Final Report

EMMAinf

European Mouse Mutant Archive Infrastructure

Integrating Activity

implemented as

Integrated Infrastructure Initiative

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Research Infrastructures Action

A. ACTIVITY REPORT

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1. EMMAinf concept and project objectives

The relevance of the mouse as a model of human disease

The mouse shows great similarities in development, physiology and biochemistry to humans. This makes it a key model for research into human disease. The identification of all the genes in mice and humans in the Human Genome Project has shown that about 99% of the genes in mice have a homologue in humans. This is important as to date around 5000 human diseases have been shown to be caused by an error in our genetic make-up. In numerous other diseases e.g. in diabetes, errors in our genetic make-up are a contributory factor. The similarity of the mouse and human genome means that genes associated with disease in humans can be investigated in mouse models. This knowledge can then be transferred to understanding and treatment of disease in humans. The key challenges for mouse functional genomics in the 21st century are to:

- Develop a series of mutant alleles for every gene in the mouse genome
- Develop and apply standardised phenotyping platforms to determine the phenotypic consequences of each mutation
- Identify mouse models for the complete disease spectrum in humans
- Provide reliable access to mouse models and associated data

To exploit the resources emerging from initiatives such as the International Knock Out Mouse Consortium (IKMC), mouse models must be preserved and made available to the entire European biomedical research community, which is wholly dependent on new mouse models of human disease. Therefore, it is imperative that a secure, well managed central repository exists for the cryopreservation and dissemination of mouse lines which will ensure pan-European access and efficient delivery of mouse models, prerequisites for maintaining Europe's leading role in the functional annotation of the mouse genome.

EMMA – the European Mouse Mutant Archive is the primary mouse repository in Europe for the deposition and distribution of mouse disease models and research tools. The EMMA network is a non-profit making organisation and is comprised of ten partners. The current membership includes the CNR Istituto di Biologia Cellulare in Monterotondo, Italy (core structure), the CNRS Centre de Distribution, de Typage et d'Archivage animal in Orleans, France, the MRC Mammalian Genetics Unit in Harwell, UK, the Karolinska Institutet in Stockholm, Sweden, the FCG Instituto Gulbenkian de Ciência in Oeiras, Portugal, the Helmholtz Zentrum München Institute of Experimental Genetics in Munich, Germany, the EMBL European Bioinformatics Institute in Hinxton, UK, the GIE-CERBM Institut Clinique de la Souris, Illkirch, France, the Wellcome Trust Sanger Institute in Hinxton, UK and the CSIC Centro Nacional de Biotecnología in Madrid, Spain. The EMMA network is directed by Professor Martin Hrabé de Angelis who also heads the IEG in Munich. The European Bioinformatics Institute is responsible for the development of the EMMA resource database. All other partners are major players in mammalian genetics research with a long standing expertise in mouse genetics, mutagenesis, phenotyping and cryopreservation. Seven partners participated in the EMMAinf project. The EMMAinf partners and their roles in the project are summarised in table 1.

EMMAinf project partners	Tasks
Consiglio Nazionale delle Ricerche Istituto di Biologia Cellulare (CNR-IBC) Monterotondo	EMMA core facility, embryo cryopreservation, distribution, cryopreservation courses
CNRS Centre de Distribution, de Typage et d'Archivage animal (CNRS-CDTA) in Orléans	Embryo cryopreservation, distribution, cryopreservation courses
MRC Mammalian Genetics Unit (MRC-MGU) in Harwell	Sperm and embryo cryopreservation, distribution, cryopreservation courses
Karolinska Institute (KI) in Stockholm	Embryo cryopreservation, distribution, production of germ-free (axenic) mice
Fondação Calouste Gulbenkian (FCG) in Oeiras	Production of germ-free (axenic) mice
Helmholtz Zentrum München – German Research Centre for Environmental Health Institute of Experimental Genetics (HMGU-IEG) in Neuherberg	EMMA Director, overall project coordination, sperm and embryo cryopreservation, distribution
European Bioinformatics Institute (EMBL-EBI) in Hinxton	Maintenance and further development of the EMMA resource database and the public EMMA website

Table 1: Partners of the EMMAinf project and their project related tasks

Objectives of EMMAinf

Building on EMMA's previous achievements and its proven ability to respond to the needs of the European biomedical research community, EMMAinf aimed to meet the future challenges presented by archiving and disseminating mouse disease models in the European Research Area as follows:

- To increase significantly the number of new medically relevant mutant mouse lines in the EMMA archive
- To renew constantly the live stock mouse strains with respect to the requests of the scientific community
- To further develop and constantly update the EMMA resource database to augment a virtual infrastructure
- To disseminate the most recent knowledge by organising cryocourses

EMMAinf has been a project of 4.5 years duration. The work was split into seven work packages. Focus of the work were Joint Research Activities that were offered as services to the scientific community. The EMMAinf activities, work packages and participating partners and deliverables are summarised in table 2.

Activity Number	**Descriptive Title**	**Short description and specific objectives of the activity**
Networking Activities		
N1	Management of CA	EMMAinf management Participants: CNR, HMGU
N2	Meetings and visits	EMMA project meetings Participants: All partners
N3	Dissemination of knowledge	Organisation of cryopreservation courses Presentation of EMMA at international conferences and general PR to advertise EMMA services and resources Participants: CNR, MRC, HMGU
Research Activities		
JRA1	Cryopreservation of mutant mouse lines	Cryopreservation of 881 new mouse mutant lines. Participants: CNR, CNRS, MRC, KI, HMGU
JRA2	Constant renewal of life stocks	Constant renewal of highly demanded live stocks. 45 mutant lines kept on the shelves per year for fast accessibility of mouse mutants which fulfil SPF-status. Participants: CNR, CNRS, MRC, HMGU
JRA3	Gnotobiology	Transfer of 20 mouse mutant lines to germ-free conditions and distribution to customers. Participants: KI, FCG
JRA4	Database development	EMMA-Resource Database (RDB) and website development Participants: CNR, CNRS, EBI

Table 2: EMMAinf activities, work packages and participating partners and deliverables

1.1 Summary of the EMMAinf activities and major achievements

A key effort of the EMMA activities is to continuously improve the **operation** of the EMMA network. Of central importance for the operation are the **EMMA IT activities** and accordingly EMMA informatics was considerably improved during the EMMAinf project by a number of means such as:

- Centralising the EMMA informatics resources at the EBI
- DB migration from an Oracle to a MySQL database management system and development of new interfaces based on Java J2EE/JSP and Spring/ Hibernate technologies
- Relaunch of an attractive, state of the art public EMMA website
- Establishing links to the International Mouse Strain Resource database (IMSR)

EMMA operations were further improved by implementing a '**Grace Period**' to encourage submissions of valuable mouse mutants while the submitting investigator awaits publication of the first paper describing the strain. In such cases a delayed release of the strain to the public website for a period of up to two years can be granted.

A major change for the EMMA operation was the implementation of a **cost recovery based distribution system**. Since July 2008 shipments of frozen embryos/sperm cost €1100, while live mice are distributed for a cost of €1700. The charges levied by EMMA are used solely to meet the animal husbandry and stock replacement costs.

Public Relations are of central importance and a broad range of measures were used to promote the EMMA services and resources. Foremost are presentations at major mammalian genetics meetings. During the course of the EMMAinf project the EMMA network was presented by a total of 61 talks and 20 poster presentations. In addition, EMMA was promoted by original publications and reviews, advertised in magazines such as the Parliament Magazine and the Public Service Review with more than 25000 readers across the EU and by the distribution of two EMMA calendars to 1500 customers worldwide.

With respect to EMMA's key services **archiving, distribution, production of germ-free mice and dissemination of knowledge** considerable progress has been made. During the EMMAinf project a total of 764.5 submissions of mouse mutants were reported for the **JRA1 activity** amongst which are numerous interesting disease models and valuable research tools (20 double/multiple mutants were counted with a factor of 2.5). A further 83.5 lines still in progress will be cryopreserved, leading to a total of 848 archived lines contributed by the EMMAinf program. The strong growth of the EMMA archive also leads to a continuously increasing number of requests. During EMMAinf a total of 1104 service requests for mouse resources were received by EMMA representing requests for 367 different mouse mutant lines from 506 different customers. Under the **JRA2 activity** a total of 180 lines spaces were available during the EMMAinf project to keep live mice on shelf and these were used to maintain 111 different demanded lines. For the lines kept on shelf under the JRA2 activity 632 requests were received accounting for 57% of all requests. Due to the JRA2 funding these mice were rapidly provided to the customers. Most of the requests EMMA received during the EMMAinf project were from European researchers. In total, EMMA received 623 requests (58 % of the total number of requests) of scientists from 23 European countries. However, when single countries are taken into account the by far best EMMA customer was the USA. The **EMMA axenic service (JRA3)** fulfilled during the EMMAinf project 20 requests for the production of germ-free mouse lines. The offered service will contribute to scientific publications of the customers. The EMMA expertise in cryopreservation techniques is disseminated by organising **cryocourses**. During the course of EMMAinf a total of 16 cryocourses were organised by EMMA partners of which 10 were EMMAinf funded. The courses were attended by 109 participants from 16 European countries.

Achievements beyond the EMMAinf project

Integration of new partners into the EMMA network

In 2008 three new partners were integrated into the EMMA network structure, namely the **Sanger Institute** (Hinxton), the **ICS Mouse Clinical Institute** (Straßbourg) and the **CNB-CSIC** (Madrid). The integration was facilitated via a **Cooperation Agreement** which was signed by all existing and the new partners. This agreement outlines the organisational structure, decision making processes and principles of operation of EMMA. According to the guidelines of the EMMA Cooperation Agreement, Prof. Hrabè de Angelis was elected by all EMMA partners as the **EMMA Director**.

Participation of EMMA in European research programmes

A central objective of the EMMA management activities was to secure further growth of the EMMA archive by ensuring that EMMA is involved in or supporting new large scale mouse functional genomics projects such as the **EUCOMM** and **EUMODIC** projects which were launched in 2006 and 2007 respectively. Both projects aim to produce a total of up to 650 knock-out lines from the EUCOMM ES cell resource which will be archived by the EMMA network. EUMODIC aims to undertake a detailed phenotypic analysis of these knock-out lines. During the EMMAinf project for about 200 mouse mutant lines produced from the EUCOMM ES cell resource germ line transmission has been established. Archiving of these lines is ongoing. Strain related data were imported into the EMMA database in January 2009 and now EUCOMM mice can be ordered via EMMA.

The EUCOMM and EUMODIC projects will be complemented by the Sanger Institute's **Mouse Genetics Program (MGP)** which aims to produce and phenotype up to 1000 mouse mutant lines. MGP resources will be distributed via EMMA. Furthermore, EMMA collaborates with the **Wellcome Trust** who has negotiated and funded the acquisition of knockout mouse strains and associated phenotypic data from Deltagen and Lexicon mouse mutant collections. This resource will be archived and distributed through EMMA. During the EMMAinf project the Deltagen / Lexicon resources were transferred to EMMA and mice were re-derived from the provided frozen embryos and then mutant lines were re-archived. Re-derived mice were made available for distribution via the EMMA website.

Another major activity of the EMMA management is to secure long term funding of the EMMA repository. Accordingly, members of the EMMA Board of Directors play active roles in the **ESFRI** process (Strategy Forum on Research Infrastructures (RI)). On October 19th 2006, ESFRI published the "European Roadmap for Research Infrastructures" which identified 35 research infrastructure projects of pan-European interest covering all scientific areas regardless of possible location. EMMA plays a key role in one of these projects termed '**INFRAFRONTIER**: Functional genomics in the mouse as a model of human disease'. The roadmap projects were eligible to apply for funding in the Capacities Specific Programme of the EC Seventh Framework Programme. The INFRAFRONTIER project started in March 2008 (www.infrafrontier.eu) and aims to organise a sustainable infrastructure by 1) the identification of the most suitable legal form, 2) developing a business plan based on a sustainable funding concept, 3) reaching a legal agreement between all partners and 4) providing a strategic plan for the construction phase.

To ensure the continuation of the EMMA activities carried out in EMMAinf, the EMMA network, including the three new partners who joined the network in 2008, submitted a project proposal entitled **EMMAservice** in response to the third call of the EC FP7 Capacities Specific Program. The proposal was positively evaluated and a grant agreement negotiated. The EMMAservice project started in January 2009.

FIMRe – EMMA goes global

EMMA is a founding member of FIMRe (Federation of International Mouse Resources), an affiliation of 17 major resource centers from four continents with the overall goal to promote sharing and preservation of genetically defined mice and to disseminate information, affiliated resources, and expertise in their use to the global biomedical research community.

Major achievements of the EMMAinf project

- 848 mouse mutant lines contributed by EMMAinf (764.5 archived, 83.5 in pipeline)[1]
- 1104 service requests from 506 customers for 367 different mouse mutant lines fulfilled
- Global distribution of EMMA mouse resources (58% of all requests from EU)
- Production and distribution of 20 germ-free mouse lines
- Centralising EMMA informatics resources at the EBI
- Improved effectiveness of the EMMA operation and the user services
- Promoting the EMMA services and resources by 81 presentations at conferences, advertisements and distribution of calendars and brochures
- Organisation of 16 cryocourses with 109 participants from 16 EU countries

Achievements beyond the EMMAinf project

- Collaboration with major European mouse functional genomics projects such as EUCOMM and EUMODIC
- Collaboration with the Wellcome Trust in the Knockout Mouse Resource Project
- Integration of new partners into the EMMA network via a cooperation agreement
- INFRAFRONTIER published on ESFRI European Roadmap for Research Infrastructures
- EMMA is shaping the European Research Area
- EMMA partners are founding members of the Federation of International Mouse Resources (FIMRe)

1: A total of 20 double/multiple mutants were counted with a factor of 2.5

1.2 Impact of the EMMAinf project on the European scientific community

The EMMAinf project had a significant impact on the scientific community in various areas.

1) Improved customer services and communication

The customer service offered by the EMMA network and the effectiveness of the operation were further improved by the EMMAinf project. This involves the following developments:

- Relaunch of attractive public EMMA website at www.emmanet.org
- Improving user friendliness of website by revising service request forms and display of available mouse resources
- Implementation of axenic service website and online request form
- Establishing links to the International Mouse Strain Resource database (IMSR)
- Improving customer communications by implementing automatic Email notifications to inform customers on progress of cryopreservation of deposited mouse mutants
- Implementation of option to register interest in deposited lines where archiving is not yet completed

2) Contribution to the implementation of the 3Rs (Replacement, Refinement and Reduction of Animals in Research)

The submission of 848 mouse mutant lines into EMMA ensures that these mutants are cryopreserved under the highest quality standards and conserve the financial, animal house and labour resources of the depositors which would otherwise be needed to maintain the breeding colonies. In addition, cryopreservation reduces duplication of effort as the EMMA archive ensures the availability of these valuable resources to the wider scientific community.

3) Development of the EMMA resource

The EMMAinf project made a significant contribution to the further strong increase in the overall number of submissions to the EMMA archive leading to a total of 1564 submissions by the end of the project. The publicly available archive currently consists of 1234 mouse mutant lines. A further 59 mouse mutant lines are archived but covered by a ‘Grace Period’ and are not yet publicly available. The most prevalent class of mutants are chemically induced mutants (483 lines). The number of transgenic lines and targeted mutant strains increased considerably to 233 lines and 366 strains with targeted mutations, respectively. Among the transgenic lines are a growing collection of currently 53 Cre-driver lines some of which comprise the most bestselling strains of the EMMA archive. The most prominent class of targeted mutants are knock-out strains of which currently 271 are distributed to EMMA customers.

4) Development of large distribution capacity

The growth and value of the EMMA mutant mouse resource is evident from the strong increase in the number of service requests from EMMA. In 2008 a total of 358 requests were fulfilled by the EMMAinf partners. Interesting disease models and valuable Cre-expressing lines that were in high demand were maintained as live stocks under the EMMAinf JRA2 activity facilitating a fast delivery to the customers. The comprehensive physical and the associated data resource of EMMA are available to support basic biomedical and preclinical translational (bench to bedside) research in Europe and globally. The available research tools and mouse models of human disease offer the opportunity to develop a better understanding of molecular disease mechanisms may facilitate the identification of potential new drug targets and provide the foundation for the development of diagnostic, prognostic and therapeutic strategies.

5) Providing unique axenic (germ-free) service

The EMMAinf project supported the European scientific community with the production of 20 germ-free mouse mutant lines. The resources provided by this service contributed to scientific publications of the customers that are currently in preparation. The EMMA axenic service is a unique service not offered by other major mouse repositories. The technology was transferred among EMMA partners during the course of EMMAinf. This may further improve the reliability and the capacity of the EMMA axenic service.

6) Dissemination of Knowledge - EMMAinf cryocourses

Annual EMMA cryopreservation courses were organised by CNR, MRC (EMMAinf funded) and CNRS (INSERM funding) to teach basic and advanced techniques in cryopreservation for banking of mouse mutant strains. During the course of EMMAinf a total of 16 cryocourses were organised by EMMA partners of which 10 were EMMAinf funded. The courses were attended by 109 participants from 16 European countries. The training by EMMA in state of the art cryopreservation technologies may contribute to an overall reduction of mice that are kept on shelf and thus supports the 3R principles.

7) EMMAinf contributed to the shaping of the European Research Area

During the EMMAinf project three new partners were integrated into the operation of EMMA. The Wellcome Trust Sanger Institute (Hinxton), the ICS Mouse Clinical Institute (Straßbourg) and the Centro Nacional de Biotecnologia (Madrid) joined the EMMA network in 2008. The collaborative work in this enlarged EMMA network is based on an 'EMMA cooperation agreement' that outlines the objectives, management structures and principles of operation of EMMA. The cooperation agreement also provides a framework for the integration of additional partners. This enlargement strengthened key member states with a strong user community and incorporated Spain as a new member state into EMMA. The integration of the new partners will be further supported by the joint participation in the INFRAFRONTIER project which commenced in March 2008. INFRAFRONTIER will organise two complementary European infrastructure networks for large scale, systemic phenotyping (PHENOMEFRONTIER) and for archiving and dissemination (ARCHIVEFRONTIER) of mouse models. ARCHIVEFRONTIER will be organised by EMMA. Additional member states not participating in EMMAservice will join ARCHIVEFRONTIER, namely Greece, Finland and Denmark. Thus, EMMA will further expand into a network of national archiving nodes with mandates from the member states and is open for new member states to join.

8) FIMRe – EMMA goes global

EMMA is a founding member of FIMRe, an affiliation of 17 major resource centers from four continents with the overall goal to ensure availability, assure quality, promote sharing and preservation of genetically defined mice, and disseminate information, affiliated resources, and expertise in their use to the global biomedical research community. EMMA's participation and active role in FIMRe will support the global distribution of EMMA's resources and will provide European researchers an easier access to the very valuable and growing collections of mouse mutant lines stocked at major repositories worldwide.

1.3 Relation of EMMAinf project achievements to state of the art

EMMA archive
With 848 newly deposited mouse mutant lines the EMMAinf project made a significant contribution to the further strong increase in the overall number of submissions to the EMMA archive leading to a total of 1564 submissions by the end of the project. The publicly available archive currently consists of 1234 mouse mutant lines and represents the largest public archive in Europe and the fourth largest worldwide next to the Jackson Laboratory the MMRRC repository and RIKEN BRC.

Distribution capacity
The growth and value of the EMMA mutant mouse resource is evident from the strong increase in the number of service requests from EMMA. In 2008 EMMA fulfilled a total of 358 service requests which is comparable to the distribution capacity of other archives such as the MMRRC and RIKEN. The EMMA archive is now clearly recognised as a global genetic resource.

Axenic service
The availability of an efficient axenic service is a speciality of EMMA and not provided by any other major repository of the global FIMRe network.

EMMA informatics
The EMMAinf project led to the implementation of a state of the art MySQL based database management system and new Java J2EE/JSP interfaces which are being continuously further developed. Up to date strain related information is displayed on the EMMA website which was relaunched in 2005 with a modern and attractive design. The user friendliness of the website was improved by revising the online service request forms and the display of strains which allows easy navigation through the available EMMA mouse mutant resources. All available EMMA resources are also displayed at the International Mouse Strain Resource database which is automatically updated on a monthly basis. The repository holdings of all major repositories and FIMRe partners are listed on the IMSR website.

EMMA Training Courses - Dissemination of Knowledge
With a total of 16 cryocourses which were organised by EMMA partners during the EMMAinf project (10 EMMAinf funded) EMMA is the key provider of training courses on cryopreservation in Europe and worldwide. The EMMA courses were attended by 109 participants from 16 European countries. In addition, the SOPs that are practiced in the courses are displayed on the EMMA website which is frequently visited. No other major repository presents cryopreservation protocols in such a comprehensive way as EMMA.

1.4 N1 Management Activity

Description of activity

The size and the scope of the EMMAinf project require particular attention to the overall management as well as the coordination of the different activities. A management framework links all project components and maintains communication horizontally between participants and activities as well as vertically between the scientific community, the Board of Activity Group Leaders (AGL), the Board of Participating Directors (BPD), the Advisory Board (AVB), the Co-ordinator, the EMMA Director, the Project Office and the EU Commission.

The management structure of the EMMA consortium was set up to ensure an effective operation of such a large and international enterprise and consists of several components (Fig. 1). EMMA is headed by the Director who leads the Board of Participating Directors (BPD), the decision making level within the consortium. The Technical Working Group develops and agrees on EMMA SOP's for quality control, archiving and distribution.

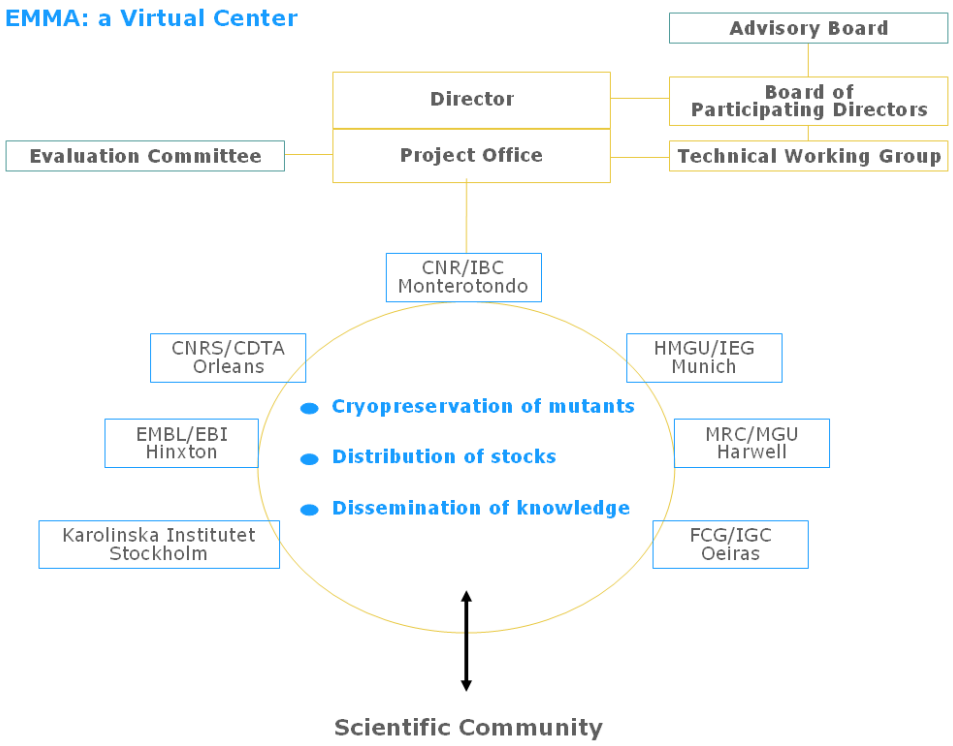

Fig. 1: EMMA management structure

To guarantee an effective communication within the virtual EMMA network an internal webpage was set up which constitutes a fundamental tool for the management of scientific, technical and logistical activities carried out by each EMMA partner. Furthermore, the EMMA resource database provides up to date information about the archiving status of mice and describes the genetic and phenotypic properties of all the mutant strains that EMMA stocks. The available strain list is displayed on the public EMMA website (www.emmanet.org). This website is the link to the scientific community and facilitates the submission of mice to EMMA and requests of mice from EMMA. Mouse strains submitted for archiving are evaluated by EMMA's external Evaluation Committee which comprises experts in the field of mouse genetics. They evaluate each submission to the EMMA repository, thereby ensuring that the research community has access to valuable mouse mutant strains with significance for current and future genetic research.

Final report N1 Management Activity
Operations of the EMMA network

A key effort of the EMMA management activities is to continuously improve the effectiveness of the operation of the EMMA network. This may involve for example hiring additional staff if bottlenecks arise, a constant reviewing and improving of SOPs, data flow and data presentation on the website and by implementing new management tools.

Of central importance for the effectiveness of the EMMA operation are the IT activities and accordingly EMMA informatics was considerably improved during the EMMAinf project by a number of means such as:

- Centralising the EMMA informatics resources at EBI
- DB migration to a MySQL based database management system and development of new Java J2EE/JSP interfaces
- Relaunch of attractive public EMMA website
- Improving user friendliness of website by revising service request forms and display of available mouse resources
- Implementation of axenic service website and online request form
- Establishing links to the International Mouse Strain Resource database (IMSR)
- Implementation of management tools facilitating quantitative assessments of the EMMA services
- Improving customer communications by implementing automatic Email notifications to inform customers on progress of cryopreservation of deposited mouse mutants

EMMA customer services and communication were further improved by appointing an additional part-time project manager and additional members for the Evaluation Committee to speed up the submission / evaluation process.

To encourage submissions of valuable mouse strains while the submitting investigator awaits publication of the first paper describing the strain a ‘Grace Period’ was implemented. In such cases a delayed release of the strain to the public website for a period of up to two years can be granted.

Furthermore, the operation was improved by the implementation of a new method called cryo IVF or speed cryopreservation which is more rapid and cost effective than in vivo production of embryos and works well for strains carrying spontaneous and induced mutations, such as targeted mutations. It involves the use of in vitro fertilization (IVF) using mutation-carrying males as sperm donors and females from a standard inbred strain as oocyte donors.

A major change for the EMMA operation was the implementation of a cost recovery based distribution system. Since July 2008 shipments of frozen embryos/sperm cost €1100, while live mice are distributed for a cost of €1700. The €1700 covers the provision of a breeding nucleus of up to three pairs of SPF mice. This new pricing structure was introduced because with the end of funding for distribution in EMMAinf (JRA2) in June 2008, EMMA's distribution costs were no longer subsidised. The charges levied by EMMA are used solely to meet the animal husbandry and stock replacement costs. A cost recovery based distribution system is a major step forward towards a more sustainable funding and operation of the EMMA repository.

Public Relations / Dissemination of Knowledge

Aims of the EMMA PR and dissemination activities are to increase the name recognition of EMMA and to provide information on the available EMMA services and resources. Public Relations are regarded as a high priority by the EMMA management and accordingly a broad range of measures were used in EMMAinf to promote the activities of EMMA such as:

- Cryocourses
- Web based activities - EMMA website
- Web based activities - Email lists
- Presentation of EMMA by talks and posters at conferences
- Distribution of brochures
- Publications / Reviews in Scientific Journals
- Advertisements
- Distribution of EMMA calendars
- Co-promotion of EMMA with other networks / societies

Cryocourses

Annual EMMA cryopreservation courses were organised by CNR, MRC (EMMAinf funded) and CNRS (INSERM funding) to teach basic and advanced techniques in cryopreservation for banking of mouse mutant strains. During the course of EMMAinf a total of 16 cryocourses were organised by EMMA partners of which 10 were EMMAinf funded. The courses were attended by 109 participants from 16 European countries.

Dissemination via the EMMA website at www.emmanet.org

The EMMA resource database (RDB) and the public EMMA homepage at www.emmanet.org are the most important and efficient tools to provide information about EMMA to the scientific community. The EMMA website is the entry point for the scientific community to the virtual EMMA network and was completely revised during the EMMAinf project. The list of available strains on the public EMMA homepage is being updated daily to provide the latest information on the available stock collection to the scientific community.

Presentation of EMMA by talks and posters at conferences / Publications

A further and widely used means to advertise the available EMMA services and resources were presentations at major mouse genetics meetings such as the annual Mouse Molecular Genetics Meetings and the IMGS Mouse Genome Conferences but also at general genetics conferences and meetings on research infrastructures. During the course of the EMMAinf project the EMMA network was presented by a total of 61 talks and 20 poster presentations. In addition, EMMA services and resources were described in reviews.

Advertisements

The EMMA network was also advertised in magazines such as the Parliament Magazine and the Public Service Review which are widely distributed within government departments, directorates and agencies in the regional and central governments of the 27 EU Member States. The readership is across all member states and is in excess of 25000.

Calendar

In 2005 and 2007 EMMA produced and distributed 1500 calendars to EMMA customers and potential new customers worldwide. The calendar provides artistic images of cryopreservation technology and information on the EMMA network and services.

The EMMAinf PR and dissemination activities are comprehensively summarised on page 44 in the chapter on USE AND DISSEMINATION OF KNOWLEDGE.

Integration of new EMMA partners

The EMMA archive and the workload for distributing mutant mouse strains are rapidly growing. Due to large scale mutagenesis projects such as EUCOMM the number of strains archived by EMMA is likely to double within the next three to four years. In order to share the increasing workload new members will be incorporated into the EMMA network and guidelines for this process were established. The selection process of prospective new members must be carefully designed to establish a structure and organisation of the EMMA network that will allow an effective management, ensures highest quality standards and cost efficiency, a centralisation on national levels and the required capacity and the appropriate coverage throughout the European Research Area. Rules for taking on prospective new members into the EMMA network were discussed by the EMMA BPD and summarised in the report of the ESFRI BMS roadmap working group report in summer 2006 (see page 41 at ftp://ftp.cordis.europa.eu/pub/esfri/docs/bms-report-roadmap-wg-2006_en.pdf).

Following the established guidelines, in 2008 three new partners were integrated into the existing EMMA network structure, namely the Sanger Institute (Hinxton), the ICS Mouse Clinical Institute (Straßbourg) and the CNB-CSIC (Madrid). The integration was facilitated via a Cooperation Agreement which was signed by all existing and the new partners. This agreement outlines in detail the organisational structure, decision making processes and principles of operation of EMMA. Furthermore this agreement represents a framework that allows integration of additional partners into the EMMA network. The EMMAinf partners and the new members of the EMMA network have a track record of successful collaboration in a number of other European projects such as EUCOMM, EUMODIC and INFRAFRONTIER.

Integration of the new partners was facilitated by their active participation in the EMMAinf project meetings of the fourth reporting period. The new partners also participated in the preparation of a new project proposal that was submitted following the third call of the EC FP7 Capacities Specific Program. The proposal was positively evaluated and a grant agreement negotiated. The EMMAservice project started in 2009 and will allow the enlarged EMMA network the continuation of the work carried out in EMMAinf.

On the occasion of an additional EMMA Board of Directors meeting which was held on January 10th 2008 in Munich Martin Hrabè de Angelis was elected as EMMA Director by all members of the enlarged EMMA network according to the guidelines established in the EMMA Cooperation Agreement.

Business Development / International Collaborations

A central objective of the EMMA management activities were to secure further growth of the EMMA archive by ensuring that EMMA is involved and partner in new large scale mouse functional genomics projects. Further developments of EMMA focussed also on a diversification of the EMMA service portfolio and integration of EMMA into an international network of repositories. A continued and sustainable funding of the EMMA repository was also addressed by the EMMA management.

Involvement of EMMA in other European research programmes

1) EUCOMM (The European Conditional Mouse Mutagenesis Program)

The EUCOMM project started in January 2006. The project was set up as a 3 year project but has now been cost neutrally extended till December 2011. The scientific and technological objectives of EUCOMM are:

- Establish a collection of 20000 mutations in ES cells by conditional gene trapping and gene targeting approaches
- Establish 320 mutant mouse lines from EUCOMM ES cell resource
- Collect existing and establish novel Cre-lines
- Develop EUCOMM database
- Disseminate EUCOMM material

EMMA's primary role in this project is the quality control of the EUCOMM ES cell resource. The quality will be assessed by establishing 320 mouse knock-out lines from selected ES cells. Involved in this EUCOMM subproject 'mouse production, archiving and dissemination' are the EMMA partners HMGU, the MRC-MGU, CNR-IBC, the ICS Mouse Clinical Institute and the Wellcome Trust Sanger Institute. The mouse production centers will convert EUCOMM ES cell lines to chimaeric mice and breed heterozygous mutants. Frozen embryos will be produced from the KO mice. Archiving and distribution of these lines will be handled via EMMA using established procedures and quality controls. In addition, EMMA will be in charge of archiving and distributing the Cre-lines established by the EUCOMM project. Archiving of the EUCOMM mouse resources is not funded by the EUCOMM project.

While first ES clones were established in the 129P2 strain, the ES cell line and mouse production is now using the C57BL/6N mouse strain. A current progress summary is available on the EUCOMM website at http://www.eucomm.org/htgt/welcome

Progress Summary

Number of genes with EUCOMM products available:

Conditional Product Type	No. of Genes
Mice	201
Targeted ES Cells	1021
Targeting Vectors	2838
Gene Trap ES Cells	4565

For about 200 mouse mutant lines produced from the EUCOMM ES cell resource germ line transmission has been established. Archiving of these lines is ongoing. All mouse production centers agreed to make mouse mutant lines available to the community as soon as germ line transmission has been established and while the cryopreservation is ongoing, provided that sufficient mice are available. Issues such as the nomenclature of the EUCOMM resources and the MTA for distribution of the resources were resolved. Strain data were imported into the EMMA database in January 2009 and EUCOMM mice can now be ordered via EMMA.

The involvement in EUCOMM is of central importance for the EMMA network. EUCOMM is focussing on conditional KO lines and these are among the most highly demanded strains from the EMMA archive. Therefore, the EUCOMM project will significantly increase the value of the EMMA archive. Furthermore, the EUCOMM project may broaden the EMMA service portfolio as the production of KO mouse lines from the EUCOMM ES cell resource may be incorporated into the EMMA service portfolio.

2) EUMODIC - The European Mouse Disease Clinic
A distributed phenotyping resource for studying human disease
The EUMODIC programme is a European research project that commenced with the Kick-off meeting in February 2007. EUMODIC will undertake a primary phenotype assessment of up to 650 mouse mutant lines. In addition, a number of these mutant lines will be subject to a more in depth secondary phenotype assessment. The EUMODIC consortium is made up of 18 laboratories across Europe who are experts in the field of mouse functional genomics and phenotyping and have a track record of successful collaborative research in EUMORPHIA. Primary phenotype assessment will be undertaken in four large-scale phenotyping centres at the Helmholtz Zentrum München (HMGU), the ICS Mouse Clinical Institute (Straßbourg), MRC-MGU (Harwell) and the Sanger Institute (Hinxton). All centres are partners of the EMMA network. Mutant mouse lines will be made available from the EUCOMM project. The 4 primary phenotyping centres (along with CNR, Monterotondo) are funded by EUCOMM to produce 320 mouse lines from the EUCOMM ES cell resource. EUMODIC will match this activity to produce up to 650 lines during the course of the programme. Embryos will be archived by EMMA from each mutant line for distribution to secondary phenotyping centres and wider dissemination to the genetics community. Archiving is not funded by the EUCOMM and EUMODIC projects.

As outlined for EUCOMM also the EUMODIC project will add significant value to the EMMA archive. Both projects will provide a total of 650 KO mouse lines to the EMMA archive. A scientific advisory board will ensure that ES cell lines with null mutations in medically and biologically relevant genes will be selected for mouse production. In addition to the physical resource foremost the available phenotype data generated by the EUMODIC programme will make the KO lines highly valuable to the scientific community. Cohort production of mouse mutant lines produced from the EUCOMM ES cell resource for phenotyping in the mouse clinics is currently under way. First phenotype data of 31 mutant lines are available and displayed at the Sanger Mouse Resource Portal at http://www.sanger.ac.uk/cgi-bin/modelorgs/mgc/index.cgi indicating the comprehensive data that will be linked to these mouse mutant lines.

The EUCOMM and EUMODIC projects will be complemented by the Sanger Institute's **Mouse Genetics Program (MGP)** which aims to produce and phenotype up to 1000 mouse mutant lines. MGP resources will be distributed via EMMA.

3) CASIMIR (http://www.casimir.org.uk/)
CASIMIR is a coordination action of the 6th Framework Programme of the European Commission and focussing on co-ordination and integration of databases set up in support of FP5 and FP6 projects containing experimental data, including sequences, and material resources such as biological collections, relevant to the use of the mouse as a model organism for human disease. CASIMIR was launched in March 2007 with a Kick-off meeting which was held in Hinxton (UK). EMMA representatives joined the CASIMIR annual meetings in November 2007 (Rome) and December 2008 (Stockholm) as well as work package specific meetings. On the occasion of the progress meeting in Corfu (October 2007) the EMMA resource database was presented as a contribution to the CASIMIR work package 7 (WP7) activities. WP7 of the CASIMIR programme is concerned with the integration of biological resources into the data network. The EMMA database has been identified as one of the initial databases that are to be used for pilot work on database integration. The CASIMIR work

package concerned with database integration is led by Damian Smedley who joined EMMA as leader of the IT group in October 2007.

4) ESFRI (European Strategy Forum on Research Infrastructures)

Another major activity of the EMMA management is to secure long term funding of the EMMA repository. Accordingly, members of the EMMA Board of Directors and the EMMA Advisory Board play active roles in the ESFRI process. ESFRI was launched in April 2002 as the Strategy Forum on Research Infrastructures (RI) which brings together representatives of EU Member States and Associated States, appointed by Ministers in charge of Research, and one representative of the European Commission. ESFRI's objective is to identify and to address the scientific needs of research infrastructures in Europe for the next 10-20 years (potential new RI or major upgrade of existing RI). In its role as stimulator and incubator ESFRI will strengthen European research capacities and establish them permanently in a world leading position. On October 19th 2006, ESFRI published the "European Roadmap for Research Infrastructures" which identifies new research infrastructures of pan-European interest corresponding to the long term needs of the European research communities, covering all scientific areas regardless of possible location. The ESFRI Roadmap is the result of an intensive two-year consultation and peer review process involving over 1000 high level European and international experts. The ESFRI Roadmap was updated in September 2008.

The 2006 Roadmap identified 35 large scale infrastructure projects, at various stages of development, in seven key research areas. Within life sciences six projects were identified. EMMA plays a key role in one of these projects termed 'INFRAFRONTIER: Functional genomics in the Mouse as a model of human disease'. The roadmap projects were eligible to apply for funding in the first call "construction of new research infrastructure (or major upgrades) – preparatory phase" in the Capacities Specific Programme of the EC Seventh Framework Programme. Accordingly, the EMMA Director Martin Hrabè de Angelis coordinated the 'INFRAFRONTIER' proposal which was submitted to the European Commission in May 2007. The INFRAFRONTIER project was positively evaluated and a grant agreement negotiated. The INFRAFRONTIER project started in March 2008 (www.infrafrontier.eu).

Infrafrontier project summary

'Medically related Life Sciences use the mouse as a model system to understand the molecular basis of health and disease in humans (>95% similarity of genes in humans and mice). An essential task for Biomedical Sciences in the 21st century will be the functional analysis of mouse models for every gene in the mammalian genome. The major bottlenecks identified by the user community will be proper characterization (Mouse Clinics), archiving and dissemination of mouse disease models to the research laboratories. The current capacities, governance structures and funding strategies of existing infrastructures will not be able to serve the upcoming urgent needs. Thus it is imperative to organise and establish now an efficient distributed infrastructure for the phenotyping, archiving and dissemination of mouse models on a well concerted, large-scale and pan-European level. This will be a prerequisite for maintaining Europe's leading role in the functional annotation of the mouse genome. Infrafrontier will guarantee the accessibility of mouse models and will be essential to facilitate their exploitation. Infrafrontier integrates 15 European laboratories with exceptional track records to implement and run large-scale infrastructures'.

The Infrafrontier preparatory phase aims to organise a stable and sustainable infrastructure by 1) the identification of the most suitable legal form, 2) developing a business plan based on a

sustainable funding concept, 3) reaching a legal agreement between all partners and 4) providing a strategic plan for the construction phase.
Following the Infrafrontier Kick-off meeting, further meetings were organised to discuss these central strategic, financial and legal issues within the consortium and with other BMS roadmap projects. The Infrafrontier project is of central importance for EMMA as one of the key goals is to develop a sustainable funding concept.

5) EMMAservice

To ensure the continuation of the EMMA activities carried out in EMMAinf, the EMMA network, including the three new partners who joined the network in 2008, submitted a project proposal entitled EMMAservice in response to the third call of the EC FP7 Capacities Specific Program. The proposal was positively evaluated and a grant agreement negotiated. The EMMAservice project started in January 2009.

Building on EMMA's previous achievements as the primary mouse repository in Europe, EMMAservice aims to meet the future challenges presented by archiving and disseminating mouse models in the ERA as follows:
- Archiving of 1224 new mouse mutant lines in support of individual depositors and also European mouse genetics programmes
- Support of eligible customers with free of charge Transnational Access for up to 20% of requested mouse resources.
- Technology development will underpin the archiving and distribution efforts by advancing current sperm freezing technology
- Training courses will promote the shipment of frozen germplasm rather than live mice
- EMMA informatics will support user services by setting new standards for user friendly accession of EMMA services, extensive data curation and cross referencing with other mouse database resources
- Outreach efforts to attract users will be widened and addressed at the translational research community

EMMAservice will contribute significantly to the development of a world leading repository and European capacity in mouse disease model archiving and distribution, supporting the needs of the wider European biomedical research community.

In addition to its involvement in major new European research programmes EMMA is involved in a project with the Wellcome Trust.

Wellcome Trust Project
Knockout Mice and Phenotypic Data from Deltagen and Lexicon

The Wellcome Trust has negotiated and may fund the acquisition of up to 200 gene knockout mouse strains and associated phenotypic data from Deltagen Inc and Lexicon Genetics Inc. This resource, which will be archived and distributed through EMMA, will provide researchers with unprecedented access to two private collections of knockout mice, providing valuable models for the study of human disease. Such comprehensive information on such a large group of mice is expected to greatly accelerate efforts to explore gene functions in health and disease. A similar project was run in the US where the NIH provided funds for the acquisition of 251 mouse mutant lines from the Deltagen and Lexicon collection. Mouse mutants and associated phenotype data are made available via the Jackson Lab and the

MMRRC repositories. A fact sheet regarding this initiative is available at http://www.nih.gov/science/models/mouse/deltagenlexicon/factsheet.html.

To implement this project the HMGU signed contracts with Deltagen, Lexicon and the Wellcome Trust and subcontracted the other EMMA partners involved in the project (MRC-MGU and CNRS-CDTA). Following this, the Trust launched a first and subsequently also a second call for proposals which offers researchers the opportunity to nominate mouse lines of the Deltagen / Lexicon collections for purchasing by the Trust (http://www.wellcome.ac.uk/Professional-resources/Biomedical-resources/Model-organisms/WTD025941.htm). The first two calls for proposals resulted in the purchasing of 86 mouse mutant lines and associated phenotype data. During the course of the EMMAinf project the Deltagen / Lexicon resources were transferred to the involved EMMA partners. Mice were re-derived from the provided frozen embryos and / or sperm and then mutant lines were re-archived. Re-derived mice were made available for distribution via the EMMA website http://www.emmanet.org/mutant_types.php. The available phenotype data are accessible via the respective strain description pages e.g. at http://www.emmanet.org/deltagen/DELTAGEN_T1228/. Mutant lines from the Deltagen and Lexicon collections are frequently requested from the EMMA repository.

In addition, to securing its own growth, development and diversification, EMMA, as a founding member of FIMRe (Federation of International Mouse Resources) continues to play a leading role in this global network of resource centers.

FIMRe

In April 2005 EMMA hosted a meeting in Rome, where FIMRe, an affiliation of 17 major resource centers from four continents was officially founded. Members of the EMMA Board of Participating Directors and Activity Group Leaders are playing leading roles in all FIMRe working groups. The EMMA Director acts as FIMRe vice chair representing Europe.

FIMRe's overall goal is to ensure availability, assure quality, promote sharing and preservation of genetically defined mice, and disseminate information, affiliated resources, and expertise in their use to the global biomedical research community. FIMRe's organisation, mission and goals were described in a publication of the FIMRe Board of Directors in Mammalian Genome (Volume 17, p 363 – 364, 2006).

In order to move FIMRe forward to implementation and to facilitate the exchange of resources among repositories an 'Agreement for International Recovery of Cryopreserved Mouse Strains from Repositories' was drafted by the legal department of the Jackson Laboratory. This document was subsequently modified and four EMMA partners were among the first FIMRe members who signed this agreement with the Jackson Laboratory. Following this, several EMMA partners negotiated and signed further agreements with the MMRRC repository at the UC Davis, BRC RIKEN in Tsukuba, the MMRRC repository in Chapel Hill and the Canadian CMMR. These contracts will provide European researchers via EMMA an easier access to the valuable and growing collections of mouse mutant lines at major repositories and in addition support the global distribution of the EMMA mutant mouse resources. In fact, in the fourth reporting period, based on the signed Cryo Recovery Agreements, frozen embryos from the MRC-MGU were sent to RIKEN where mice were re-derived for the Japanese customer.

1.5 NETWORKING ACTIVITIES

1.5.1 Activity N2: Meetings and visits
Final report N2 (reporting period 7/2004 – 12/2008)

Objectives: Organise regular project meetings with joined and separate meetings of the Board of Directors (BPD) and the Technical Working Group (TWG) to discuss project progress, technical and strategic issues. Project meetings foster a culture of cooperation between all partners of the virtual EMMA network and support the development of a corporate identity.

Deliverables: Organise eight project meetings and four annual Advisory Board meetings. In addition a total of 16 visits of partner facilities by the EMMA Director or the Project Manager was foreseen but revised to the organisation of additional meetings of TWG members.

During the course of the EMMAinf project eight project meetings were held mainly at the core facility in Monterotondo but also alternating at other EMMA nodes. This project deliverable has been fulfilled. Minutes of the project meetings were summarised in the annexes-1 of the periodic reports and are available for download from the internal EMMA website. An additional BPD meeting was held on January 10th in Munich to discuss new project proposals, the extension of the EMMAinf project and an amendment of the technical annex.

At EMMAinf meetings held in the first project period the need for additional specific meetings of the different activities and work packages has been recognised. Accordingly, the EMMA database group (including the Project Office) met an additional four times to discuss priorities for the further development of the EMMA resource database. In addition, the IT group organises regular telephone conferences. The JRA1 and JRA2 activity leaders met in November 2007 and October 2008 with AGL members of the CNR site in Monterotondo on the occasion of the EMMA cryocourses to discuss specific issues of these work packages. In the fourth reporting period a first 'germ-free' service workshop was held in Oeiras (September 2008). In addition to the Gulbenkian Institute providing this service, representatives from the CNRS Orleans and the MRC-MGU and the Project Office participated. The EMMA node in Orleans has extensive experience in Gnotobiology but is not offering this as a service via EMMA. The MRC is currently building up Gnotobiology expertise. At the meeting experience in QC, sterilisation procedures and health monitoring etc. was exchanged. In addition, possible collaborations between the centers e.g. maintaining demanded lines as backups and technicalities of shipping germ-free mice between the EMMA nodes generating and maintaining germ-free mice were discussed. Thus, also the revised deliverable of organising additional meetings focussing on technical and IT issues has been fulfilled.

At the 6th, 7th and 8th EMMAinf meeting representatives of the new EMMA partners ICS, Sanger and CNB joined the meetings as first steps towards integration.

As originally foreseen the Project Manager visited the EMMA partner sites in Harwell and Orleans (October 2005) to discuss requirements for the further development of the EMMA database.

A dedicated Advisory Board (AVB) and Board of Directors (BPD) meeting was not organised during the course of EMMAinf.. However, the coordinator, the EMMA Director and the Project Officer met members of the Advisory Board regularly at conferences, e.g. at the International Mouse Genome Conference and at ESFRI meetings and discussed on these occasions issues related to EMMA. Therefore, the overall objective and function of the AVB was not affected as members of this Board regularly discussed progress of the EMMAinf project with members of the BPD.

All deliverables fulfilled under the EMMAinf N2 activity are summarised in table 3.

Date	**Title/subject of meeting/ workshop**	**Location**	**Number of attendees**	**Website address**
20-21/01 2005	1st BPD and AGL meeting	Rome	22	http://internal.emmanet.org
23-24/06 2005	2nd BPD and AGL meeting	Stockholm	22	http://internal.emmanet.org
10/ 2005	Visit of EMMA node Harwell	Harwell	3	
10/ 2005	Visit of EMMA node Orleans	Orleans	3	
30/11 - 1/12 2005	3rd BPD and AGL meeting	Rome	23	http://internal.emmanet.org
8 – 9/05 2006	4th BPD and AGL meeting	Harwell	28	http://internal.emmanet.org
22 – 23/06 2006	AGL (JRA1, JRA2) meeting	Rome	3	
14 - 15/12 2006	5th BPD and AGL meeting	Rome	27	http://internal.emmanet.org
27 - 28/6 2007	6th BPD and AGL meeting	Oeiras	29	http://internal.emmanet.org
13 – 16/11 2006	AGL (JRA1, JRA2) meeting	Rome	3	
20/9 2006	AGL (JRA4 meeting)	Rome	3	
27/9 2006	AGL (JRA4 meeting)	Hinxton	7	http://internal.emmanet.org
13 - 14/12 2007	7th BPD and AGL meeting	Rome	26	http://internal.emmanet.org
10/1 2008	BPD meeting	Munich	13	http://internal.emmanet.org
20 - 21/10 2008	8th BPD and AGL meeting	Munich	26	http://internal.emmanet.org
5 – 6/11 2007	AGL (JRA4) meeting	Munich	7	http://internal.emmanet.org
3 – 4/4 2008	AGL (JRA4 meeting)	Hinxton	5	http://internal.emmanet.org
18 – 19/9 2008	AGL (JRA3 meeting)	Oeiras	8	http://internal.emmanet.org

Table 3: Meetings organised under activity N2

1.5.2 Activity N3: Dissemination of knowledge
Final report N3 (reporting period 7/2004 – 12/2008)

Objectives: Dissemination of knowledge available in the EMMA consortium by organising cryocourses and PR activities to advertise the available EMMA services and resources.

Deliverables: 1) Organisation of five cryocourses at CNR and after a budget reallocation an additional 5 courses at MRC 2) Participation of the EMMA Director or the Project Manager in 16 international conferences 3) Advertisements in journals or magazines

EMMA cryopreservation courses
The annual EMMA cryopreservation courses were organised by CNR, MRC (EMMAinf funded) and CNRS (INSERM funding) to teach basic and advanced techniques in cryopreservation for banking of mouse mutant strains. Several methods for cryopreservation of mouse embryos, gametes and ovaries are presently available and no single method is adequate for all the various strains of mice being developed. Therefore, a variety of methods must be taught. The setup and performance of state of the art, comprehensive, theoretical and practical courses on cryopreservation of mouse embryos and gametes is essential to disseminate the most advanced techniques on embryo handling, *in vitro* fertilisation, sample cryopreservation, thawing and culture, quality control and database management.

The schedule and general plan of the Monterotondo courses were set up by CNR in collaboration with the Jackson Laboratory and the members of the course faculty. In addition, to the joint effort of the main EMMA cryocourse, which is held by scientists of the Jackson Lab and EMMA, the MRC-MGU is hosting additional cryocourses which are exclusively organised by EMMA scientists. In addition, the French EMMA node in Orleans offered courses in cryobiology. All courses were announced on the public EMMA web site (http://www.emmanet.org/about/courses.php).

During the course of EMMAinf a total of 16 cryocourses were organised by EMMA partners of which 10 were EMMAinf funded. The courses were attended by 109 participants from 16 European countries. The EMMAinf funded courses are listed in table 4, page 24 .

Public Relations activities
Participation in international conferences
A further and widely used means to advertise the available EMMA services and resources are presentations at major mouse genetics meetings such as the annual Mouse Molecular Genetics Meetings and the IMGS Mouse Genome Conferences but also at general genetics conferences and meetings on research infrastructures. During the course of the EMMAinf project the EMMA network was presented by a total of 61 talks and 20 poster presentations, mainly by the EMMA Director and the Project Manager. The presentations reported under the EMMAinf activity N3 are listed in table 4.

Deliverable/ Milestone No.	Deliverable/Milestone Name	Lead Contractor	Achieved (in months)
D1	2004 EMMA Cryo-Course	1/CNR.IBC	November 2004
D2	2004 18th International Mouse Genome Conference (Seattle)	6/HMGU	Oct. 2004
D3	General Assembly Eumorphia, Madrid, Spain (16 - 18th of March 2005).	6/HMGU	March 2005
D4	2004 ISAG meeting, Tokyo	6/HMGU	Sept 2004
D5	2004 FENS Forum Meeting, Lisbon	6/HMGU	July 2004
D1	2005 EMMA Cryo-Course	1/CNR.IBC	November 2005
D2	2005 19th International Mouse Genome Conference (Straßbourg)	6/HMGU	November 2005
D3	Mouse Molecular Genetics Meeting, Heidelberg	6/HMGU	September 2005
D4	EuroMouse Conference Venice	6/HMGU	October 2005
D5	General Assembly Eumorphia, Barcelona, Spain	6/HMGU	February 2006
D1	2006 EMMA Cryo-Course	1/CNR.IBC	November 2006
D1	2006 EMMA Cryo-Course	3/MRC	August 2006
D1	2007 EMMA Cryo-Course	3/MRC	January 2007
D2	2006 20th International Mouse Genome Conference (Charleston)	6/HMGU	November 2006
D3	Mouse Molecular Genetics Meeting, CSHL	6/HMGU	September 2006
D4	1st MUGEN Conference Athens	6/HMGU	October 2006
D5	ECRI meeting, Hamburg	6/HMGU	June 2007
D1	2007 EMMA Cryo-Course	1/CNR.IBC	November 2007
D1	2008 EMMA Cryo-Course	1/CNR.IBC	October 2008
D1	2007 EMMA Cryo-Course	3/MRC	August 2007
D1	2008 EMMA Cryo-Course	3/MRC	January 2008
D1	2008 EMMA Cryo-Course	3/MRC	August 2008
D2	2007 21st International Mouse Genome Conference (Kyoto)	6/HMGU	Oct / Nov 2007
D2	2008 22nd International Mouse Genome Conference (Prag)	6/HMGU	November 2008
D3	Mouse Molecular Genetics Meeting, Hinxton	6/HMGU	September 2007
D4	2nd PRIME EUROMOUSE Meeting, Heathrow	6/HMGU	July 2007
D4	3rd ESF Meeting on Functional Genomics, Innsbruck	6/HMGU	October 2008
D5	ICG, Berlin	6/HMGU	July 2008
D7	EMMA advert in Parliament Magazine and in the Public Service Review	6/HMGU	Dec 2007 Sept 2008

Table 4: Deliverables fulfilled under activity N3

Advertisements

In addition to promoting EMMA and its services at scientific meetings the EMMA network was also advertised in magazines such as the Parliament Magazine and the Public Service Review. The Parliament Magazine has been published for the last 10 years and regularly works with EU co-funded projects when they wish to run dissemination and mainstreaming messages to the 12,000 readers in the European Parliament, European Commission and throughout the EU. On December 10th 2007 a special Research Review was published. In addition to the standard readership it was also distributed to 5000 Research heads and was made available at high profile European Commission research events throughout 2008. http://www.e-pages.dk/dods/16/ Two page EMMA advertisement on pages 18 and 19

The EMMA Network

European Mouse Mutant Archive

Using mice as models of human disease
On the way to evidence based medicine

The relevance of the mouse as a model of human disease

The mouse shows great similarities in development, physiology and biochemistry to humans. This makes it a key model for research into human disease. It also has a very similar genetic make-up. The identification of all the genes in mice and humans in the Human Genome Project has shown that about **99% of the genes in mice have a homologue in humans.** This is important as, to date, around 5000 human diseases have been shown to be caused by an error in our genetic make-up, for example: Cystic fibrosis and Down syndrome. In numerous other diseases, as in diabetes, genetics is a contributory factor. The similarity of the mouse and human genetic make-up means that genes associated with disease in humans can be investigated in mouse models. Conversely, fundamental research using mouse models can identify genes associated with disease. This knowledge can then be transferred to understanding and treatment of disease in humans.

The key challenge for mouse functional genomics in the 21st century will be the generation of a mutant mouse for each gene in the mouse genome. By the collaborative effort of the International Mouse Knockout Consortium more than 30000 mutations in ES cells will be engineered and thousands of mouse disease models will become available over the next years. The bottleneck for the exploitation of this valuable resource will be access to a systematic functional and molecular characterisation. In addition, mouse models should be preserved and made available to the entire European mouse genetics, biomedical and translational research community which is strongly dependent on new mouse disease models.

EMMA – The European Mouse Mutant Archive is a resource centre for the deposition and distribution of mouse disease models and research tools. Mouse mutant lines are stored as frozen embryos or sperm and the most demanded lines are kept as live mice. The EMMA network is a non-profit making organisation and is currently comprised of ten partners who operate as the primary mouse repository in Europe. EMMA is funded by the participating institutes and the European Commission Research Infrastructures Programme.

Objectives of EMMA

- Develop a world class repository for maintaining and distributing mutant mouse strains
- Develop a dedicated resource database containing data of cryopreserved mouse strains
- Organise courses in cryopreservation
- Develop links and common procedures with other repositories worldwide

Access and submission to the EMMA repository

All applications for archiving and requests for mutant mouse strains are submitted through the EMMA website at http://www.emmanet.org. Since its inception the number of mutant mouse strains submitted to EMMA and the number of requests has steadily increased. Up-to-date more than 1300 mouse mutant lines were submitted to EMMA and nearly 800 requests of customers worldwide were fulfilled by the EMMA network. Among the mutants archived by EMMA are targeted mutant strains including numerous Cre-expressing lines and knock-outs, transgenic lines and ENU-induced mutant strains. Phenotypes of archived strains cover neurological defects, hearing defects and strains with skeletal malformations among many others.

Value for research community

The mouse is the key model organism to study mammalian gene function mainly due to its excellent genetics and a plethora of available mutants modelling human diseases. These **mouse mutants offer the opportunity to decipher molecular disease mechanisms and provide a basis for the development of diagnostic, prognostic and therapeutic strategies.** Therefore it is essential that these valuable resources are retained in a central repository from which they can be readily made available to interested investigators. Thus EMMA plays a crucial role in exploiting the potential benefits to human health presented by the research in mammalian genetics.

Infrafrontier - The European Infrastructure for phenotyping and archiving of model mammalian genomes (www.infrafrontier.eu)

Existing facilities across Europe can only offer capacity for the phenotype analysis, archiving and dissemination of a few hundred disease models per year. Thus it is imperative to organise and establish now an efficient distributed infrastructure for the phenotyping, archiving and distribution of mouse models on a well-concerted, large-scale and pan-European level. This will be a prerequisite for maintaining Europe's leading role in the functional annotation of the mouse genome. Infrafrontier will organise two complementary European infrastructure networks for large scale, systemic phenotyping in mouse clinics (Phenomefrontier) and for archiving and dissemination (Archivefrontier) of mouse models. EMMA will co-ordinate Archivefrontier.

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ADVERTISEMENT

A similar advert was published in the Public Service Review: European Union, Issue 16 in September 2008, pages 350 to 351. In addition, EMMA was advertised on the outside back cover of this issue. The review is distributed free of charge, by name, to individuals within government departments, directorates and agencies in the regional and central governments of the 27 Member States. The readership is across all member states and is in excess of 25000.

The deliverables defined for activity N3 were fulfilled and are listed in table 4. It has to be noted that in addition to the five cryocourses originally planned, an additional 11 courses were offered during the EMMAinf project. EMMA is indeed the most active provider of cryocourses worldwide. Furthermore, EMMA was advertised by 81 presentations, 5 times more than the contractual deliverables. Also a number of diverse measures were used to promote the EMMA services in addition to advertisements in magazines. A comprehensive list and description of all EMMA PR activities is given in the chapter on Use and Dissemination of Knowledge page 44.

1.6 JOINT RESEARCH ACTIVITIES

Core EMMA services – archiving and distribution

To control the quality of the EMMA processes Standard Operation Protocols (SOPs) regarding freezing procedures, health status and animal handling were developed (www.emmanet.org). The first control step after a mouse is taken into an EMMA facility is the geno- and / or phenotype verification of the respective mutation (Fig. 2). This is followed by a test freezing of either sperm or embryos. The ability to reconstitute the stock from frozen material will be ascertained at the time the strain is being frozen. A mutant line is considered to be reconstituted as soon as live offspring bearing the appropriate geno- and / or phenotype has been raised to maturity. Health monitoring is performed on all in- and outgoing mouse lines. All mice supplied to the customer have a specific-pathogen-free (SPF) status according to FELASA guidelines.

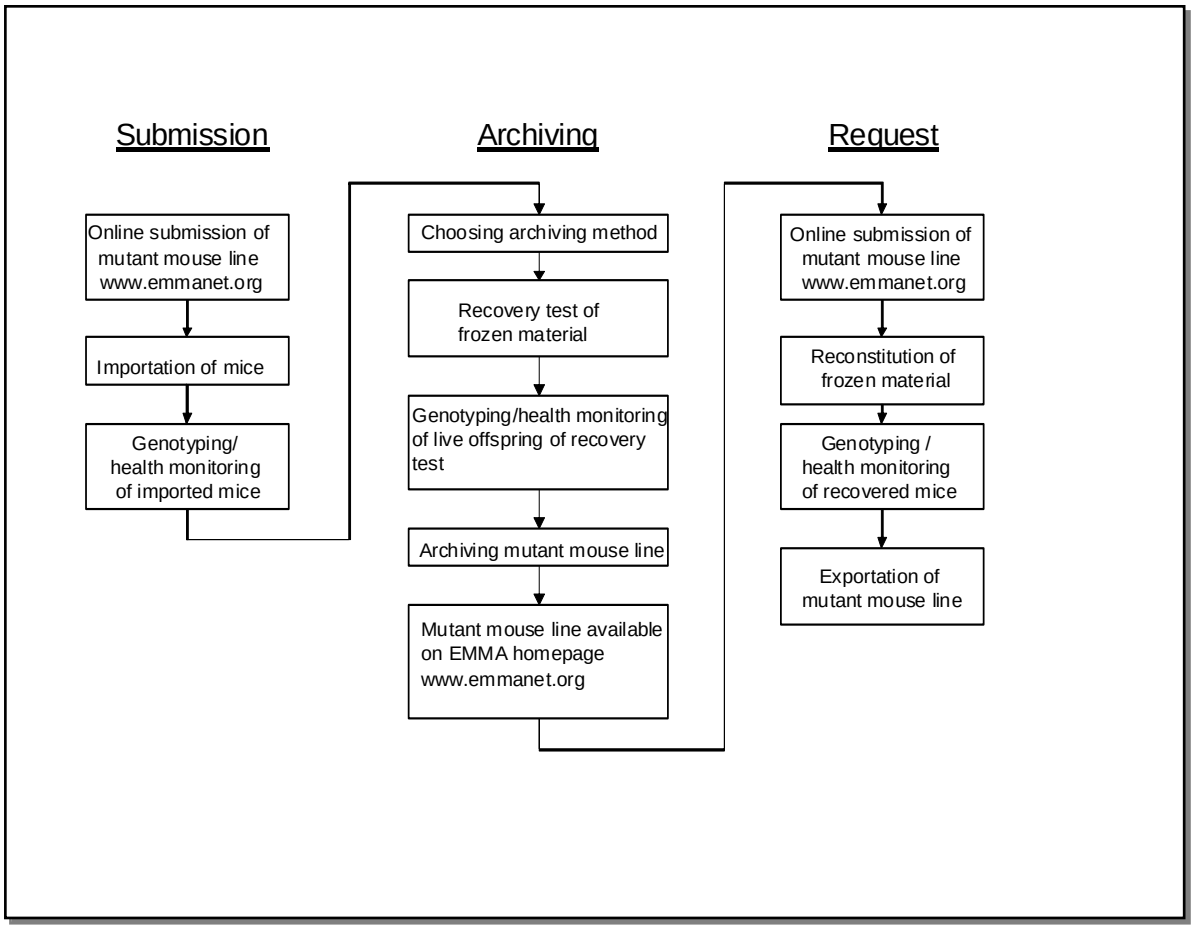


Fig 2: For each mutant mouse line archiving upon submission and / or reconstitution upon request is accurately processed according to the workflow presented

1.6.1 Activity JRA1: Cryopreservation of mutant mouse strains

Description and Objectives

Within this joint research activity the participants aimed to cryopreserve 881 new mouse mutant lines. Only mutant strains of general interest and importance for the scientific community were accepted for the EMMA program. Of special interest were knock-out mice serving as models for human diseases, gene-trap mice and transgenic mouse lines.

Final report JRA1 (reporting period 7/2004 – 12/2008)

The deliverable of this activity for the individual participants was revised with respect to the original implementation plan as part of an amendment of the EMMAinf technical annex. Revised deliverables for the cryopreservation of mouse mutant lines as frozen embryos or sperm for entire EMMAinf project and the project achievements of the participants are:

Participant short name	CNR - IBC	CNRS – CDTA	MRC - MGU	KI	HMGU	Total
Deliverable EMMAinf total	216	210	225	30	200	881
Archived lines	130	188.5	225	29	192	764.5
Lines in progress	53	21.5	-	1	8	83.5
Total EMMAinf project	183	210	225	30	200	848

(Note: For the calculations mutant lines with double/multiple mutations (n = 20) were counted with a factor of 2.5 according to the EMMAinf Annex-I, page 31)

By the end of the EMMAinf project in December 2008 a total of 764.5 (87%) mouse mutant lines were archived by EMMAinf and made publicly available via the EMMA website at www.emmanet.org (20 double/multiple mutants were counted with a factor of 2.5). Additional 83.5 mouse mutant lines were submitted during the course of the EMMAinf project but the cryopreservation of these mutants is not yet finished. Archiving of these lines is expected to be completed by mid 2009 based on average archiving times resulting in a total of 848 archived lines by the EMMAinf program representing 96% of the final deliverable of 881 lines. A complementary report on the lines still in progress will be provided by the end of 2009. The resources needed to finalise the EMMAinf project will be provided by the partners involved. For strains cryopreserved as sperm the average archiving time was about 4 months and for lines archived as embryos 6.5 months (referring to the beginning of the freezing process till a line is quality controlled and publicly listed on the EMMA website). However, in some instances, the cryopreservation of strains as embryos required up to 30 months. Of the 764.5 archived lines 504.5 were archived as embryos, 241 as sperm and for 19 lines, both embryos and sperm were cryopreserved. Of the lines still in the EMMAinf pipeline 76.5 will be frozen as embryos and 7 via sperm.

Archiving of 848 lines by the EMMAinf project (when archiving of lines in the EMMAinf pipeline is finished) is a significant achievement. The slight deviation from the original objective of cryopreserving 881 mouse mutant lines is e.g. due to the rejection or retraction of about 5% of all submission received during the EMMAinf project. Lines were retracted if mice can't be provided because of breeding difficulties. Furthermore it has to be noted that by the EMMAinf project numerous lines were cryopreserved that are generally regarded as

difficult to archive such as homozygous mutants, low fertility strains and double mutants. In such cases the breeding effort involved in the archiving process is far more extensive as in the case of fertile mutants that are archived as heterozygotes. The average archiving time of strains for freezing lines in form of embryos is about 6.5 months. Within EMMAinf lines were cryopreserved where the archiving process took up to 16.5 months at the CNR and up to 30 months at the CNRS due to the technical difficulties outlined above. For some lines the cryopreservation process was terminated for technical reasons. For this report only double/multiple mutants were counted with a factor of 2.5 to reflect the higher effort needed to cryopreserve these lines. Mutants with breeding difficulties were counted with a factor of 1. The enormous effort undertaken to cryopreserve technically challenging lines clearly accounts for the slight deviation of the JRA1 achievement from the final deliverable for this activity.

The EMMAinf project made a significant contribution to the further strong increase in the overall number of submissions to the EMMA archive leading to a total of 1564 submissions by the end of the fourth reporting period. The increase in the overall number of submissions received by EMMA is shown in Fig. 3.

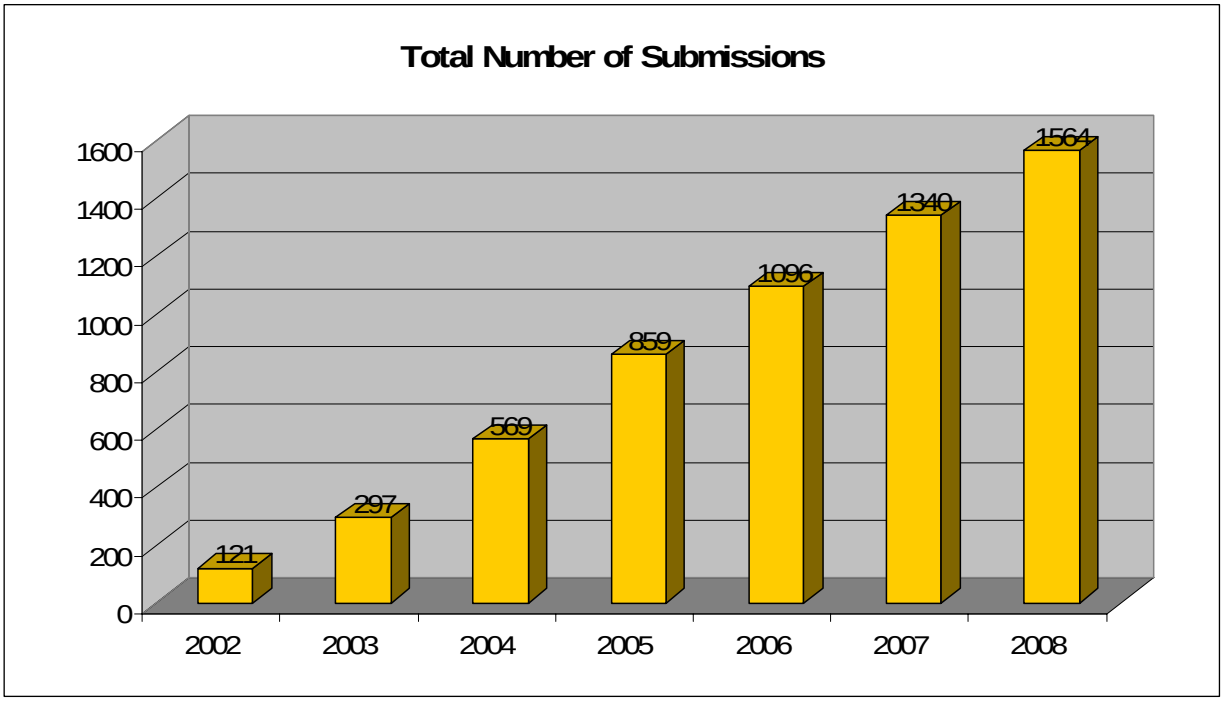


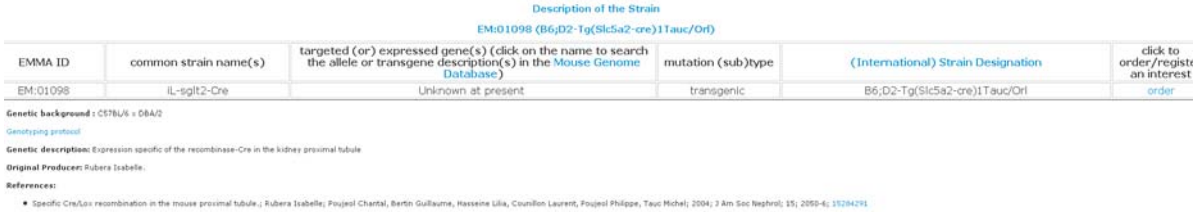
Fig 3: Total number of submissions received by EMMA at end of respective years

The publicly available archive currently consists of 1234 mouse mutant lines. A further 59 mouse mutant lines are archived but covered by a 'Grace Period' and are not yet publicly available. The most prevalent class of mutants are chemically induced mutants (483 lines). The number of transgenic lines and targeted mutant strains increased considerably to 233 lines and 366 strains with targeted mutations, respectively. Among the transgenic lines distributed by EMMA are a growing collection of currently 53 Cre-driver lines some of which comprise the most bestselling strains of the EMMA archive. The most prominent class of targeted mutants are knock-out strains of which currently 271 are distributed to EMMA customers. Phenotypes of archived strains cover neurological defects, hearing defects and strains with skeletal malformations among many others. Several strains representing interesting disease models and valuable Cre-expressing lines that were in high demand were

maintained as live stocks under the EMMAinf JRA2 activity facilitating a fast delivery to the customers.

Among the newly submitted strains are numerous very interesting mouse mutant lines representing human disease models and valuable research tools such as Cre-recombinase expressing strains. Representative examples of bestselling lines submitted and archived during the EMMAinf project are:

EM:01098	**B6;D2-Tg(Slc5a2-cre)1Tauc/Orl**
Specific expression of the Cre recombinase in the kidney proximal tubule	



Description of the Strain

EM:01098 (B6;D2-Tg(Slc5a2-cre)1Tauc/Orl)

EMMA ID	common strain name(s)	targeted (or) expressed gene(s) (click on the name to search the allele or transgene description(s) in the Mouse Genome Database)	mutation (sub)type	(International) Strain Designation	click to order/registe an interest
EM:01098	iL-sglt2-Cre	Unknown at present	transgenic	B6;D2-Tg(Slc5a2-cre)1Tauc/Orl	order

Genetic background : C57BL/6 x DBA/2

Genotyping protocol

Genetic description: Expression specific of the recombinase-Cre in the kidney proximal tubule

Original Producer: Rubera Isabelle.

References:

- Specific Cre/Lox recombination in the mouse proximal tubule.; Rubera Isabelle; Poujeol Chantal, Bertin Guillaume, Hasseine Lilia, Counillon Laurent, Poujeol Philippe, Tauc Michel; 2004; J Am Soc Nephrol; 15; 2050-6; 15284291

EM:01822	**Langerin-DTREGFP**
Knock-in of an EGFP cassette into the 3'UTR of the mouse Langerin gene	

EM:01822 (Langerin-DTREGFP)

EMMA ID	common strain name(s)	targeted (or) expressed gene(s) (click on the name to search the allele or transgene description(s) in the Mouse Genome Database)	mutation (sub)type	(International) Strain Designation	click to order/registe an interest
EM:01822	Langerin-DTREGFP	CD 207 antigen	targeted/knock-in	Langerin-DTREGFP	order

Genetic background : C57BL/6J

Phenotype description: none

Genotyping protocol

Genetic description: An IRES-EGFP cassette was targeted into the 3'UTR of the mouse Langerin gene.

Original Producer: Kissenpfennig Adrien.

References:

- Dynamics and function of Langerhans cells in vivo: dermal dendritic cells colonize lymph node areas distinct from slower migrating Langerhans cells.; Kissenpfennig Adrien; Henri Sandrine, Dubois Bertrand, Laplace-BuilhÃ© Corinne, Perrin Pierre, Romani Nikolaus, Tripp Christoph, Douillard Patrice, Leserman Lee, Kaiserlian Dominique, Saeland Sem, Davoust Jean, Malissen Bernard; 2005; Immunity; 22; 643-54; 15894281

EM:02112	**18**	**Rosa-tdRFP**
Faithful activation of a red fluorescent protein in "knock-in" Cre-reporter mice ideally suited for lineage tracing studies		

EM:02112 (Rosa-tdRFP)

EMMA ID	common strain name(s)	targeted (or) expressed gene(s) (click on the name to search the allele or transgene description(s) in the Mouse Genome Database)	mutation (sub)type	(International) Strain Designation	click to order/registe an interest
EM:02112	Rosa-tdRFP	Rosa26Sor	targeted/knock-in	Rosa-tdRFP	order (limited quantities as st being archived

Genetic background : C57BL/6

Phenotype description: Homozygous females exhibit a somewhat reduced fertility when compared with C57BL/6 wildtype animals

Genetic description: A targeting vector was designed to contain the "tandem-dimer red fluorescent protein" gene (kind gift of R.Tsien/San Diego) in opposite orientation to Rosa26 transcription and downstream of a loxP-flanked stop sequence (promoterless neomycin resistance gene and three copies of the bovine growth hormone polyadenylation sequence). This entire construct was inserted into the Gt(ROSA)26Sor locus via gene targeting of C57BL/6-derived BRUCE4 embryonic stem (ES) cells. Correctly targeted ES cells were

Original Producer: Fehling Hans Joerg.

References:

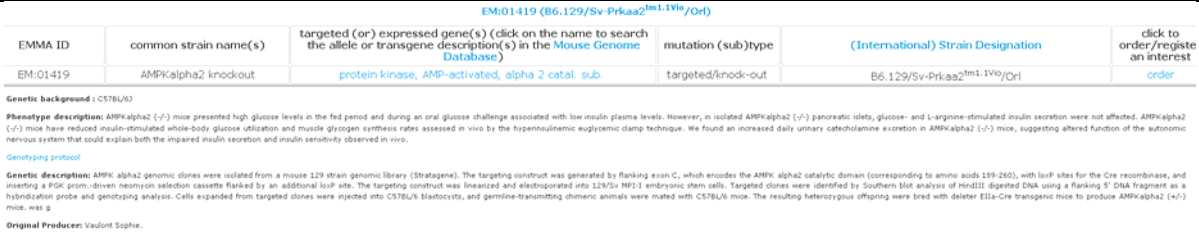
- Faithful activation of an extra-bright red fluorescent protein in "knock-in" Cre-reporter mice ideally suited for lineage tracing studies.; Luche HervÃ©; Weber Odile, Nageswara Rao Tata, Blum Carmen, Fehling Hans; 2007; Eur J Immunol; 37; 43-53; 17171761

Availability:

- Live mice on shelf. Delivered in 4 weeks. Price €1700.

More detail on pricing and delivery times

EM:01419	**17**	**B6.129/Sv-Prkaa2<tm1.1Vio>/Orl**
AMPKalpha2 (-/-) mice: The AMP-activated protein kinase alpha2 catalytic subunit controls whole-body insulin sensitivity		



EM:01419 (B6.129/Sv-Prkaa2$^{tm1.1Vio}$/Orl)

EMMA ID	common strain name(s)	targeted (or) expressed gene(s) (click on the name to search the allele or transgene description(s) in the Mouse Genome Database)	mutation (sub)type	(International) Strain Designation	click to order/registe an interest
EM:01419	AMPKalpha2 knockout	protein kinase, AMP-activated, alpha 2 catal. sub.	targeted/knock-out	B6.129/Sv-Prkaa2$^{tm1.1Vio}$/Orl	order

Genetic background : C57BL/6J

Phenotype description: AMPKalpha2 (-/-) mice presented high glucose levels in the fed period and during an oral glucose challenge associated with low insulin plasma levels. However, in isolated AMPKalpha2 (-/-) pancreatic islets, glucose- and L-arginine-stimulated insulin secretion were not affected. AMPKalpha2 (-/-) mice have reduced insulin-stimulated whole-body glucose utilization and muscle glycogen synthesis rates assessed in vivo by the hyperinsulinemic euglycemic clamp technique. We found an increased daily urinary catecholamine excretion in AMPKalpha2 (-/-) mice, suggesting altered function of the autonomic nervous system that could explain both the impaired insulin secretion and insulin sensitivity observed in vivo.

Genotyping protocol

Genetic description: AMPK alpha2 genomic clones were isolated from a mouse 129 strain genomic library (Stratagene). The targeting construct was generated by flanking exon C, which encodes the AMPK alpha2 catalytic domain (corresponding to amino acids 189-260), with loxP sites for the Cre recombinase, and inserting a PGK prom.-driven neomycin selection cassette flanked by an additional loxP site. The targeting construct was linearized and electroporated into 129/Sv MPI-1 embryonic stem cells. Targeted clones were identified by Southern blot analysis of HindIII digested DNA using a flanking 5' DNA fragment as a hybridization probe and genotyping analysis. Cells expanded from targeted clones were injected into C57BL/6 blastocysts, and germline-transmitting chimeric animals were mated with C57BL/6 mice. The resulting heterozygous offspring were bred with deleter Ella-Cre transgenic mice to produce AMPKalpha2 (+/-) mice. was g

Original Producer: Vaulont Sophie.

EM:01789	12	Conductin (Axin2)-lacZ
Axin2 null mutation, knock-in of NLS-lacZ in frame following Axin2's ATG start codon for developmental analyses		

EM:01789 (Conductin (Axin2)-lacZ)

EMMA ID	common strain name(s)	targeted (or) expressed gene(s) (click on the name to search the allele or transgene description(s) in the Mouse Genome Database)	mutation (sub)type	(International) Strain Designation	click to order/registe an interest
EM:01789	Conductin (Axin2)-lacZ	axin2	targeted/knock-in	Conductin (Axin2)-lacZ	order

Genetic background : C57BL/6N

Phenotype description: no; minor: craniosynostosis

Genetic description: Axin2 null mutation, knock-in of NLS-lacZ in frame following Axin2's ATG start codon. Antisense PGK-Neo cassette flanked by loxP-sites following lacZ. Only splice acceptor and donor of first coding exon (exon 2) left.

Original Producer: Jerchow Boris.

References:

- The role of Axin2 in calvarial morphogenesis and craniosynostosis.; Yu Hsiao-Man; Jerchow Boris, Sheu Tzong-Jen, Liu Bo, Costantini Frank, Puzas J, Birchmeier Walter, Hsu Wei; 2005; Development; 132; 1995-2005; 15790973
- Negative feedback loop of Wnt signaling through upregulation of conductin/axin2 in colorectal and liver tumors.; Lustig Barbara; Jerchow Boris, Sachs Martin, Weiler Sigrid, Pietsch Torsten, Karsten Uwe, van de Wetering Marc, Clevers Hans, Schlag Peter, Birchmeier Walter, Behrens JÃ¼rgen; 2002; Mol Cell Biol; 22; 1184-93; 11809809

While the overall number of submissions received by EMMA is continuously growing a view on the origin of the submissions reveals some striking differences between the member countries of the EMMA network. By far most of the submissions were received from the UK, Germany and from France. Only few submissions were received from either countries in Southern Europe or from Scandinavia although the number of submissions received from Scandinavia increased in recent reporting periods. Only few submissions were received from outside Europe (see Fig. 4).

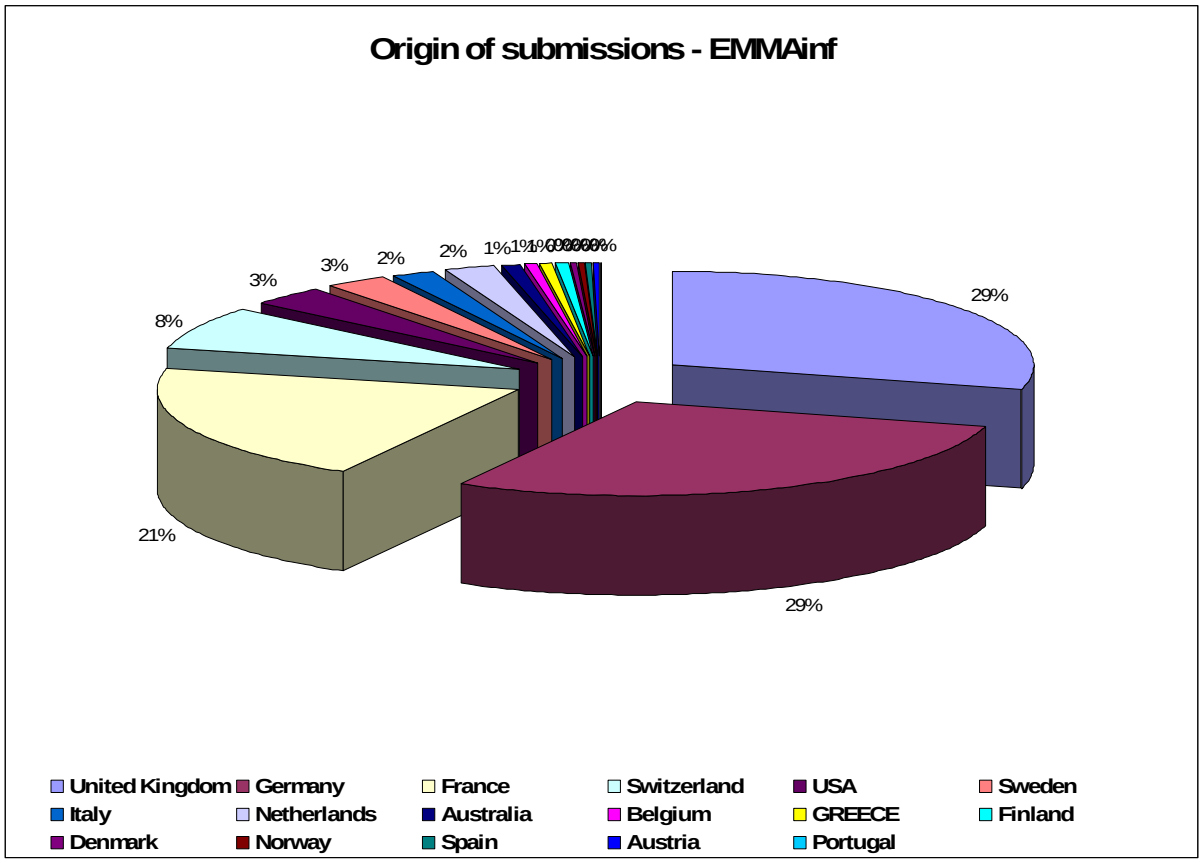


Fig. 4: Origin of submissions (received in EMMAinf)

1.6.2 Activity JRA2: Constant renewal of live stocks

Description of Activity JRA2 and Objectives

This joint research activity ensured that the most important strains were readily available to the scientific community. This objective was achieved by a constant renewal of the highly demanded stocks. Only strains of general interest and importance for the scientific community were kept as live stocks for a limited time within the EMMA program. The participants of EMMA currently hold 40 - 120 mouse lines each year as live stocks that are processed in the JRA1 activity. Within this joint research activity the participants kept 45 additional lines on the shelves each year and distributed these mice to the scientific community upon request. EMMA only sends out live animals under SPF conditions. This is particularly important for users of the EMMA infrastructure. Only a tested and guaranteed health status ensures that disease free colonies will become more and more the standard for the European mouse research community. The constant renewal of mouse lines ensures:

- The most important strains are available with a minimum delay
- EMMA's distribution list reflects the needs of the community
- Repeated requests for popular stocks justifies their maintenance
- The efficient use of EMMA's resources

Final report JRA2 (reporting period 7/2004 – 12/2008)

Contractors participating in JRA2 during EMMAinf

Participant number	1	2	3	6
Participant short name	CNR - IBC	CNRS - CDTA	MRC - MGU	HMGU

The deliverable of this activity for the EMMAinf project was to keep 45 mutant lines per year on shelf to be able to provide highly demanded strains quickly to the scientific community. With respect to the number of mutant lines kept on shelf by the EMMA partners and the overall objective of this research activity this goal has been achieved. All the strains charged to this activity of EMMAinf are publicly available and listed on the EMMA website at www.emmanet.org. It must be noted that this joint research activity of EMMAinf formally ended by June 30th 2008, the original end of the funding period, which was cost-neutrally extended till Dec 31st 2008. The line spaces reported under this activity were kept on shelf till June 30th or longer. The request data that are reported here is however for the entire EMMAinf reporting period (July 2004 – Dec 2008). In July 2008 EMMA implemented a cost recovery based distribution system. Since July 2008 shipments of frozen embryos/sperm cost €1100, while live mice are distributed for a cost of €1700. The charges levied by EMMA are used solely to meet the animal husbandry and stock replacement costs. No costs for the maintenance of lines on shelf after the implementation of the cost recovery system were charged to the EMMAinf project.

In particular, at EMMA centers obtaining many requests such as the CDTA / CNRS and the CNR, keeping requested lines on shelf proofed to be very valuable in quickly providing demanded lines to researchers. Although mainly designated for the maintenance of highly requested strains, some of the line spaces were used to breed strains in order to build up the archive, particularly at EMMA centers receiving fewer requests. Especially in the case of

ENU mutant strains, depositors were not always able to allocate a sufficient number of males in a manageable time frame. Therefore, a sufficient number of animals for cryopreservation had to be produced using the JRA2 line spaces. Thus, these line spaces were extremely valuable to be responsive to the demands of the depositors and to support the JRA 1 activity.

Development of distribution capacity during EMMAinf

During the course of the EMMAinf project, the number of requests received by EMMA increased annually reaching a total of 1220 requests at the end of the project in December 2008. This reflects the strong growth and development of the EMMA archive by the EMMAinf project as summarised in the final report for the JRA1 activity. During EMMAinf a total of 1104 requests for mouse mutant lines were received by EMMA. The numbers of requests per year and the total number of requests at the end of years are shown in Fig. 5 and 6, respectively (Status in Dec. 2008). The implementation of a cost recovery based distribution system in July 2008 did not significantly impact the number of requests compared to the 1st half of 2008.

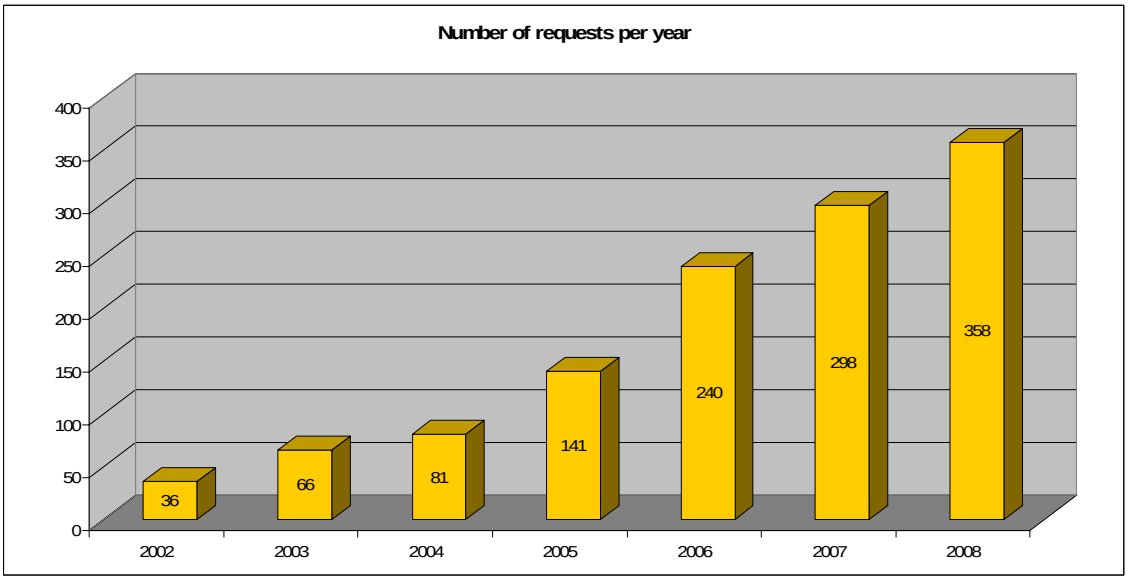


Fig. 5: Number of requests per year

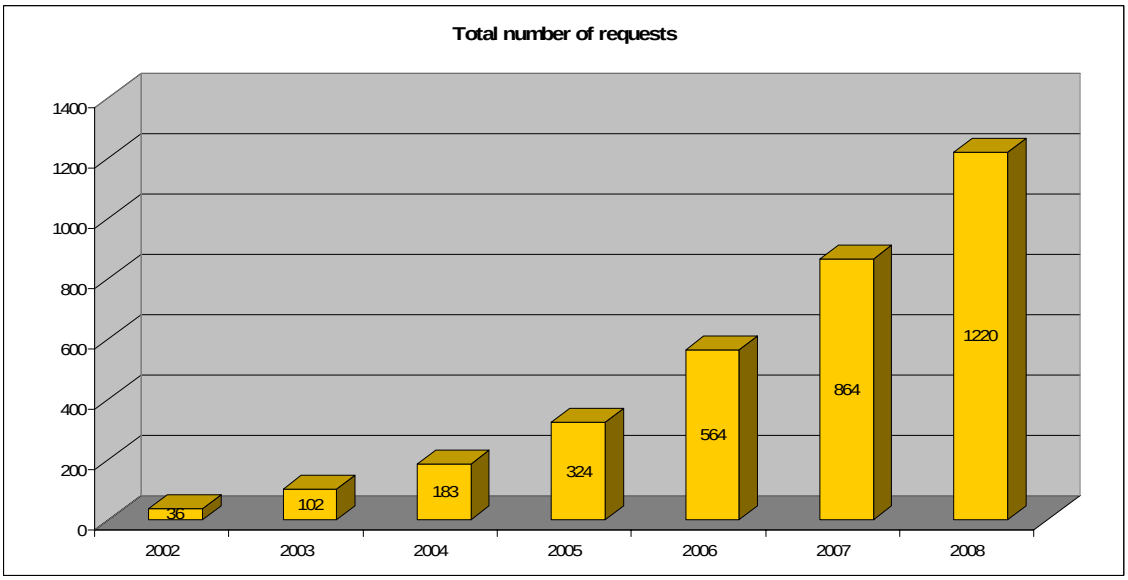


Fig. 6: Total number of requests at end of each year (cumulative data from Fig. 5)

Distribution capacity of EMMA centers

By far most of the requests were handled by the CDTA and the CNR which fulfilled 73% of all service requests for EMMA mouse resources. The requests per centre during the EMMAinf project are summarised in Fig. 7. The total number of requests received during the project was 1104.

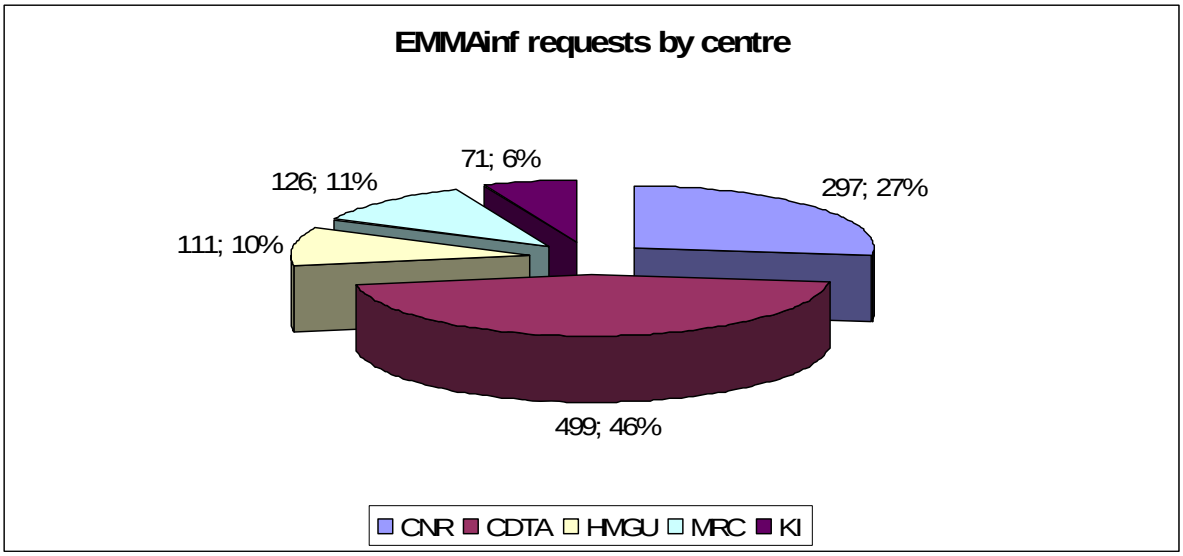


Fig. 7: Requests per EMMA centre

Requested material

By far most of the requests received by EMMA concerned live mice whereas only a minor fraction of the orders were for either frozen embryos or sperm (see table 5). However, during the course of the EMMAinf project the number of requests for frozen resources significantly increased to about 30 % of the orders. Shipment of frozen formats is strongly promoted by the EMMA centres by personal communication with the EMMA customers. However to significantly increase the shipments of frozen formats other strategies and incentives are needed such as a pricing strategy that will support orders of frozen materials and training courses for handling frozen resources.

	Period 1	Period 2	Period 3	Period 4
Live mice	**89%**	**79%**	**69%**	**72%**
Frozen embryos / sperm	**11%**	**21%**	**31%**	**28%**

Table 5: Percentage of mice and frozen formats on requested resources

In case of requests for live mice that are not kept on shelf EMMA offers a rederivation service. The rederivation of mice from frozen embryos or sperm allows EMMA to provide customers with live mice within 4 to 6 months. Live mice on shelf can be shipped to customers within 2 to 4 weeks. The strong increase in the number of requested mouse mutant strains from the EMMA archive, the high demand of customers for live mice and the fast provision of live mice on shelf to customers clearly indicates the value of the JRA2 research activity for the scientific community.

Bestselling strains

The total number of requests received during the course of the EMMAinf project is 1104, representing requests for 367 different mouse mutant lines from 506 different customers. A total of 143 lines were requested twice or more and account for 80% of the total 1104 requests. A fraction of 27 lines was requested 10 x or more and accounts for 44% of all requests. These 27 bestselling lines are listed in table 6. A further 224 mouse mutant lines were requested only once.

Under the JRA2 activity a total of 180 lines spaces were available during the EMMAinf project to keep live mice on shelf and these were used to maintain 111 different demanded lines. For the lines kept on shelf under the EMMAinf JRA2 activity 632 requests were received accounting for 57% of all requests. Due to the JRA2 funding these mice could be rapidly provided to the customers (within 1 month) whereas re-derivation from frozen stock would have taken between 4 and 6 months. This demonstrates the tremendous value of the JRA2 activity for the research community.

EMMA ID	Nr of requests / EMMAinf	Strain name
EM:01098	46	B6;D2-Tg(Slc5a2-cre)1Tauc/Orl
EM:00055	33	B6.129-Rag2<tm1Fwa>Cx3cr1<tm1Litt>/WeiOrl
EM:00254	33	B6.129X1-Th<tm1(cre)Te>/Kieg
EM:00715	33	B6.Cg-Tg(Tek-cre/ESR1)1Arnd/ArndIbcm
EM:01822	24	Langerin-DTREGFP
EM:01713	21	B6;D2-Tg(Ttr-cre/Esr1)1Vco/Orl
EM:00115	19	B6.129-Igf1r<tm1.2Mhz>/Orl
EM:00253	19	C57BL/6J-Tg(tetO-cre)1Lin/Kieg
EM:00753	18	B6;C-Tg(tetO-cre)LC1Bjd/BjdIbcm
EM:02112	18	Rosa-tdRFP
EM:01419	17	B6.129/Sv-Prkaa2<tm1.1Vio>/Orl
EM:00044	16	B6.FVB-Tg(Itgax-DTR/EGFP)57Lan/Orl
EM:00603	16	STOCK Tg(Alb1-cre)7Gsc/Ibcm
EM:00158	15	B6;129S7-Prnp<tm1Cwe>/CweIbcm
EM:01417	15	B6.129/Sv-Prkaa1<tm1Sbj>/Orl
EM:01819	15	Langerin-EGFP
EM:00181	13	B6;129S7-Prnp<tm1Cwe>Tg(Prnp)a20Cwe/CweIbcm
EM:01420	13	B6.129/Sv-Prkaa2<tm1Vio>/Orl
EM:01783	13	HLA-A2+HLA-DR1+/IAß°ß2m
EM:02125	13	B6.FVB-Tg(Camk2a-cre/ESR1)2Gsc
EM:00133	12	B6.129 Rag2<tm1Fwa>Tg(TcraH-Y,TcrbH-Y)1Pas/Pas
EM:01153	12	B6.FVB-Tg(Camk2a-cre)2Gsc/Ibcm
EM:01789	12	Conductin (Axin2)-lacZ
EM:00162	11	B6.129S6(Cg)-Rag2<tm1Fwa>/FwaOrl
EM:01372	11	C57BL/6-Tg(rtetR-tetO-cre)40Mhz/Orl
EM:00047	10	C57BL/6-Cd3e<tm1Mal>/Orl
EM:00404	10	B6.Cg-Tg(Cebpb-rtTA2S*S2)1Bjd/Ibcm

Table 6: Mouse mutant lines requested 10 x or more during EMMAinf

The by far most prominent class of mouse mutant lines among the bestselling strains are knock-out lines and Cre-recombinase expressing strains. This clearly underpins the importance of the new projects EMMA is part of such as EUCOMM and the collaboration with the Wellcome Trust. Both projects focus on the production of knock out mouse strains and new Cre-expressing strains and will significantly add to the value of the EMMA archive. In order to provide the EMMA customers a faster and direct access to these mouse mutant lines all Cre lines are double listed in the public strain list according to their mutation type and are in addition also grouped into the category Research Tools / Cre expressing strains. This approach will be further refined and it is planned to list mouse mutant lines representing disease models also according to their research areas e.g. oncology or immunological research etc. The information if a submitted mouse mutant line represents a model of human disease for a specific research area is now captured with the revised EMMA submission form.

Origin of requests

Most of the requests EMMA received during the EMMAinf project were from European researchers. In total, EMMA received 623 requests (58 % of the total number of requests) of scientists from 23 European countries. However, when single countries are taken into account the by far best EMMA customer is the USA. EMMA received in this project 320 requests from US researchers and 26 from Canada. The number of requests from Asia, Australia and New Zealand accounts for 9% of all requests. The origins of EMMA requests is summarised in Fig. 8.

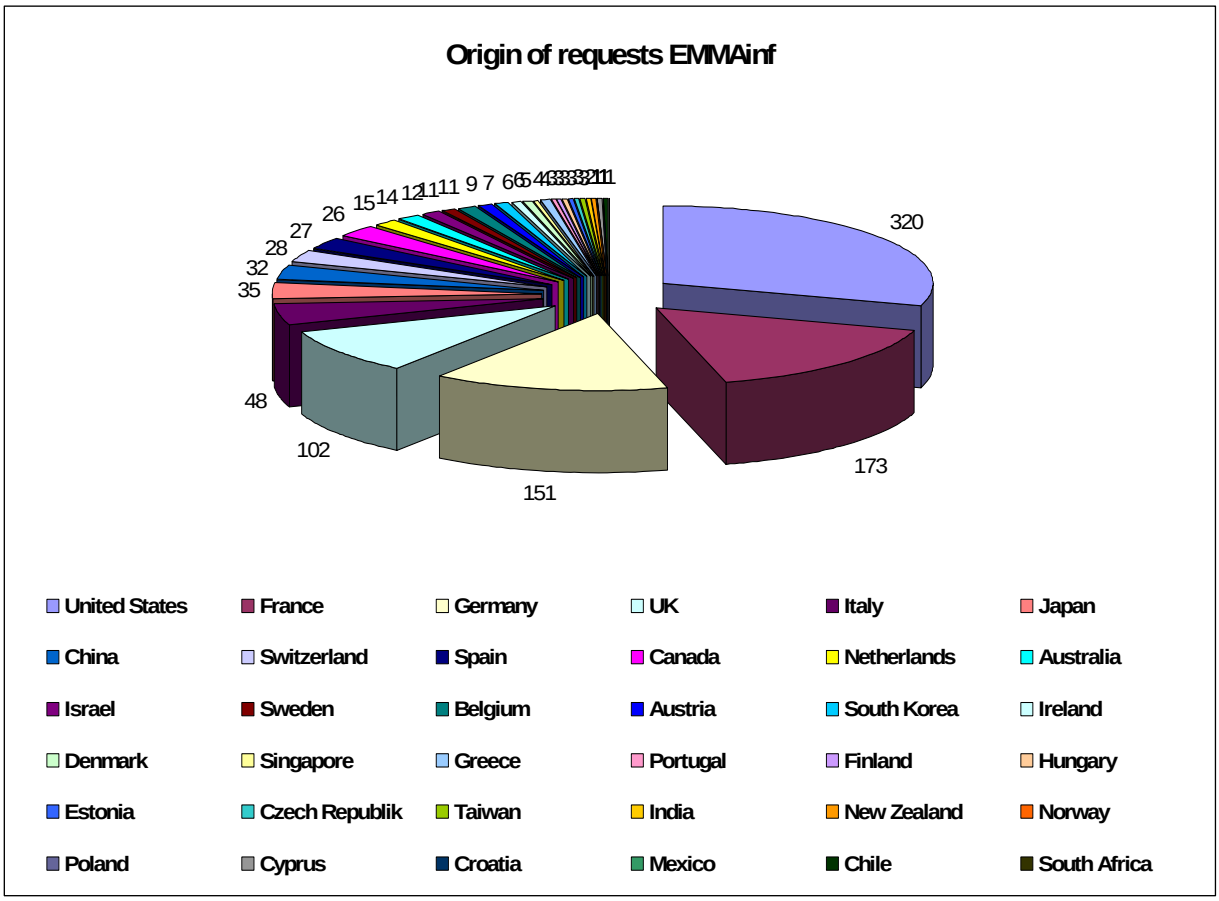


Fig. 8: Origin of requests received during the EMMAinf project

1.6.3 Activity JRA3: Gnotobiology

Description and Objectives

Selected mouse strains were transferred to germ-free conditions upon specific request by European investigators. Within this joint research activity the participants prepared 20 germ-free mouse lines. The service offered by EMMAinf guaranteed the transfer to a germ-free status of 2 litters from a provided pair of parent mice and their maturation to a maximum of 6 weeks of age. Two EMMA nodes were involved in this JRA, the Karolinska Institute (KI) and the Instituto Gulbenkian de Ciência (FCG-IGC).

Progress report JRA3 (reporting period 7/2004 – 12/2008)

Contractors participating in JRA3 during the EMMAinf project

Participant number	4	5
Participant short name	KI	FCG - IGC
Deliverable	Cleansing of 8 mouse lines	Cleansing of 12 mouse lines

Rationale for the JRA3 on gnotobiology

The production of genetically modified mice that serve as models of inherited diseases or as tools to dissect biological mechanisms has proven essential to the progress of biomedical science. Mice, like humans, are heavily colonized by microorganisms that can be pathogenic, innocuous or beneficial commensals. In human and mice the microflora roughly represents 90% of the cells that compose an individual. Therefore, the phenotype associated with a specific mouse genome modification may result from disruption of the interactions between the host and its microflora. These preoccupations are not novel but regained interest with the development of probiotics and the clear evidence that occidental societies tend to decrease the diversity of their microflora. Commonly, mice are raised in the now standard Specific Pathogen Free (SPF) condition, which does not significantly modify the extreme diversity and number of colonizing micro-organisms. The techniques of gnotobiology allow for the generation and maintenance of animals in a germ-free (GF) environment and by extension with the possibility to restore specific components of the microflora. The comparative analysis of a given mouse line raised in SPF and in germ-free condition, reveals the contribution of the microflora to the phenotype associated with a specific mouse genotype. This approach has been essential, for instance, to discriminate between autoimmunity and inflammatory immunopathologies in various mouse models. Beyond inflammation and immunology, germ-free raised animals should also help to understand the host-commensal interaction in processes of tissue regeneration, for instance of the intestinal epithelium. The equipment and expertise necessary to raise mice in a germ-free environment are sophisticated and exclusive to this use. Very few centers in Europe have the capacity to invest in developing locally this technique, although many contribute to the generation and analysis of novel mouse models of inherited diseases. Accessibility of the biomedical community to a European center that performs transfer of mouse lines to germ-free conditions offers the possibility to better exploit the biological and medical potential of the available international mouse mutant collection.

From the axenic service request to germ-free mice

To ensure the proper processing of each request, a specific online service request form has been designed which is available on the EMMA website. Once the form is submitted by the requester it is sent to each center offering the germ-free service and to an external evaluation committee. The external committee is composed of Prof. Jonathan Howard, Köln and Prof. Dan Holmberg, Umea. They evaluate the application with respect to its scientific interest and its feasibility. Upon approval the service request is assigned to KI or FCG for processing the request. Assignment to the centers offering the service depends on geography, shortest delays and scientific interests of the centers. A regular procedure of importation of the parental strains is followed, including careful evaluation of health report and potential re-derivation by embryo transfer into SPF conditions. In some instances frozen embryos were received. The transfer of SPF mouse lines to GF isolators is performed by foetus transfer. Foetuses are collected from close to term pregnant donor females after Caesarean-section and promptly adopted by foster mothers bred and raised inside the GF barrier. The GF status of the isolators is confirmed every other week, while the foster colony is tested once every other month. The foster mother is confirmed GF in the week following adoption and the requested mice specifically tested at 4 weeks of age and on the day of analysis. The age and mode of analysis of the GF progeny is variable and specific to each project. In some instances tissues or fluid have been sent to the investigators, in others investigators were hosted at the Institute where the GF facility is operating. The requester covers the costs associated with the transport of parent animals or frozen embryos as well as those associated with GF animal analyses. All other costs were covered by the EMMAinf project.

Value for the scientific community

The equipment and expertise necessary to raise mice in a germ-free environment are sophisticated and exclusive to this use. Very few centers in Europe have the capacity to invest in developing locally this technique. Accessibility of the biomedical community to a European center that performs transfer of mouse lines to germ-free conditions offers the possibility to better exploit the biological and medical potential of the available international mouse mutant collection. The service offered by EMMinf allowed a total of 20 either pilot or finalised experiments with no cost for the requester except the shipment of mice. Without the service and support offered by EMMAinf under this activity most of the 20 experiments may not have been performed.

Contribution to publications

Individual contacts with each of the requesters confirm that the results of the concluded studies performed under the JRA3 activity are either being submitted for publication or included in various manuscripts currently in preparation.

Infrastructure development

During the Infrafrontier project, the FCG-IGC has upgraded and expanded the GF isolators. After evaluation with the EMMA partner CDTA in Orleans, all isolator connections for direct and safe exchanges of GF mice between the centers were adapted. The IGC progressively acquired new isolators and associated equipment and has now available 6 isolators and 1 transfer chamber. This set-up allows the maintenance of 2 independent colonies of the fostering strain, to keep in breeding the most demanded strains and to regularly transfer foetal litters at a rate of 4 attempts per month.

Networking with other EMMA-nodes

The extensive experience in gnotobiology that is available at the CDTA in Orleans supported the implementation of a functional set up for the production of germ-free mice at the FCG-IGC. The chosen compatibility of equipment between the CDTA and the IGC served to exchange germ-free animals safely. Both centers have identical levels of bio-containment and use the same strain (C3H) as foster colony. The CDTA occasionally provided foster mothers to the IGC in cases of multiple service requests. For instance, this substantial increase in the number of foster mothers allowed the IGC to process simultaneously 3 requests in the same month without causing any delay. The EMMA node at Harwell also initiated a gnotobiology program and decided to make its equipment compatible with the CDTA and the IGC set up. The IGC provided technical support for the implementation of the Harwell gnotobiology program. The EMMA node at CNR-Monterotondo contributed to the JRA3 activity by providing SOPs and guidelines for microbiologic and molecular assessment of a GF status. In addition, IGC sent GF sentinel mice or tissues to the CNR for evaluation of the GF status. A germ-free workshop was organized at the IGC for exchange of know-how in GF technology and GF monitoring as well as to critically assess the service provided to the EMMA customers. Four EMMAinf partners participated in the workshop. Standardisation of SOPs among the nodes and strategies to promote the axenic service were discussed.

Promotion of the EMMA axenic (germ-free) service

The JRA3 activities are advertised on a dedicated web site at www.emmanet.org. The use, application and contribution of GF mice to biomedical science are described.

Production of germ-free mice under the EMMAinf JRA3 activity

Table 7 lists all mouse mutant lines that were transferred to a germ-free status upon request

	KI	**FCG**
1st reporting period	MYD88 Strain retracted by owner	-
	ILR1 Strain retracted by owner	-
2nd reporting period	NOD	C57BL/6
	ob/ob	C57BL/6 Rag2-/-
	TLR4	Congenic Thy1.1 IgMa
		TGF beta receptor mutant
3rd reporting period	MyD88 KO	C57BL/6 Scurfy
	ApoE x TGFbetaII double KO	C57BL/6
	CD40 KO	C57BL/6 Rag2-/-
	AhR KO	NMRI
4th reporting period	Floxed PPARg KO	C57BL/6 IKK2 F/F KI /K14Cre Tg (2x)
		C57BL/6 NEMO F/F KI K14Cre Tg (2x)
		C57BL/6
		C57BL/6 hIgA KI
		C57BL/6 Caspase 8* Tg

Table 7: Mouse strains converted to germ-free conditions during EMMAinf

1.6.4 Activity JRA4: Database Development

Description and Objectives
An essential objective of the EMMA project is the establishment and constant update of a dedicated resource database (EMMA-RDB). This database classifies and describes all the mutant strains that EMMA is stocking and their genetic and phenotypic properties. The database is made available to the scientific community via the public EMMA homepage.

Contractors participating in the JRA4 during EMMAinf

Participant number	1	2	7
Participant short name	CNR - IBC	CNRS - CDTA	EMBL - EBI

Final report JRA4 (reporting period 7/2004 – 12/2008)
The objective of JRA4 (Database Development) has been the implementation, management and constant update of a dedicated resource database (EMMA-RDB). This database classifies and describes all the mutant strains that EMMA is stocking and their genetic and phenotypic properties. The database strain records are available to the scientific community at the public EMMA web site (www.emmanet.org). According to the tasks and deliverables defined in the contract technical annex, the design, implementation and update of the database model, management system, user interfaces and interoperability were carried out by members of the EMMA DB group, with constant interaction with the EMMA BPD and AGL groups and feedback from external users and other database groups at collaborating institutions.

The constant update of database information of stored strains and stocks (Task 4.1; D1) aimed at maintaining the EMMA-DB and its applications up-to-date to the latest developments in related areas of mouse genetics and bioinformatics research. The actual database records (strain attribute values), as well as data model/schema and application software (user interfaces, data import/export and statistical analysis routines, etc.) were constantly reviewed and updated. This was achieved by a constant collaboration among the members of the database group and feedback from all staff members at EMMA partner sites.

The **public strain web list** (http://www.emmanet.org/mutant_types.php) was revised and updated with a new text search tool and presentation of specific sub-lists, according to certain strain characteristics, such as mutation type/sub-type, application as research tools (Cre-, Tet-expression systems, etc.) and contributing project (e.g. Wellcome Trust Knockout Mouse Resource project (Deltagen / Lexicon collection), EUCOMM, EUMODIC, etc.).

Specific order links (**'order-limited quantities'**) for strains with small number of live mice available before archiving is completed were also implemented, as well as a new **registration-of-interest** (ROI) on-line form for strains not yet archived, with specific links on public strain list and description pages ('register interest' if not yet archived, or 'order' if archived).

Individual **strain description pages** were extensively revised, including automatic links to MGI gene/allele names/symbols and MEDLINE bibliographic abstracts, inserting MGI gene/allele ID and PubMed ID values, as unique link keys. These pages were also modified to include strain-specific links to downloadable genotyping protocols (as verified and curated by

the archiving EMMA partner) and original producer's material transfer agreements/license documents, when applicable.

The strain-specific indication of different types of available frozen/live material was implemented, according to newly defined strain accessibility (public, confidential) and production status values (e.g.: in evaluation, accepted, archiving, archived, etc.), as well as distinct values of internal stock and under distribution material.

As of July 4th 2008, public strain pages also display new husbandry/stock replacement contribution costs, according to the type of requested material and strain's archiving funding source.

Ad hoc routines were implemented for the auto-connection and monthly upload of EMMA-DB public strain data to the **MGI-IMSR strain search resources**, using the EMMA strain ID (EM:xxxxx) value as the unique link key. This allows the integrated search of all EMMA and other major public strain collections, according to the procedures established by the Federation of International Mouse Resources (FIMRe), co-founded by the EMMA partners and other international repository infrastructures. This work allows the many users of the IMSR website to be automatically redirected to EMMA for mouse requests, substantially raising the profile and usefulness of EMMA for the international mouse community.

A section describing the **axenic (germ-free) service** with dedicated, explanatory documentation and on-line request form were implemented.

The **internal website** was also fully revised and updated, with new, specific routines for automatic, daily reporting with formatted lists, statistics and graphic charts of submissions, requests, partner/external users mail/address list, etc.

Specific versioning systems were adopted for concurrent development and update, by the EMMA partners, of EMMA-DB and internal/external websites, using initially the CVS (Concurrent Versioning System) and later the SVN (SubVersion) repository at EMBL-EBI.

The updating and improvement of DB models, management system and user interfaces (Task 4.2; D2, D3, D4) was carried out, according to the ongoing revisions and modifications of workflow procedures, as implemented by the EMMA partners. There was also a constant focus on updating the software used for the EMMA-DB and application development, aiming at testing, adopting and deploying the most stable and efficient versions.

The DB schema and models were developed and constantly updated, according to the procedures and protocols actually applied to the management of strain archiving (strain model) and stock submissions and requests (importation/shipping model) and of strain genotyping and phenotyping (quality control model). Current DB schema and package models, as well as descriptions of DB implementation and interfaces and a resume of current dataflow, are accessible to registered users at the project's internal website (http://internal.emmanet.org).

UML (Unified Modelling Language)-compliant DB models were initially produced with Oracle Designer and Rational Rose and then updated with Poseidon for UML, which enables direct code generation for Java and Aqua Data Studio tools. The object-relational persistence

and query services were initially implemented with Castor, and subsequently revised and updated with Hibernate, allowing the use of distinct tools to generate the Java classes and Hibernate mapping files, making future changes in the DB structure easier to implement. Apache Ant was extensively tested and deployed, for Java-based project building and DB software development.

The Oracle Server 8.0 DB management system was initially adopted and subsequently replaced with **MySQL Server 5.0**, transferring the schema metadata from the Oracle data dictionary and implementing new user interfaces based on **Java J2EE/JSP** technology. MySQL was chosen as the world's most popular open source database management system, with excellent technical support readily available on-line. It is in fact used by a number of leading, large-scale bioinformatics projects, such as Ensembl (http://www.ensembl.org) and the UCSC (http://genome.ucsc.edu/) genome browsers. The EMBL-EBI partner works almost exclusively with MySQL which further justified the switch to this new relational database management system as then the EMMA-RDB development could take advantage of the existing experience and infrastructure.

As mentioned above, the EMMA-DB and associated interfaces have evolved over a number of years as requirements changed. These interfaces have been developed by several of the partners, using their own particular programming expertise at the time. This has led to the production of a codebase which, although functional, is not the ideal solution for the EMMA users, archiving centres and developers, who need to maintain and develop the interfaces. An initial set of web accessible DB-user interfaces was produced with Perl-WDBI and subsequently with Java J2EE/JSP, which can work on different data management systems, such as Oracle, MySQL, PostgreSQL, etc. The JSP interfaces were first developed by CDTA as "strain-centric" access tools to the local database and were therefore adapted and updated for the EMMA-DB schema according to the new MySQL implementation outlined above.

In the last two years the revised management of EMMA IT activities has involved **centralizing the project's informatics resources at the EMBL-EBI**, with an associated increase in personnel at this centre. This decision was made to take advantage of EMBL-EBI's excellent infrastructure and expertise, being the major centre for bioinformatics in Europe. In addition, during the last few years, ideal software solutions for building database interface have gained in maturity and popularity. Hence it was decided to re-implement the current EMMA interfaces using such a solution, based on the application of **Spring/Hibernate** technologies. At the same time the DB group took the opportunity to redesign how the interfaces will appear to the EMMA customers and archive centres, to enable a simpler and more consistent user experience. So far updates to the EMMA submission and request interfaces have been released.

The production of new tools for automated data export/import (Task 4.3; D5) was carried out, following the XML (Extensible Markup Language) standards and definitions. XML is a mark-up language, similar to HTML (HyperText Markup Language) and used to display the data on the web, but its tags are not predefined. XML was originally designed to describe, store, carry and exchange data and uses DTD (Document Type Definition) or an XML schema to self-describe them. The DB group worked on the production and periodic revision of a specific XML schema, according to actual changes in the DB structure, applying JAXB to generate Java objects from the schema, and Hibernate for object-relational persistence, as outlined above.

The **EMMA XML exporter** was developed on the basis of the prototype developed by the DB group. The EMMA exporter was deployed in the production environment and is currently used to produce the daily-updated list of publicly available mouse mutant strains, with automatic search/retrieve routines that are applied by collaborating DB projects (Ensembl, MGI-IMSR, MUGEN, etc.).

The **XML importer** has completed its testing phase and is currently used for DB insertion of strain data from the revised version of the on-line strain submission form and for data insertion from on-line forms for strain requests and registration of interest. Dedicated importer versions are being completed for bulk insertion of large strain datasets, produced by collaborating projects (EUCOMM, EUMODIC, the Wellcome Trust Knockout Mouse Resource, etc.).

The application of common rules and control vocabularies for use and integration in the EMMA resource database (Task 4.4; D6) is an essential task in order to keep the EMMA-DB comparable and compatible with other reference databases, thus forming a part of the integrated world-wide network of mouse and mammalian genomics bioinformatics resources.

The DB group has focused, in particular, on the application of international rules and standards for the assignment and review/update of the strain nomenclature ("http://www.informatics.jax.org/mgihome/nomen"), according to approved definitions and control vocabularies for gene, allele, background names/symbols. Specific automated routines and manual curation procedures were implemented for:
- Checking if mutant alleles or expressed transgenes carried by each EMMA strain, have an assigned name and ID in the International Mouse Genome Database (IMSR-MGD), using the specific, current DB definition of the strain name
- Inserting a preliminary strain nomenclature in the relevant EMMA-DB strain record (name status: EMMA checked), according to the IMSR allele/transgene name and the strain background name (based on the information provided in the strain submission form and related publications)
- Submitting the preliminary strain international name to IMSR for review and approval.
- Inserting/updating approved IMSR strain names and strain IDs in the EMMA DB (the strain name status is then set to "IMSR approved")

Specific tools for search/selection by submitting users of approved gene/allele/background names and IDs were incorporated in the revised version of the on-line strain submission form.

The development, testing and application of software for automatic annotation (Task 4.5; D7, D8) was carried out by deploying the improved version of the XML importer and its utilization with the revised on-line submission form. This resulted in the production and application of specific software routines for submitter-initiated automatic search and selection of strain-associated data from reference databases including:
- MGI-curated gene, allele, etc. names, symbols and IDs, for automatic linking to MGI, ENSEMBL and other annotated genomics/proteomics resources,
- PubMed-curated bibliographic reference IDs, for automatic linking to PubMed/ENTREZ and other annotated biomedical bibliography resources and auto-insertion of bibliographic references details, from the EMBL-EBI OpenBQS local server,
- OMIM-curated reference IDs, for automatic linking to OMIM/ENTREZ and other annotated

genomics/proteomics resources associated with human pharmacological/clinical applications,
- EMMA-curated lists of genetic background names/symbols and research application areas, according to international nomenclature standards and definitions

Specific tools were also developed and applied for **DB insertion of large strain datasets**, produced by collaborating projects (EUCOMM, EUMODIC, the Wellcome Trust Knockout Mouse Resource, etc.), automatic input of strain description data and linking to the extensively annotated WT-Deltagen/Lexicon and EUCOMM, EuroPhenome genotype/phenotype datasets.

The DB group activities are currently focused on the **development and testing of specific software for future adoption of distributed querying technologies (BioMart, Web services**, etc.), according to specific standards for database integration and interoperability. This work can take advantage of the EMBL-EBI partner's participation as work package leader in the FP6-funded CASIMIR (Coordination and Sustainability of International Mouse Informatics Resources) Coordination Action ("http://www.casimir.org.uk/"), which also includes CNR-IBC and other major European genomics and phenomics informatics centres as partners. The overall focus of this project is on the coordination and integration of the experimental and material resources relevant to the mouse as a model organism to study human diseases. In particular, EMBL-EBI leads the activities concerning the technical issues affecting database compatibility and interoperability. Essentially this involves reviewing the latest technologies to solve these issues, publishing the recommendations of the CASIMIR consortium and working with the major international resources to adopt these strategies. A major part of the strategy is the adoption of distributed architectures to enable federated data access, such as Web Services and BioMart, and the use of recognized ontologies and minimal information standards. EMBL-EBI's leading involvement in CASIMIR will ensure that the EMMA-RDB adopts the latest standards for annotating its strains and for sharing strain data with other resources. This approach will be essential for implementing simple and efficient interfaces, that users can apply for querying the latest results of the International Mouse Mutagenesis Consortium and related large-scale mutant production projects (EUCOMM, KOMP, NorCOMM, etc.), and finding the relevant strains for ordering from EMMA.

2. Use and Dissemination of Knowledge

Aim of the EMMA PR and dissemination activities are to increase the name recognition of EMMA and to provide information on the available EMMA services and mutant mouse resources. Public Relations are regarded as a high priority by the EMMA management and accordingly a broad range of measures were used during the EMMAinf project to promote the activities of EMMA such as:

- Cryocourses
- Web based activities - EMMA website
- Web based activities - Email lists
- Presentation of EMMA by talks and posters at conferences
- Brochures
- Publications / Reviews in Scientific Journals
- Advertisements
- Calendar
- Co-promotion of EMMA with other networks / societies

1) Cryocourses

The annual EMMA cryopreservation courses were organised by CNR, MRC (EMMAinf funded) and CNRS (INSERM funding) to teach basic and advanced techniques in cryopreservation for banking of mouse mutant strains. Several methods for cryopreservation of mouse embryos, gametes and ovaries are presently available and no single method is adequate for all the various strains of mice being developed. Therefore, a variety of methods must be taught. The setup and performance of state of the art, comprehensive, theoretical and practical courses on cryopreservation of mouse embryos and gametes is essential to disseminate the most advanced techniques on embryo handling, *in vitro* fertilisation, sample cryopreservation, thawing and culture, quality control and database management.

The schedule and general plan of the Monterotondo courses were set up by CNR in collaboration with the Jackson Laboratory and the members of the course faculty. In addition, to the joint effort of the main EMMA cryocourse, which is held by scientists of the Jackson Lab and EMMA, the MRC-MGU is hosting additional cryocourses which are exclusively organised by EMMA scientists. In addition, the French EMMA node in Orleans offered courses in cryobiology. All courses were announced on the public EMMA web site (http://www.emmanet.org/about/courses.php).

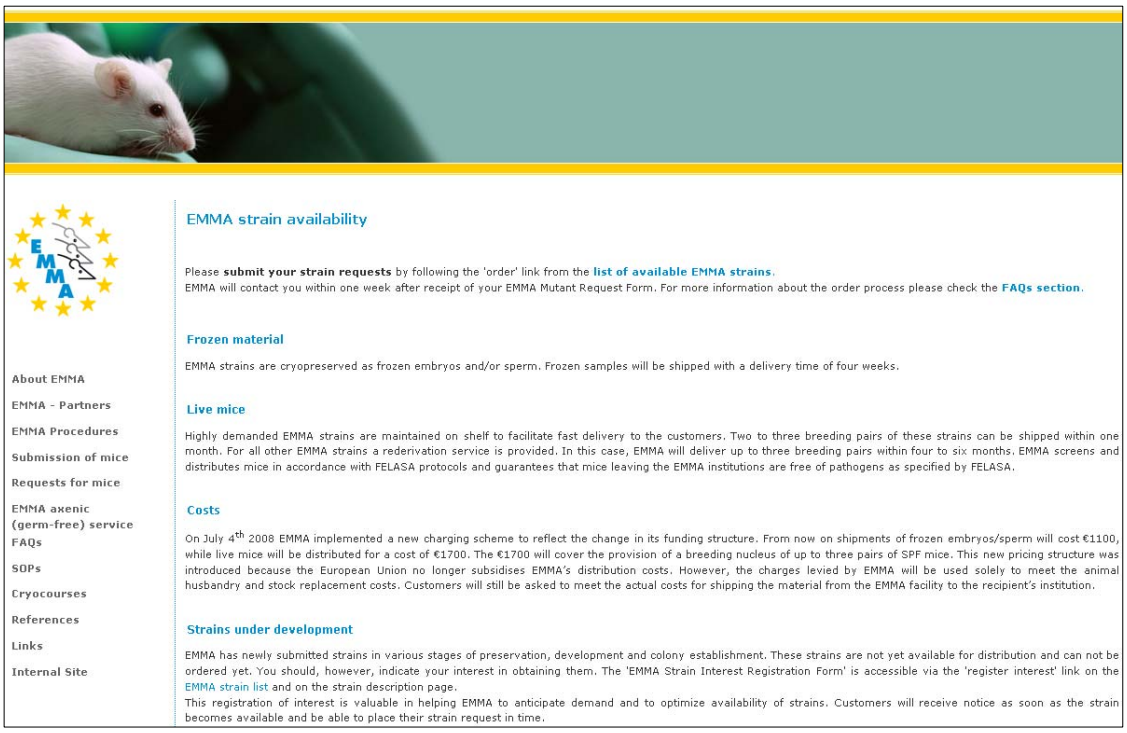
During the course of EMMAinf a total of 16 cryocourses were organised by EMMA partners of which 10 were EMMAinf funded. The courses were attended by 109 participants from 16 European countries.

The SOPs that are practiced in the courses are also displayed on the public EMMA website.

2) Web-based activities – Dissemination via the EMMA website at www.emmanet.org

The EMMA resource database (RDB) and the public EMMA homepage at www.emmanet.org are the most important and efficient tools to provide information about EMMA to the scientific community. One of the essential roles of the EMMA-RBD is to foster the virtual coupling of the EMMA centers. Aiming at this fundamental goal, an internal web site was designed and installed to create a virtual network between the different partners (http://internal.emmanet.org). This site is frequently used by all the EMMA members and used as a platform to share and discuss scientific protocols and technical and logistical procedures. From this page the EMMAinf technical annex and all internal reports of EMMA activities are available, including the agenda, the minutes of the EMMAinf meetings and posters and presentations of talks presented by EMMA members. The availability of standard presentations facilitates a corporate communication of the consortium.

Entry point for the scientific community to the virtual EMMA network is the public EMMA website (www.emmanet.org) that was completely revised during the EMMAinf project.



The list of available strains on the public EMMA homepage is being updated daily to provide the latest information on the available stock collection. The submission as well as the request form were revised several times and improved and these forms are now available as pdf files for the customer. The submitting and requesting processes were automated to speed up the service. Furthermore, SOP's that are used by EMMA are available on the public EMMA webpage. Constant interaction with the International Genetic Nomenclature Committee and the MGD allows the efficient assignment and updating of specific international nomenclature to each strain that is imported, maintained and distributed by EMMA. Each EMMA strain is uniquely identified by an automatically assigned DB-ID. Strong collaborations exist with other reference databases, including MGD, IMSR, ENSEMBL and other leading mouse mutant resources aimed at developing common web sites and database access interfaces. Presently the EMMA-RDB is linked to the IMSR (International Mouse Strain Resource) and data entries are updated monthly.

3) Web-based activities – Promoting the EMMA services and resources via Email lists
A brief synopsis of the available EMMA services and mouse resources was circulated via prominent and widely used Email lists such as the 'MGI List', the 'Transgenic List' and the UK mouse locator.

4) Presentation of EMMA by talks and posters at conferences and by articles
A further and widely used means to advertise the available EMMA services and resources are presentations at major mouse genetics meetings such as the annual Mouse Molecular Genetics Meetings and the IMGS Mouse Genome Conferences but also at general genetics conferences and meetings on research infrastructures. During the course of the EMMAinf project the EMMA network was presented by a total of 61 talks and 20 poster presentations, mainly by the EMMA Director and the Project Manager. Key talks about EMMA were given by the EMMA Director Prof. Hrabè de Angelis at the following conferences:

- 18th International Mouse Genome Conference in Seattle, USA (18th - 21st of October 2004)
- 2nd Mouse Resource Roundtable, Rome, Italy (21st - 23rd of April 2005)
- 6th Transgenic Technology Meeting, Barcelona (September 11th – 13th, 2005)
- EUROMOUSE Conference, Venice (October 14th – 15th, 2005)
- AAAS Meeting, St. Louis (February 17th, 2006)
- 54th Annual meeting of the Japanese Society of Animal Sciences, Tokio, (May 25th – 28th)
- ECRI, 4th European conference on research infrastructures (Hamburg, June 5th – 6th 2007)
- EUROMOUSE II Meeting, Heathrow (July 5th – 6th, 2007)
- IMGS Mouse Genome Conference, Kyoto (October 28th – November 1st, 2007)
- 1st FANG Conference, Functional Annotation of the Mammalian Genome, Tegernsee, (January 23rd – 25th, 2008)
- International Congress of Genetics 2008 (Berlin, July 12th – 17th)

5) Brochures
At major mouse genetics conferences where EMMA was presented also brochures on the EMMA network were distributed. At the Helmholtz Zentrum München a brochure was produced which describes the German Mouse Clinic and EMMA. The brochure was translated into English and in July 2006 also made available for download at the HMGU website.
http://www.helmholtz-muenchen.de/fileadmin/GSF/pdf/publikationen/broschueren/GMC_EMMA_web__en.pdf

EuroMouse Info Pack
EMMA is also represented with a project flyer in a pack entitled 'Mouse as a Model of Human Disease" produced by the PRIME Project Office at the MRC Mammalian Genetics Unit. This brochure contains flyers of major EC funded mouse genetics programmes. The EuroMouse brochure can be ordered at the PRIME Project Office and is being distributed at conferences by representatives of the projects which contributed to this brochure. For example about 300 copies were distributed by the PRIME Project Office at the European Human Genetics Conference in Nice (June 2007).

6) Publications

EMMA is in addition advertised by original publications and reviews. Published during EMMAinf were the following articles and reviews:

- EMMA – The European Mouse Mutant Archive
  Michael Hagn, Susan Marschall and Martin Hrabè de Angelis
  Review in 'Briefings in Functional Genomics and Proteomics' 2007 Sep; 6(3):186-92.

- FIMRe: Federation of International Mouse Resources: global networking of resource centers. Davisson M, FIMRe Board of Directors, Mamm Genome. 2006 May;17(5):363-4.

- Helicobacter typhlonius was detected in the sex organs of three mouse strains but did not transmit vertically. Scavizzi F, Raspa M, Lab Anim. 2006 Jan;40(1):70-9

- Risk Assessment of Mouse Hepatitis Virus Infection via In Vitro Fertilization and Embryo Transfer by the Use of Zona-Intact and Laser-Microdissected Oocytes[1]
  Dominika D. Peters, Susan Marschall, Esther Mahabir, Auke Boersma, Ulrich Heinzmann, Jörg Schmidt and Martin Hrabé de Angelis, Biol Reprod. 2006 Feb; 74(2):246-52.

- Auwerx J, Avner P, Baldock R, Ballabio A, Balling R, Barbacid M, Berns A, Bradley A, Brown S, Carmeliet P, Chambon P, Cox R, Davidson D, Davies K, Duboule D, Forejt J, Granucci F, Hastie N, de Angelis MH, Jackson I, Kioussis D, Kollias G, Lathrop M, Lendahl U, Malumbres M, von Melchner H, Muller W, Partanen J, Ricciardi-Castagnoli P, Rigby P, Rosen B, Rosenthal N, Skarnes B, Stewart AF, Thornton J, Tocchini-Valentini G, Wagner E, Wahli W, Wurst W. The European dimension for the mouse genome mutagenesis program Nat Genet. 2004 Sep;36(9):925-7.

7) Advertisements

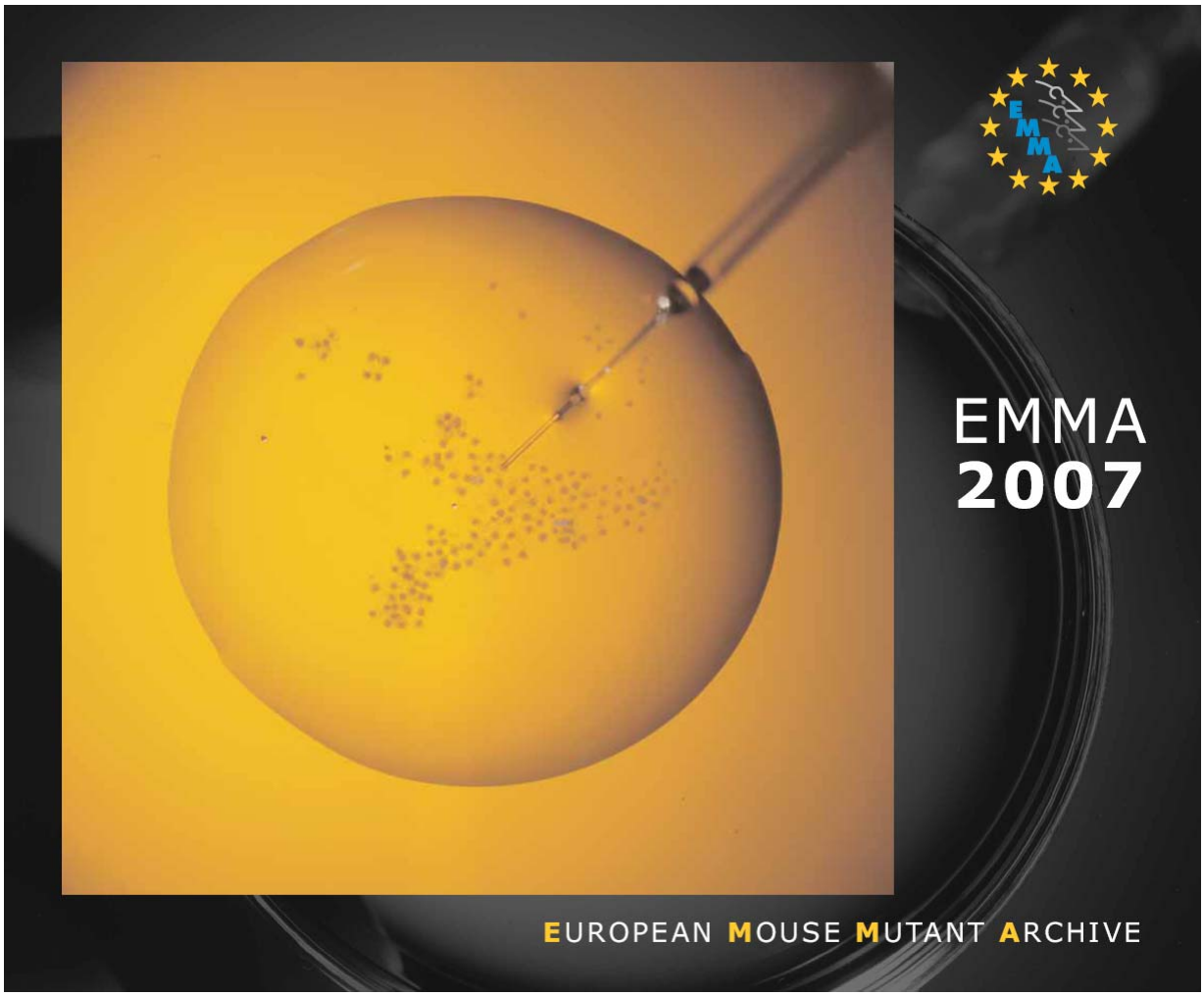
Furthermore, EMMA was also advertised in magazines such as the 'Parliament Magazine' and the 'Public Service Review'. The Parliament Magazine has been published for the last 10 years and regularly works with EU co-funded projects when they wish to run dissemination and mainstreaming messages to the 12,000 readers in the European Parliament, European Commission and throughout the EU. On December 10th 2007 a special Research Review was published. In addition to the standard readership it was also distributed to 5000 Research heads and was made available at high profile European Commission research events throughout 2008.

http://www.e-pages.dk/dods/16/ two page EMMA advertisement on pages 18 and 19

A similar advert was published in the Public Service Review: European Union, Issue 16 in September 2008, page 350 to 351. In addition EMMA was advertised on the outside back cover. The review is distributed free of charge, by name, to individuals within government departments, directorates and agencies in the regional and central governments of the 27 Member States. The readership is across all member states and is in excess of 25000.

8) Calendar

In 2005 and 2007 EMMA produced and distributed calendars that were very popular. A total of 1500 copies of the calendars were sent to EMMA customers and potential new customers worldwide. The calendar provides artistic images of cryopreservation technology and information on the EMMA network and the EMMA services and procedures. The produced images are also used for general EMMA PR activities.



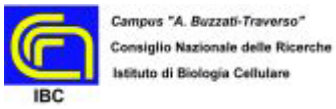
9) International Society for Transgenic Technologies (ISTT) and EMMA Memorandum of Understanding / Co-promotion of EMMA and ISTT

The ISTT and EMMA signed a memorandum of understanding (MoU) in 2008 that they will explore effective ways of collaboration beyond the mutual promotion organised throughout cross-referenced URL links from corresponding WEB sites www.transtechsociety.org and www.emmanet.org. The co-organization and/or co-sponsorship of courses, meetings and workshops of common interest are envisaged as activities where ISTT and EMMA could extend their collaboration. The MoU was signed as a private agreement between Lluis Montoliu as president of ISTT and Prof. Hrabè de Angelis representing EMMA.

B. MANAGEMENT REPORT (FINANCIAL INFORMATION)

EMMAinf project partners

1 (CO)	Consiglio Nazionale delle Ricerche, Instituto di Biologia Cellulare	CNR-IBC	IT



The **Consiglio Nazionale delle Ricerche (CNR)** is the largest public, multidisciplinary research agency of the Italian Government. In 1996 CNR led the foundation of the EMMA network as a major international infrastructure for the European biomedical research community. **The CNR Istituto di Biologia Cellulare (CNR-IBC)** at the "A. Buzzati-Traverso" International Campus at Monterotondo (Roma) is responsible for the management of the EMMA core structure and for the administrative co-ordination of the EMMAinf project. It is responsible for the organization of the annual Monterotondo cryopreservation course, in collaboration with the Jackson Laboratory, the Univ. of California at Davis-MMRRC, HMGU and MRC-MGU. With an estimated total capacity of 50,000-70,000 live animals and 100,000 frozen embryo/gamete vials, the CNR-IBC facility is the largest mouse mutant repository in Italy and the only Italian archive performing complete in-house processing and quality control of banked strains. The local quality control laboratory is a member of the Laboratory Animal Health Monitoring Club. The Institute is a partner of the **EUMODIC**, **MUGEN** and **EUCOMM** European Consortia for functional genomics in the mouse model and of the **CASIMIR** European Coordination Action.

Prof. Glauco Tocchini-Valentini is the director of the CNR-IBC Monterotondo international research programme. Since the creation of the EMMA network in 1996, he has been the co-ordinator of the EMMA contracts under the EU Framework Programmes. **Dr. Marcello Raspa** and **Dr. Ferdinando Scavizzi** manage the EMMA Monterotondo units for importation, cryopreservation, SPF breeding, distribution and quality control of archived strains. **Dr. Raffaele Matteoni** and **Dr. Richard Butler** manage the EMMA resource database and web site (www.emmanet.org), in collaboration with EMBL-EBI, CNRS-TAAM, HMGU and the other EMMA partners. All members of personnel have been participating in the EMMA network activities since its beginning.

2	Centre National de la Recherche Scientifique	CNRS-TAAM	FR

INTRAGENE is a trans-national core facility operated by the National Centre for Scientific Research (**CNRS**) in France. It includes two units which are devoted to mouse genetic analysis: a **core facility, TAAM including the CDTA, for Transgenesis archiving and distribution of model animals**; and a research unit, IEM, focusing on mouse models of human diseases (Infection and Trisomy 21). The TAAM service unit has been a founding member of the European Mouse Mutant Archive since 1996 and is a well-known national infrastructure devoted to mouse genetics since 2001 inside the Inter-organism network (RIO)

and now the **French network for Infrastructure for life science and agronomy (www.IBiSA.fr).** The Institute was integrated in and participated to several EU projects in FP4 **(EMMA)**, in FP5 **(EMMAnet, EMMAwork, Eurocomp, Eumorphia, OxPrions and T21-TARGETS)** and in FP6 **(EMMAInf, EUmodic, Aneuploidy, TB-React, MPCM)** and is a founding member of the Federation of International Mouse Resources (www.FIMRe.org). Since 2008, the Institute is certified for quality management system following the ISO 9001/2000 guidelines, in particular for cryopreservation, rederivation of mouse lines and research project management.

Y. Hérault is a mouse geneticist, the scientific coordinator of the Institute, the director of the TAAM-CDTA unit and the leader of a research group in the UMR6218 Molecular Embryology and Immunology. He worked on mouse development using genetic approaches for more than 15 years. Since 1998 he started to develop a series of techniques for chromosomal engineering with the aims to study gene regulation at the genomic level, using the Hox genes as a paradigm. Now his research interests are focused 1) on evaluating the consequences of gene dosage effect and copy number variation studying pathological situation (Dow syndrome and Trisomy 21) and polymorphism in the mouse and 2) on deciphering new pathways controlling morphogenesis using random mutagenesis in the mouse and in ES cells. **J.-L. Thomas** is the Secretary General of the unit. He joined the centre in 2008 and was involved previously in a French Public/Private structure aiming at developing new quality standard for livestock. He is supervising and regulating the administrative activity and the management of the project. **S. Paturance** is the coordinator of the animal facilities. He has a long expertise in managing animal houses and has participated to the development of experimental procedures using mouse as a model system. **C. Fremond** is the Veterinarian of the institute. She is taking care of the animal welfare and responsible for the health sanitary control. **A. Diet** is the coordinator of the Cryopreservation/Rederivation unit. He is the head of a service with 6 collaborators working on cryopreservation and rederivation of mouse strains.

3	Medical Research Council	MRC-MGU	UK

The **Mammalian Genetics Unit (MGU)** (Director: **Steve Brown**) is a major international centre at the forefront of studies in mouse functional genomics with excellent facilities and expertise in mouse genetics and genomics, phenotyping (from the molecular to the physiological), informatics, computational biology, pathology and archiving. The MGU focuses its efforts on the study of mouse models of human diseases and has divided its activities across four divisions - Functional Genomics, Developmental Genetics, Neuroscience, and Hormonal and Metabolic studies. The research groups are supported by several core facilities providing services in genotyping, mutation detection, sequencing, arrays, proteomics and embryo and sperm freezing. In addition, the MGU's activities are supported by the **Mary Lyon Centre** which is a state of the art SPF mouse facility with housing for 60000 adult mice and their progeny.

The work of the EMMAinf project was conducted by the frozen embryo and sperm archive **(FESA)** core which is recognised as a global genetic resource with considerable expertise in

the cryopreservation and dissemination of novel mouse mutants to the worldwide scientific community. FESA currently holds 1450 stocks, plus sperm samples from 8000 individual males and has access to 3 laboratories within the Mary Lyon Centre.

The FESA core comprises a team of 10 members of staff with extensive experience of cryopreserving/rederiving of the laboratory mouse. This service is managed by **Martin Fray** who has 20 years research experience, plus 7 years of cryopreservation experience. His deputy manager, **Amanda Pickard**, has 15 years research experience in reproductive biology.

4	Karolinska Institute	KI	SWE

The **Karolinska Institutet (KI)** is a leading medical university in Europe, with approximately 3000 employees, and carries out front-line research in many areas of medicine and biology. KI has a large core facility for production, cleansing and archiving of genetically modified mice. This unit, the **Karolinska Center for Transgenic Technology (KCTT**, www.kctt.ki.se) also organizes international conferences, most importantly the International Series of Transgenic Technology Meetings. The Karolinska Center for Transgene Technologies, founded by Prof. **Urban Lendahl** and under the direction of Assoc. Prof. **Johannes Wilbertz** and Dr. Stephan Teglund, is a core facility for generation and banking of genetically modified mice, including all major techniques in the above areas. KCTT performs quality assured core facility functions, and is linked to the cryobank unit and portal for export and import of mice to and from the Karolinska Institute. The cryobank unit is housing the Scandinavian node for the EMMA consortium. The mouse mutant bank today contains embryos from over 300 stocks. Principal staff for this operation is MSc. **Hanna Karlsson**, who is coordinating the core facility functions, and Dr. Olga Lund, who is coordinating the cryobank at the portal.

5	Fundação Calouste Gulbenkian, Instituto Gulbenkian de Ciencia	FCG-IGC	PT

The **Instituto Gulbenkian de Ciência (IGC)** was founded and is supported by the **Fundação Calouste Gulbenkian** to carry out biomedical research and education. The IGC operates as a 'host institution', offering excellent facilities and services to foreign and Portuguese research groups or individual scientists, in particular to young post-doctoral fellows who are expected

to develop their projects and form their groups in complete autonomy. The Institute's scientific interests are focused on the genetic basis of development and the evolution of complex systems and concentrates on organism-centred approaches in experimental models that include plants, yeast, flies and mice, and on the genetics of complex human diseases.

The IGC mouse facility is partitioned into 5 independent areas, each with a specific bio-containment level, including germ-free and strict SPF. The facility hosts about 30000 mice and maintains about 100 different inbred strains, which are available to in-house and associated research groups and to visiting scientists. Production and experimental areas are set to serve active research in various fields of biology (development, neurobiology, infectious diseases, immunology and genetics). Associated with the IGC mouse facility, the Unit for Gene Manipulation provides services for the generation of transgenic and knock-out mice, embryo re-implantation, embryo and sperm freezing.

António Coutinho is the Director of the IGC since 1998. **Jocelyne Demengeot** is the head of the mouse facility and is representing the IGC in the EMMA Board of Participating Directors. **Moises Mallo** is supervising the Gene Manipulation Unit. **Tatiana Vassilevskaia** is responsible for the germ-free service and the management of the collection of frozen strains.

6	Helmholtz Zentrum München German Research Centre for Environmental Health GmbH	HMGU	DE

HelmholtzZentrum münchen
German Research Center for Environmental Health

The **Helmholtz Zentrum München - German Research Centre for Environmental Health GmbH (HMGU)** - located in Neuherberg / Munich - is a member of the Helmholtz Association, the largest research organisation in Germany. The **Institute of Experimental Genetics (IEG)** is interested in the functional analysis of mammalian genomes using the mouse as a model organism to carry out analyses of gene function and to elucidate the pathogenesis of diseases. Within a large scale ENU mutagenesis screen numerous new mutant lines are produced, leading to the identification of new genes and to valuable insight into gene function. In the **German Mouse Clinic (GMC)** standardized and comprehensive phenotypic analysis of mouse mutants from various sources are developed and offered. To accomplish the increasing number of mutants the expertise in cryopreservation and archiving has been built up since 1997, resulting in an archive of over 800 mutant mouse lines (sperm and embryos). Complemented with reproductive techniques, cryopreservation of germplasm provides a secure and economical management of storing the enormous numbers of new mutations generated enabling their use for future research.

Prof. Dr. Martin Hrabé de Angelis is head of the Institute of Experimental Genetics as well as the **EMMA Director**. In addition, he is co-ordinator of the **INFRAFRONTIER** project. Among his responsibilities as EMMA director are the overall scientific coordination of the EMMA consortium and the supervision of the **EMMA Project Office** that is also located at the institute. **Dr. Michael Hagn** and **Dr. Sabine Fessele** are the **EMMA project managers** running the Project Office since 2005. **Dr. Susan Marschall**, responsible for the Cryo-Unit of the IEG, has worked in the field of cyropreservation for many years.

The HMGU-IEG is a partner of the **PRIME**, **EUCOMM** and **EUMODIC** European Networks and of the National Genome Research Network of the German Federal Ministry of Education and Research (**NGFN II**).

7	European Molecular Biology Laboratory European Bioinformatics Institute	EMBL-EBI	DE

The **European Bioinformatics Institute (EBI)** is a non-profit academic organisation that forms part of the European Molecular Biology Laboratory (EMBL). The EBI is a centre for research and services in bioinformatics. The Institute manages databases of biological data including nucleic acid, protein sequences and macromolecular structures. The mission of the EBI is to ensure that the growing body of information from molecular biology and genome research is placed in the public domain and is accessible freely to all facets of the scientific community in ways that promote scientific progress. Ensembl is a joint project between the EMBL-EBI and the Wellcome Trust Sanger Institute that aims at developing a system that maintains automatic annotation of large eukaryotic genomes. Access to all the software and data is free and without constraints of any kind. It is a comprehensive source of stable annotation with confirmed gene predictions that have been integrated from external data sources. Ensembl annotates known genes and predicts new ones, with functional annotation from InterPro, OMIM, SAGE and gene families. The EBI is the largest centre for bioinformatics in Europe and has extensive expertise and experience in most of the issues under investigation in the proposed EMMAservice project.
Dr. Ewan Birney is a Senior Scientist at EMBL working at the EBI outstation. He is the head of the EBI side of **Ensembl**, a project to analyse large metozoan genomes, in particular Human and Mouse. Additional current projects are: **Reactome,** a project to store pathway data in particular in Human; **VectorBase,** A project involved in the malaria-carrying mosquito; and **ENFIN**, a Network of Excellence intended to make computational systems biology accessible to bench scientists throughout Europe and beyond. **Dr. Damian Smedley** is also based at the EBI outstation, working on the Ensembl project. He has a background in both molecular biology and bioinformatics and is currently the Project Leader for mouse informatics within Ensembl. He has been with Ensembl for 4 years and for the majority of the time was developing the BioMart data management software. Damian is supported by **Phil Wilkinson** who is the EMMA web developer.