte pour continuer dans ses réflexions locales.

Le rapport d'évaluation a suscité au sein de l'Unité quelques demandes de corrections et commentaires. Ces éléments sont joints à ce courrier.

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


Jacques FONTANILLE





Limoges, le 5 Avril 2011

M. Le Président de l'AERES

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Objet : Commentaires sur le Rapport du comité de visite,

**Unité de Génétique Moléculaire Animale (UMR1061, Université de
Limoges-INRA)**

M. Le Président

Nous vous remercions pour tout le travail fait par le comité de visite ainsi que pour les recommandations formulées. Nous vous prions de trouver ci-dessous quelques commentaires et demandes corrections sur le rapport du comité de Visite de notre Unité.

I- Observations sur le rapport d'évaluation

Le rapport relate deux faiblesses qui méritent des commentaires :

- 1- A propos du rayonnement à l'International, L'unité a dans son bilan plusieurs réalisations :
 - Durant les 5 dernières années, l'Unité a fortement contribué dans 2 projets européens : Le Projet GeMQual (terminé en 2006) et le Projet TRACE (terminé en décembre 2009).
 - De plus depuis 2009, nous coordonnons un projet ANR cofinancé par la France et la Hongrie.
 - 2 thèses en co-tutelle avec l'Italie dans la période de référence
 - Coopérations scientifiques avec l'Allemagne, l'Italie et les USA.
 - Accueil de 6 Chercheurs invités et 3 stagiaires (Italie, Hongrie, Irlande, Algérie, Maroc).
 - Un projet de coopération Recherche et Formation avec le Liban vient d'être signé.

- 2- A propos des niveaux des publications (Impact Factors)

L'impact Factor moyen de toutes les publications de l'Unité est de 3.86 avec une participation à un travail publié dans Nature Genetics (IF : 26). L'IF moyen de l'Unité est à considérer en prenant en prenant en compte les éléments suivants :

- Les missions de l'Unité (UMR INRA-Université de Limoges) sont fondamentales et finalisées. Les travaux conduits en interaction avec les professionnels de la Génétique Animale ne se prêtent pas toujours à des valorisations dans des journaux de forts impacts.

- L'IF moyen des publications du département de Génétique Animale de l'INRA est de 2.0. Notre IF est par conséquent très honorable par rapport à l'IF moyen d'un département de plusieurs dizaines de chercheurs.

Le rapport indique également deux recommandations :

- 1- A propos des thématiques de l'Unité, le comité a bien apprécié le recentrage thématique sur le muscle squelettique combinant des projets de recherche fondamentaux et finalisés (3^o paragraphe du sommaire, page 4 et, 1^{er} paragraphe de la page 6). Nous avons le souci de maintenir cette direction en exploitant au mieux nos spécificités et compétences.
- 2- A propos des projets transversaux aux 3 groupes thématiques de l'Unité, nous avons déjà engagé plusieurs actions transversales. Des projets transversaux assez conséquents sont décrits dans le dossier de l'Unité et des thèses (2 actuellement) sont positionnées à l'interface entre des groupes.

II- Corrections mineures

- 1- Affiliations des membres du comité : S. Leibovitch (INSERM), P. Maire (INSERM)
- 2- page 3, paragraphe 2, début ligne 5 : "phenotypes in this species" au lieu de "... breed » ; dernière ligne « color » au lieu de « colour ».
- 3- page 4, paragraphe 2 du Sommaire. Nous proposons la formulation suivante: "During the last four years, the Unit produced 80 publications, 35 were directly related its scientific field, with ...".
- 4- page 7, Axe 3, paragraphe 3, ligne 2 : "The international ANR/NKTH programme

Nous vous prions d'agréer, Monsieur le Président, l'expression de nos sincères salutations.

M. Abderrahman MAFTAH
Directeur de l'UMR1061