



**European Cooperation  
in Science and Technology  
- COST -**

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**Secretariat**

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**Brussels, 9 June 2011**

**COST 4139/11**

**MEMORANDUM OF UNDERSTANDING**

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Subject : Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action TD1101: A collaborative European Network on Rabbit Genome Biology (RGB-Net)

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Delegations will find attached the Memorandum of Understanding for COST Action TD1101 as approved by the COST Committee of Senior Officials (CSO) at its 182nd meeting on 17 May 2011.

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**MEMORANDUM OF UNDERSTANDING**  
**For the implementation of a European Concerted Research Action designated as**  
**COST Action TD1101**  
**A COLLABORATIVE EUROPEAN NETWORK ON RABBIT GENOME BIOLOGY**  
**(RGB-NET)**

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4154/11 Rules and Procedures for Implementing COST Actions, or in any new document amending or replacing it, the contents of which the Parties are fully aware of.
2. The main objective of the Action is to establish a multidisciplinary and cooperating network of experts in different research areas and applied fields interested in developing new scientific and commercial opportunities, resources and tools from the European rabbit genome and to strengthen and consolidate Europe as a leader in the scientific and economic exploitation of the European rabbit and related species.
3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 72 million in 2011 prices.
4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.
5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter IV of the document referred to in Point 1 above.

## **A. ABSTRACT AND KEYWORDS**

The European rabbit (*Oryctolagus cuniculus*) is a key species in biology. Basic discoveries have been made investigating this mammal whose genome has been recently sequenced. The rabbit is a livestock, an animal model, a wild resource, a pest and a fancy animal and comprises a large number of breeding stocks/lines. This COST action will bring together experts in all rabbit research areas and in other complementary research fields (breeders, geneticists, bioinformaticians, physiologists, evolutionists, embryologists, immunologists, industry experts, etc.) in order to facilitate the transition of rabbit genomic information from experimental data into usable benefits and applications by means of networking expertise. Four Working Groups will be focused on (i) the refinement of the European rabbit genome resource and the development of genome-based platforms, (ii) genetic aspects in meat, fur and pet rabbits and biodiversity resources, (iii) the rabbit as a model in basic biology and human diseases and as a tool for biotechnology applications and (iv) genetic and comparative genomic aspects for the study, exploitation and management of wild lagomorphs. The outcome is a coordination of rabbit research activities and a transfer of knowledge which will produce a strong European added value across a broad spectrum of biology research fields.

**Keywords:** European rabbit, lagomorphs, genome biology, translational research, networking expertise

## **B. BACKGROUND**

### **B.1 General background**

The order *Lagomorpha* includes several species of relevant interest in different fields of applied biology. The most important species is the European rabbit (*Oryctolagus cuniculus*) that is considered not only as livestock (for meat and fur production), but also as an animal model used to address many biological questions, a pest or a wild resource species in several regions, and a fancy animal with a broad spectrum of different phenotypes. The rabbit industry in Europe produces about 0.45 million tons of rabbit meat per year and is second only to Chinese production (of about 0.66 million tons per year). World rabbit meat production reaches about 1.5 million tons and it is, on average, increasing by 4.5% each year.

The value of rabbit meat production per year in Europe is ~1.6 billion euro. The European rabbit breeding industry is a worldwide leader in actively producing and exporting genetically improved lines for the efficient production of meat rabbits that generate, on the whole, an annual income of ~35 million euro. Despite the progress made by traditional selection approaches toward development of efficient rabbit lines for production and reproductive traits, other traits with low heritability or that are difficult to measure, such as disease resistance and feed efficiency, have not been improved. Considering the way in which meat rabbits are farmed, these latter traits can make the difference between profitable and non-profitable enterprises. In striking contrast to current practice for all other major livestock species, the use of genomic information to improve selection efficiency in rabbit meat production has not yet been initiated.

European rabbit fancy breeders maintain a large collection of breeds and lines (differing in size, morphological traits, coat colour, etc.) that constitute very valuable natural genetic resources. The value of the European fancy rabbit sector is estimated to be ~60-80 million euro/year.

Domestication of the rabbit has been a progressive and recent event (from 1200 to 400 years ago) as compared to other livestock making this leporid a very interesting model to evaluate domestication processes comparing domesticated stocks and wild populations that are present together in the domestication center (Spain-France) as well as in most other European countries. On the other hand, the rabbit serves as a keystone species and an ecosystem engineer in its native range. The European rabbit has been introduced in South America, Australia and many islands in which it is considered a pest. The use of viruses (e.g. myxoma virus) has been tested experimentally to control these wild populations. Myxomatosis is caused by a poxvirus that evolved in *Sylvilagus* lagomorphs, making important the links between the European rabbit and other wild leporids. These related species that are represented in Europe by several species of hares (genus *Lepus*) are essential components of wild fauna (and game species) for which monitoring and management should be improved.

The rabbit is one of the most common animal models in biomedicine. It is used in all research areas, ranging from basic research to clinical disciplines. Although the rabbit appears rodent-like in respect to some morphologic features, DNA and protein sequence data demonstrate that the rabbit is more closely related to primates than to rodents. Its size and its specific anatomy and biology make the rabbit a more appropriate model than the rodents in several fields. In Europe, ~0.4 million rabbits are used every year as laboratory animals.

Pharmaceutical companies have developed therapeutic rabbit antibodies and transgenic rabbits for production of humanized proteins used as therapeutic agents for several disease treatments. Polyclonal and monoclonal antibodies produced from rabbits are widely marketed commercially. Its world-wide annual market is estimated to be of 3 billion euro, with an annual growth rate of ~10%.

The European rabbit genome has been recently sequenced at ~7X coverage (OryCun2 version). This resource now opens new perspectives in all fields mentioned above, eliminating disadvantages and limits of the rabbit compared to other species and creating additional opportunities in several rabbit applied biology areas and related fields paving the way to an “omic” vision of rabbit biology. However, although this information could represent the central tool to foster all applied biology fields in which rabbit is involved, improvements in the assembly and annotation are still needed, and related genomic tools have not been developed yet. Moreover, the paucity of coordinated research funding on one hand and the dispersed but broad range of expertise and applications on the other hand, both focused and based on the European rabbit, are serious limitations to the scientific advancement of genome biology studies around this species and related lagomorphs.

The main aim of this COST Action (RGB-Net) will be to create an interdisciplinary community within Europe which will bring together scientists and stakeholders whose research and applied activities are focused on, or can take advantage of the European rabbit genome, with full exploitation at the different levels described above. This interdisciplinary network will provide opportunities for more coordinated activities and exchange of knowledge among different and complementary research areas. It will make use of genomics and post-genomics information to generate societal and economic benefits and improve the competitiveness of breeding industries, pharmaceutical companies and related private and/or public organizations. It will strengthen the European role in rabbit breeding and production, providing an effective management of wild leporid resources. The development of rabbit-associated biotechnologies and applications in many fields of basic research will constitute other prime benefits of this COST Action. RGB-Net is essential to overcome the limitations resulting from the fragmentation of a broad range of expertise on different rabbit biology fields. This COST Action will lead to highly productive networking of European researchers and laboratories to create a critical mass able to answer new questions in this area, an area exploiting the breaking-through technology of genome analysis.

## B.2 Current state of knowledge

The European Union has funded activities on the European rabbit directly or indirectly related to the focus of this COST Action in just a few programmes: 1) RESGEN (Genres CT95-060, 1996-2000; supported under Regulation EC 1467/94 on the conservation, characterization, collection and utilization of genetic resources in agriculture) that aimed at evaluating rabbit genetic resources for conservation and utilization of biodiversity in this livestock species

(<http://ec.europa.eu/agriculture/res/gen/60a.htm>); 2) FA Action 848 (Multi-facetted Research in Rabbits: a Model to Develop a Healthy and Safe Production in Respect with Animal Welfare (End date: June 2005; [http://www.cost.eu/domains\\_actions/fa/Actions/Multi-facetted\\_Research\\_in\\_Rabbits](http://www.cost.eu/domains_actions/fa/Actions/Multi-facetted_Research_in_Rabbits)), mainly focused on husbandry aspects of rabbit meat production.

A few other projects have been funded at national, bi-national and tri-national levels focusing on other aspects of basic or applied European rabbit industry/biotechnology and related leporid biology (i.e., characterization of rabbit stem cells, development and characterization of several rabbit models for human diseases, development of new transgenic rabbits for antibody production, QTL mapping in meat rabbits, genetic improvement of meat rabbit lines and so on). However, none of them have included partners across many European countries.

During the last few years several genomic projects have contributed to complete the sequencing (at different levels of coverage) of the genome of different mammals. The sequencing of the European rabbit genome derives from a project carried out by the Broad Institute (USA) in collaboration with INRA (France) aimed to contribute to mammalian comparative genomics and to inform the human sequence. Even though this sequencing was carried out with standard Sanger technology, it reached a quite good level of coverage (~7X) but numerous assembly problems still have to be solved.

Next generation sequencing platforms are changing the way in which genomic and transcriptomic information are obtained. Current projects in the USA are being initiated to take advantage of these technologies to exploit the European rabbit genome and the transcriptional landscape of key tissues. Other similar projects are planned in China, including also the aim to complete the sequence of the genome of other leporid species. Therefore, it is right time for exploitation of actual and next available genomic and transcriptomic information in the European rabbit filling the gaps that Europe is acquiring in this field. A translational vision of this information should be to the advantage of Europe and this COST Action will address this issue. The multi-faceted roles of the European rabbit in many basic and applied biology fields require participation of individuals with expertise in a large number of research areas, all present in Europe, that are the source of the interdisciplinary network of this COST Action.

### **B.3 Reasons for the Action**

The European rabbit is a key species in several research and applied fields that embrace two research domains: Food and Agriculture (FA) and Biomedicine and Molecular Biosciences (BMBS). This Action is very timely as it is addressed toward a full exploitation of an important resource that will benefit these two major research areas – the sequenced European rabbit genome. As a first step, coordinated activities and additional contributions are needed to refine this resource, improving assembly and annotation, as well as develop and exchanging genomic tools based on it. Different biological areas will provide needs, methods and resources for these preliminary activities. The interdisciplinary nature of RGB-Net will be the right forum to efficiently organize activities in this direction, avoiding unnecessary duplications and optimizing bioinformatic and genomic resources. Then, many specialized research and applied fields will find their own way to translate this resource into more advanced studies and applications. This COST Action will provide a framework to facilitate advancements and exchange of knowledge within specialized fields. Moreover, transfer of knowledge among different research areas will be important to create synergies between scientists from different disciplines who usually do not have any opportunity to talk together. This COST Action will establish a collaborative network to exploit all potentials of interdisciplinary approaches focused on rabbit genome biology.

Recognizing that the European rabbit is studied and exploited by many disciplines and sectors, the Action is not only aimed at European scientific/technological advance but also at European economic/societal needs towards the enhancement of the competitiveness of European rabbit industries that have already expressed interest in participating to this COST Action.

This COST Action will provide advantages to the European research community at different levels:

- avoiding duplication of research activities in European countries;
- reducing the limits of fragmented research efforts on European rabbit and related species;
- improving exchange between basic and applied biology areas focused on these species;
- improving dissemination of acquired advances and training for Early Stage Researchers (ESRs).

#### **B.4 Complementarity with other research programmes**

As mentioned in Section B.2, few research programs and supported activities have been funded at the European level on the European rabbit and no other current or planned European research programme exists that is focused on the same objectives of this COST Action. There is complementarity between RGB-Net and several ongoing European research projects that, however, do not directly include the European rabbit or that only marginally involve leporids:

- EU FP7 LUPA (Unraveling the Molecular Basis of Common Complex Human Disorders Using the Dog as a Model System; <http://www.eurolupa.org/>) (2008-2011);
- EU FP7 Quantomics (From Sequence to Consequence: Tools for the Exploitation of Livestock Genomes; <http://www.quantomics.eu/>) (2009-2013);
- EU FP7 ConGRESS (Conservation Genetics for Effective Species Survival) (2010-2013).

At the international level this COST Action is linked to the Mammalian Genome Project of the Broad Institute of MIT within which the Rabbit Genome Project was born (<http://www.broadinstitute.org/scientific-community/science/projects/mammals-models/rabbit/rabbit-genome-project>). The Broad Institute is listed within the non-COST Action country interested groups. RGB-Net will represent a step forward from this US initiative. Furthermore, this COST Action will complement several ongoing national, bilateral and trilateral research projects, e.g. PASTEURELLOSE, PCH-Utique, NSM, NYUL\_HUS, IGRABBIT, PLURABBIT, AGL2008-05514-C02, etc.

RGB-Net closely aligns with objectives of the strategic research agendas and vision documents of the Sustainable Farm Animal Breeding & Reproduction Technology Platform (FABRE-TP; <http://www.fabretp.info/Home.aspx>) and European Technology Platform for Global Animal Health (ETPGAH; <http://www.etpgah.eu/>).

## **C. OBJECTIVES AND BENEFITS**

### **C.1 Main/primary objectives**

The aim of this Action is to establish a multidisciplinary and cooperating network of experts in different research and applied fields interested in developing new scientific and commercial opportunities, resources and tools from the European rabbit genome and to strengthen and consolidate Europe as a leader in the scientific and economic exploitation of the European rabbit and related species.

### **C.2 Secondary objectives**

The objectives of this COST Action are:

- to improve the annotation and assembly of the European rabbit genome;
- to promote the development and exchange of genomic tools based on this resource;
- to establish a first systems biology platform for this species;

- to obtain an improved comparative genome view across lagomorphs;
- to disseminate the potential role of genomic and post-genomic applications in all rabbit biology fields and transfer of knowledge to interested parties;
- to develop new approaches in rabbit breeding and in wild species management;
- to foster studies in basic and applied biology fields using the European rabbit, considering the strengths and limits of this species compared to the rodents;
- to better investigate the potential of the European rabbit as a model for human diseases based on the exploitation of genomic information;
- to better define the role of the European rabbit in biotechnology applications and explore new avenues for its exploitation in this area;
- to stimulate collaborative plans and research activities among complementary research fields;
- to promote the rapid transfer of innovations to end-users;
- to coordinate research efforts in different rabbit applied biology areas;
- to disseminate acquired advances and to train Early Stage Researchers (ESRs).

### **C.3 How will the objectives be achieved?**

The Action will facilitate close cooperation among groups working in different research areas and with complementary expertise maximizing possibilities for translational applications of rabbit genome information. European fragmented researches in this and related fields will have the opportunity to maximize their efficiency by avoiding duplications and establishing exchanges of tools and information, taking advantage of the dissemination of knowledge, experience, and mobility of researchers for training and collaboration. Working Groups (WG) will hold regular inter-related workshops. The website will highlight the latest findings from the members of the Action and other important research outcomes, as well as Conference and Workshop programmes, proceedings and will content tools and databases developed according to the WG activities. Training Schools and STSM will ensure knowledge transfer and research links among member groups. A Kick-off Meeting will establish the current state of the art and will focus the priorities of this COST Action. A periodical Newsletter, a final Conference and Dissemination Document will allow the full achievements of the COST Action to be disseminated to European authorities, end-users and scientists providing a springboard for the long term sustainability of this network.

### **C.4 Benefits of the Action**

From the scientific community and European research perspectives RGB-Net will help to fill the gaps that Europe has acquired on rabbit genomics, strengthening Europe as a global leader in the exploitation of the European rabbit genome from different points of view. It will derive that this Action will increase the competitiveness of European scientists working in basic and applied biology research fields. The results will be accelerated research progress, increased publications and accelerated transfer of knowledge to end-users for practical applications and creation of new networks.

From the society and consumer perspectives this COST Action will help to improve the identification of genes that contribute to human diseases and to develop new biotechnology applications (production of antibodies, pharmaceutical biomolecules, etc.) with effects on human health, in the long term. A public concern is the use of the European rabbit as a laboratory animal. This COST Action will improve basic knowledge on biological mechanisms that in turn can make it easier to better focus research activities with consequent reductions in the numbers of rabbits used in experiments. In addition, fancy breeders will find new value and motivations for their activities. In fact, fancy breeders maintain a large number of breeds that represent a fundamental genetic resource that will be innovatively exploited in basic (rabbit as animal model) and applied (rabbit as a livestock) activities. Important impacts will be derived from the activities related to improvement of rabbit meat production. For example, improving disease resistance in meat rabbits will reduce the risk linked to the excessive use of antibiotics in farmed animals (i.e. residues in meat, acquired resistance of bacteria, etc.). Indeed, rabbit is the livestock in which husbandry practises make the largest use of antibiotics compared to all other livestock species.

This COST Action will enlarge its interest to population genetic aspects and basic knowledge of wild rabbit populations and other leporids. Even if wild European rabbit has earned a poor reputation in areas where it has been introduced, within its native range of the Iberian Peninsula, there is great concern about its status. Many carnivores, including the world's rarest cat, the Iberian lynx, and the Spanish imperial eagle, rely on healthy rabbit populations for their own survival. Understanding of the genome of rabbits, and the distribution and variability of rabbit genetics, will assist conservation efforts in the endangered Mediterranean scrub ecosystem. In addition, about a quarter of the 90 species of lagomorph are threatened with extinction. Some of the rarest mammals in the world are lagomorphs. This COST Action will lead to significant by-product effects in the efforts to understand the genetics of these forms and improve attempts to recover their populations and to understand the role of introduced pathogens in declining populations.

From the employment perspective this COST Action will facilitate end-user applications with direct positive impacts for biotechnology companies, rabbit breeding enterprises and rabbit farms. Moreover, the training and mobility activities will produce a cohort of highly qualified scientists in a large number of research fields with interdisciplinary backgrounds, with a variety of career opportunities in academia, breeding companies, biotechnology and pharmaceutical industries in Europe.

### **C.5 Target groups/end users**

This COST Action has several target groups:

- all scientific groups in Europe undertaking studies on European rabbit and other lagomorphs from different points of view, considering basic and applied biology aspects, will gain access to refined resources (rabbit genome), new tools and newly emerging applications;
- scientific groups working in human medicine and in other species will be able to find new tools for improved exploitation of the European rabbit for their studies;
- the world-wide scientific community will benefit from the creation of an interdisciplinary network and research tools;
- rabbit breeding companies, fancy breeders, and national breeder organizations will benefit from the innovation deriving by the exploitation of the European rabbit genome. A direct link to them is derived by their involvement during the preparation of this Action and through the links they already have with scientists involved in this COST Action;
- biotechnology and pharmaceutical companies producing transgenic rabbits, antibodies, therapeutic proteins, etc., several of them directly involved in this COST Action, will derive new procedures, methods, tools and ideas to foster their business activities;
- wildlife managers, agencies and organization will be the end-users of all information and application that will be derived and developed for their sectors.

## **D. SCIENTIFIC PROGRAMME**

### **D.1 Scientific focus**

It is now possible to unravel a complete genome using next generation sequencing platforms at an unprecedented speed and low cost. However, a major bottleneck in the exploitation of the potential of sequenced genomes will be the achievement of good annotation and, even more, a correct assembly. Efforts in this direction for the European rabbit genome will be coordinated by RGB-Net, together with activities aimed to facilitate translation of genomic information into applications in all fields in which the European rabbit is scientifically or economically important.

The objectives will be achieved by creating a multidisciplinary network of scientists and industry experts with in-depth knowledge of many basic and applied biology sectors. An intense discussion among all the scientists and experts who have expressed an interest in taking part to this Action to date has suggested the following Action strategy:

- focus resources and infrastructures for the annotation and improvement of the assembly of the European rabbit genome as a key issue for many other applications (Working Group 1, WG1);
- develop genomic tools and platforms to interface the European rabbit genome with all users (WG1);
- differentiate activities according to scientific areas and specialized fields in which the European rabbit is exploited or could be a reference point (WG2, WG3, WG4);
- promote inter-activity contacts, training, transfer of knowledge and dissemination in order to create a multidisciplinary network that will benefit all areas (WG1, WG2, WG3 and WG4).

### **D.2 Scientific work plan, methods and means**

The issues described above have led to the implementation of 4 Working Groups (WG) as already mentioned, divided in several tasks whose activities, coherence, interaction and objectives are described below.

*Working Group 1: Refinement of the European rabbit genome resource and development of genome-based platforms*

The OryCun2 European rabbit genome assembly represents a resource of paramount importance that, however, needs improvements and refinements. Considering the smaller scientific community around this species than that around other animals (e.g. rodents, cattle), it is important to put together all European groups interested in further improvement of this resource in order to proceed toward advanced scientific applications and translational activities that can be derived from it. Therefore WG1 will provide data, resources and platforms for this purpose and will coordinate actions and programs to improve annotation and assembly of the European rabbit genome. Moreover, WG1 will coordinate the exchange of already available genomics and transcriptomics tools and information as well as the development of new and more advanced tools, methods and platforms considering the tremendous expected progress in data generation by the genomic sector through the use of next generation sequencing and high throughput genotyping technologies. Furthermore, dissemination of these technologies and approaches to interested member groups will be coordinated by this WG.

*Task 1. Improvement of the annotation and assembly of the European rabbit genome.*

Groups working in comparative genomics, bioinformatics and computational biology will devote resources and platforms to this task establishing appropriate procedures and rules for sharing data. Particular attention will initially be focused on specific regions with direct translational interest, such as the major histocompatibility complex, immunoglobulin genes, and several other immunity-related loci. Additional chromosomal regions will be prioritized based on feedback from other WG about needed refinements for their translational activities. *In silico* activities will be complemented with BAC sequencing and anchorage using resources already available. Data from next generation sequencing generated for single nucleotide polymorphisms (SNP) discovery and transcriptomic analysis will be provided by Action groups and used for these activities. In addition, as a basic activity, the entire European rabbit genome will then be improved.

*Task 2. Sharing and development of genomic tools and information.*

Resources already available within the Action members (e.g. large DNA fragment libraries) will be shared and/or screened in a coordinated way upon request for the needs of the different groups. SNP and other information on structural variation derived by next generation sequencing of European rabbits of different breeds/lines will be used to improve annotation of the rabbit genome. SNP will be used to develop high throughput genotyping tools for this species. Characteristics of SNP based tools will be discussed with member of the translational WG. Platforms for copy number variation analysis (based on array comparative genome hybridization, aCGH) and results of these studies will be shared or produced and developed *ex novo*.

*Task 3. Sharing and development of transcriptomic tools and expertise.*

Resources already available within Action members (e.g. cDNA microarray) will be networked. There is a common interest on the use of next generation sequencing technologies for transcriptomic analysis (RNA-seq) but a major drawback is the cost that prevents the use in labs with small budgets and low computational capacities. WG1 will coordinate the acquisition of needed expertise and will explore the use of RNA-seq for practical applications in targeted experiments. In addition, data obtained by Action members with these platforms will be used in Task 1. According to the needs of the other WG, WG1 will provide coordination for the design of a DNA chip based on the improved annotated European rabbit genome, adding features that may be useful in several applications, including inter-species analysis.

*Task 4. Systems biology platform.*

Task 4 will develop dedicated analysis platforms and a relational database collecting data from several experiments provided by the Action members (e.g. transcriptomic data) and derived from public databases. The platform will include tools for the construction of gene coexpression networks and for their integration with interactomic and regulatory networks, and with metabolic and signalling pathways. The platform will address the issues related to the inter-species comparison of important biological modules, with particular focus to the assessment of the functional similarity between human and rabbit. This resource will be available through the restricted area of the COST Action web site.

*Deliverables of WG1:* annotated regions of the European rabbit genome; a new assembly version of the European rabbit genome; new genomic sequences and data about polymorphisms (SNP and copy number variation); SNP genotyping platforms; transcriptomic data; transcriptomic platforms; aCGH platforms; databases; a systems biology platform; scientific publications; STSMs; a Training School.

*Working Group 2: Genetics in meat, fur and pet rabbits and biodiversity resources*

WG2 is focused on application of genomic information and tools to the rabbit breeding industry considering the different use of this species and exploiting genetic resources for production purposes.

*Task 1. Genetics of phenotypic and production traits.*

This Task will explore the possibility of linking production traits and/or massive phenotypes (phenomics) in rabbits to genotypes based on genomic tools already available or that will be developed in the framework of WG1. A few rabbit resource populations for QTL and gene mapping have been already developed. These resources will provide valuable experience for the constitution of other resource populations that will be coordinated by WG2. Particular attention will be given for traits like disease resistance, feed efficiency and reproduction performances that should need improvements mainly in meat rabbits. Phenotypic traits will be considered in pet rabbits and in the activities of WG3. The use of other phenotypes (e.g. surrogate traits, metabolites, etc.) will provide additional data for a more advanced exploitation of these populations.

*Task 2. New breeding programs.*

The aim of Task 2 is to simulate and theoretically design applications of new breeding schemes in rabbits using information that will be obtained by the activities of Task 1 or that will be possible through the use of high throughput SNP genotyping platforms (WG1). Aspects related to the particular structure and implementation of the current breeding plans and the characteristics of the species will be considered in proposing genomic selection schemes. As crossbreeding is commonly used in meat rabbit production, how genetic marker information will help to predict combining ability of different lines and heterosis, will be evaluated. Practical implementation of some of these aspects will be coordinated by this WG. Designs and practical results will provide useful information for application of genomic selection programmes in other species that share similar breeding structure, i.e. the pig, but have longer generation period.

*Task3. Biodiversity resources.*

This Task will provide an updated list of rabbit genetic resources available in Europe and in several developing countries linked to the Action members integrating all information from other databases (e.g. FAO DAD-IS, EFABIS), national breeder associations, breeding companies, local breeders, fancy breeders, laboratory animal providers and biotechnology companies. A dedicated database will be established for this purpose with a description of specific phenotypes and traits, with particular attention to fancy breeds and lines (useful for Task 1 and in WG3).

*Deliverables of WG2:* phenotyping and genotyping strategies, including protocols; rabbit resource populations; QTL for production and phenotypic traits; genomic selection simulations; new breeding schemes including genome information; inventory of rabbit genetic resources; databases; scientific publications; STSMs; a Training School.

*Working Group 3: The European rabbit as a model in basic biology and human diseases and as a tool for biotechnology applications*

The rabbit is the third laboratory mammals after the mouse and the rat. A large number of basic and applied research studies have been conducted using rabbits. Several characteristics make the rabbit a more appropriate model than the rodents in different biomedical aspects, however a better definition of this issue is needed. One of the limits that have prevented use of the rabbit in biomedical disciplines more widely, has been the lack of a sequenced genome and related tools. WG3 will transfer tools developed in WG1 to basic research studies and to improve biotechnology applications derived via exploitation of various aspects of rabbit biology.

*Task 1. Development of a database on the use of the rabbit as model in basic biology and in human diseases.*

This task will provide a broad view of the role of the European rabbit in basic biology studies and will address the needs for the development of genomic tools and their potential applications by the scientific community. Data provided will be utilized to define the advantages/disadvantages of the use of the European rabbit as an animal model compared to the rodents in the biomedical sector. Reviews of particular aspects will be issued.

*Task 2. Application of genomic tools and information to the study of basis biology aspects and for the exploitation of different rabbit models.*

**The** Action members studying the rabbit as a model for/in i) early embryo development, gastrulation, germ line development and placentation, ii) diabetogenic embryo-fetopathies, iii) metabolic syndrome diseases, iv) lipid metabolism and atherosclerosis, v) hypertrophic cardiomyopathy and long QT syndrome, vi) pulmonary diseases, vii) tumorogenesis, viii) neurobiology, ix) toxicology, x) immunology, xi) etc., will evaluate potential applications of genomic and transcriptomic tools and information in their experiments and will provide data that can be shared with other Action member and/or used to feed the systems biology platform.

*Task 3. Exploitation of rabbit genetic resources to define natural models of human diseases.*

The large number of fancy breeds and lines will be evaluated to identify interesting phenotypes and genetic diseases that will help to study the pathological mechanisms in human diseases. Specific experimental plans or populations will be developed and genome based tools will be applied.

*Task 4. Rabbit as a model/tool for biotechnology applications.*

It will include activities to characterize embryonic stem cells and develop methods, protocols and resources for cloning, transgenesis, reproduction biotechnologies, production of therapeutic molecules, etc.

*Deliverables of WG3:* databases, scientific reviews, transcriptomic and genomic data; new rabbit models; rabbit resource populations; protocols; biomedical resources; scientific publications; STSMs; a Training School.

*Working Group 4: Genetics and comparative genomic aspects for the study, exploitation and management of wild lagomorphs*

Introduced pathogens, control measures, and unsustainable sport hunting have driven wild European rabbit populations to be severely threatened in the native range of this species. On the other hand, introduction of this species in other areas has caused many types of damage. Climate changes are modifying environments and are also affecting European hare populations and dynamics. Many other related lagomorphs are threatened with extinction or are of particular concerns as they might serve as pathogen reserves. WG4 will address the translation of comparative information derived by the European rabbit genome to study all these issues in wild European rabbits and related wild species.

*Task 1. Comparative genomics.*

The analysis of sequences that will be generated from wild and domesticated European rabbits will provide additional clues about the domestication process and its consequences on the modification of domesticated rabbit biology compared to the wild counterparts. The European rabbit genome will serve to anchor and compare all genomic information and sequences that will be generated from other lagomorphs. Focus will be mainly on a few *Lepus* species for which virtual genome maps will be produced.

*Task 2. Population genomics of wild lagomorphs.*

Comparative genomic resources will be used for the development of genomic tools and information that will be important for population genomics studies of wild lagomorphs. This would represent the basis for a thorough understanding of the current status of wild populations spread all over Europe.

*Task 3. Conservation and management plans.*

WG4 will devote resources and activities to exploit genomic information in wild European rabbit and other lagomorphs for the implementation of new conservation and management plans aimed at preserving rare genetic variants and the overall genetic diversity in a scenario of climate changes. *Deliverables of WG4:* wild rabbit and hare genomic data; comparative and virtual genomic maps; protocols for managing/evaluating lagomorph populations; scientific publications; STSMs; a Training School.

## **E. ORGANISATION**

### **E.1 Coordination and organisation**

The organization of this COST Action will follow rules and regulations described in the “Rules and Procedures for Implementing COST Actions” (doc. COST 4154/11). The Management Committee (MC) will be convened by representatives of the participating countries as described in the COST guidelines. The MC will elect a Chair and a Vice Chair by majority vote. A Core Group will be established within the MC to support the Chair in his/her duties and to manage short term scientific mobility (STSM).

The MC will be charged with the following responsibilities:

- appointment of the Working Group (WG) coordinator and deputy coordinator and the website/publicity manager (Milestone MS1);
- creation and maintenance of a dedicated website (MS2), that aims to maintain and enhance communication among the partners and to disseminate results obtained in the different WGs. The website will contain a restricted access page for registered participants of the COST Action in order to give access to relevant information, tools and databases;
- planning and coordinating the different meetings/workshops, including MC meetings (MS3), and the final conference (MS9);
- promoting collaborations and exchange of data, tools and results across WG, maximizing interactions among partners;
- promoting exchange of information among COST Action members through a dedicated newsletter disseminated by using an appropriate mailing list (MS4);
- establishing programmes for short term scientific mobility (STSM), (MS5);
- organizing training schools in collaboration with each WG (MS6);
- monitoring and assessing the different activities (meetings, scientific exchanges, training schools, website, databases, publications) to ensure that they meet the objectives defined for this COST Action;
- eventually propose changes of activities in order to better fulfil the objectives;
- preparation of the annual (MS7) and final reports (MS8);

- coordination of national research activities and programmes, creating a dedicated list hosted in the restricted password space of the website in order avoid duplication of research studies and identify possible synergies among groups;
- coordination of the preparation of new proposals for application to European or multilateral calls;
- establishment of collaborations between WG and other related Actions and scientific programmes in Europe and world-wide;
- increasing visibility of the Action and promoting and managing interactions with non members;
- promoting interactions with end-users and dealing with issues relating to exploitation of results.
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Moreover, MC will establish priorities for all activities in agreement with the objectives of the COST Action. All Action events will be carefully managed according to the available budget in order to avoid waste of funds and time. MC meetings will take place once a year, linked to WG meetings and workshops or other Action events, in order to maximize efficiency, reduce costs and ensure coordination activities.

## **E.2 Working Groups**

Four Working Groups (WG) will be established to fulfil the COST Action working plan and objectives: WG1, focused on the refinement of the European rabbit genome resource and development of genomics, transcriptomics, and bioinformatics tools and structure based on it; WG2, focused on European rabbit breeding and genetics aspects; WG3, focused on the European rabbit as a model in basic biology and human diseases and as a tool for biotechnology applications; WG4, focused on genetics and comparative genomic aspects linked to the study, exploitation and management of wild lagomorphs. There will be annual WG meetings, separately or combined by WG where the results of the WG will be discussed with all members of the network and end-users. Each of the WG will be managed by a WG coordinator and a WG deputy coordinator. WG coordinators will have the following main tasks:

- participate in the meetings of the MC;
- plan the details of the scientific meetings and training schools within their WG;
- coordinate the activities within their WG to meet the COST Action objectives;
- promote the exchange of information between tasks of the same WG and across WG;
- promote the set-up of joint research and STSM;
- coordinate and manage the writing of reports for publication in the Newsletter, fact-sheets and on the website from their WG.
- coordinate the development of databases from the activities of their WG;
- report the WG progress to the Action Chair and to the MC.

Meetings of the WG will be organized on an annual basis at different partner locations. RGB-Net will hold an annual three-day meeting for each WG. The first and the second day (or part of it) of such meetings will allow exchange of specific information and ideas related to WG topics, and encourage collaborations between scientists, institutions and end-users, stimulating the planning of joint experimental work and translational activities. The second day of the meeting will include a combined session with the other WG. This would enhance integration of activities from the different fields and promote interface between WG. For example, feedback from the WG2-4 will be important to the activities of tasks of WG1, other integrations are needed to exchange data and results between WG2 and WG3 and so on. The final day will involve the planning of exchanges of early-stage researchers for the following year, planning of a programme of training schools, the implementation of web site tools and databases, the preparation of reports and materials for distribution to other WG via the website and publications. This will further enhance the exchange of materials and ideas between the different WG.

### **E.3 Liaison and interaction with other research programmes**

In section B4 of this document a number of European and International pertinent ongoing related programmes have been described. RGB-Net will interact with them establishing specific plans and exchanging relevant information.

In addition, interactions will be established through exchange of information with other COST Actions focused on arguments directly or indirectly linked to the activities of RGB-Net:

- *BMBS BM0901* (European systems genetics network for the study of complex genetic human diseases using mouse genetic reference populations – SYSGENET; end date: Nov. 2013), that aims to contribute to the discovery of gene networks that are involved in the development of complex genetic diseases in human;
- *BMBS BM1006* (Next Generation Sequencing Data Analysis Network; end date: Dec. 2014), that aims to develop a coordinated action plan to help deal with the flood of Next Generation Sequencing data;
- *FA1002* Farm Animal Proteomics (end date: Nov. 2014) that aims to apply proteomic science to resolve problems in farm animal production and post-harvest change: an improved annotation of the European rabbit genome is fundamental for proteomic studies in this species.

#### **E.4 Gender balance and involvement of Early-Stage Researchers**

Specific rules will be observed for the constitution of the MC and for all relevant roles and activities in RGB-Net to favour the inclusion and the role of women. A 50% gender balance will be considered for the nomination of WG coordinators and deputy coordinators and for any other key role in this COST Action. Moreover, gender best practices will be implemented within project management and research activities. Family issues will be considered when choosing the dates for meetings and other events. Gender balance will be also observed in the workshops, teaching activities and STSMs.

Early Stage Researchers (ESRs) will be encouraged to join WG and to actively participate in workshops and conferences, including helping to plan and organise such events. Special awards for the best research planned or presented by ESRs will be established for different COST Action events.

## F. TIMETABLE

The life time of the action is four years, with continued activity beyond that period via collaborations, website and networking activities. The Action will be initiated with a kick-off meeting. Below is a schematic timetable for the different actions including milestones as defined in section E.1.

<i>Action</i>	<i>Milestone</i>	<i>Year 1</i>				<i>Year 2</i>				<i>Year 3</i>				<i>Year 4</i>			
Coordination		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Kick-off meeting	MS1	x															
Homepage and databases	MS2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MC meeting	MS3	x				x				x				x			
WG1 meeting	MS3	x				x				x				x			
WG2 meeting	MS3	x				x				x				x			
WG3 meeting	MS3	x				x				x				x			
WG4 meeting	MS3	x				x				x				x			
Newsletter	MS4		x		x		x		x		x		x		x		x
Training schools	MS5			x				x				x				x	
STSM	MS6		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Reporting	MS7/MS8				x				x				x				x
Final conference	MS9																x

MC meeting: Management Committee meeting

WG meeting: Working Group meeting/workshop

STSM: Short Term Scientific Missions to be initiated after the first MC and WG meetings

## **G. ECONOMIC DIMENSION**

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: AT, BG, CZ, DE, EL, ES, FI, FR, HR, HU, IT, PL, PT, RS, SE, SI, SK, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 72 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

The following non-COST countries expressed their intention to participate: China, Japan, Taiwan, USA, South Africa.

## **H. DISSEMINATION PLAN**

### **H.1 Who?**

The findings and results of the COST Action will be disseminated to the varied target groups including other researchers in the field; other research frameworks; research and agricultural institutes and universities; rabbit, food, biotechnology and pharmaceutical industry; European level policy makers in the DG for Agriculture & Rural Development, DG for Research and DG for Health and Consumers of the European Commission; Government policy makers in Departments of Agriculture and Departments of Industry or Commerce; Region and City planners and policy makers; and the general public.

Collaborations will be established with the World Rabbit Science Association (<http://world-rabbit-science.com/>), the Lagomorph Specialist Group (<http://www.ualberta.ca/~dhik/lsg/INDEX.HTM>), the World Lagomorph Society (<http://www.worldlagomorphsociety.org/Home>), the European Association for Animal Production (<http://www.eaap.org/>), the Federation of European Laboratory Animal Science Associations (<http://www.felasa.eu/>) to disseminate the scientific results to a broad scientific community.

## **H.2 What?**

The results of the COST Action will be disseminated to the target groups by:

- Press releases;
- Public access website;
- Internet discussion forum;
- Scientific publications;
- Non-technical publications (Newsletter);
- Workshops and conferences and related proceedings;
- National and international conferences;
- Short-Term Scientific Missions;
- Teaching activities.

## **H.3 How?**

### *Press releases*

The activity of the COST Action will be drawn to the attention of the scientific community, governments, policy makers and the citizens of Europe by production of a press release in all Cost Action countries, at the beginning and at the end of the Action.

### *Public Access Website*

A public access Website will be established in order to provide a portal to the mass of information generated for access by the international scientific community (e.g. publications; contact details of Action members; details of courses including on-line content and other teaching material; calls for STSM; reports of workshops and meetings of the Action, final reports). The Website will also facilitate communication between the partners and WG of this project.

### *Internet Discussion Forum*

In association with the website a password protected discussion forum will be established for communication and exchange of information among members of the Action.

### *Scientific Publications*

The scientific results of the project will be published in peer-reviewed scientific journals. Review articles, book chapters and trade journal articles will also be encouraged in order to disseminate results to a broader, less specialized public.

### *Non-technical publications*

The COST Action results and activities will be also published in non-technical and trade journals (agricultural, veterinary and biotechnology journals) to provide information to farmers, breeders, veterinarians, technicians and related professions.

### *Workshops and conferences and related proceedings*

Kick-off Meeting, Final Conference and WG workshops will inform interested scientists, regulatory bodies and policy makers about the results of the project and about new technologies developed throughout the project. These sessions will be organised in different geographic regions to allow participants from across Europe to gain access to the leading European expertise in rabbit (and other animals) genomics. Efforts will be made to have the proceedings of the conferences published in special issues of genetics and/or farm animal related international peer-reviewed journals. Members of the Action are either on editorial boards of such journals or have contact with the editorial boards.

### *National and international conferences*

The COST Action members will participate in international and national conferences on genetics, genomics, bioinformatics, animal production, lagomorphs, rabbit science, such as the World Congress on Genetics Applied to Livestock Production, the International Society for Animal Genetics (ISAG) Congress, the European Conference on Computational Biology, the International Conference on Bioinformatics and Computational Biology, the European Association for Animal Production (EAAP) Meeting, the World Rabbit Congress, the World Lagomorph Conference (WLC), the European Laboratory Animal Science Associations (FELASA) Meeting, and the Transgenic Technology Meeting in order to disseminate the knowledge and data resulting from the COST Action activities. Action members attending such conferences will promote the novel technology and know-how generated by RGB-Net and will make efforts to organise satellite symposia in association with such conferences.

### *Short-Term Scientific Missions*

Short-Term Scientific Missions (STSM) will allow dissemination of accumulated knowledge of RGB-Net to early-stage as well as senior scientists acquiring knowledge of genomics for the first time. Thus the STSM will facilitate technology and knowledge transfer within the COST Action by stimulating the shared use of rabbit-based genomic tools and information by farm animal research and biomedical research groups, thus increasing the opportunity for synergy between expert and ESRs in both areas.

### *Teaching activities*

Knowledge and results produced by the Cost Action will be taught in Universities at undergraduate and post-graduate level. ESRs and bio-engineers in COST countries will have the opportunity during their educational experiences to become fully acquainted with the state-of-the-art technology for genomic and post-genomic applications to rabbit science and related biomedical areas. The dissemination plan will be updated during the course of the COST Action taking into account the progress of the Action as well as the results of its evaluation.

Training Schools will be established for young researchers (e.g. PhD student level and early postdoctoral level). These training schools will cover multidisciplinary aspects or will be specialized in a particular field as it will be defined by the MC in collaboration with the WG. Training Schools will cover a period of 3-5 days, with experts from the RGB-Net, their associated international research groups, and experts in the targeted fields.

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