European Cooperation in the field of Scientific and Technical Research - COST -

Secretariat

Brussels, 11 June 2009

COST 216/09

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM0901: European systems genetics network for the study of complex genetic human diseases using mouse genetic reference populations (SYSGENET)

Delegations will find attached the Memorandum of Understanding for COST Action BM0901 as approved by the COST Committee of Senior Officials (CSO) at its 174th meeting on 26-27 May 2009.

MEMORANDUM OF UNDERSTANDING

For the implementation of a European Concerted Research Action designated as

COST Action BM0901

EUROPEAN SYSTEMS GENETICS NETWORK FOR THE STUDY OF COMPLEX GENETIC HUMAN DISEASES USING MOUSE GENETIC REFERENCE POPULATIONS (SYSGENET)

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

1. The Action will be carried out in accordance with the provisions of document COST 270/07 "Rules and Procedures for Implementing COST Actions", or in any new document amending or replacing it, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to contribute to the discovery of gene networks that are involved in the development of complex genetic diseases in human.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 36 million in 2009 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter V of the document referred to in Point 1 above.

A. ABSTRACT AND KEYWORDS

SYSGENET will contribute to the discovery of gene networks that are involved in the development of complex genetic diseases in human. Mouse genetic reference populations (GRPs) will be used as model systems to investigate the biological mechanisms and gene regulatory networks involved in infectious diseases, behavioural abnormalities, metabolic diseases, regeneration, and others. The proposed network will establish an infrastructure to provide the EU research community with access to existing and future GRP resources. At present, there is no European network integrating ongoing national research projects in this field. SYSGENET will create an ideal basis for the European research community to make major scientific contributions in the field of complex genetics, systems biology and development of sophisticated experimental model systems for the better understanding and treatment of human diseases. SYSGENET will also reach out to activities in the United States and Australia.

Keywords: Complex genetics of human disease, mouse model systems, systems genetics, genetic reference populations

B. BACKGROUND

B.1 General background

Most diseases and predispositions to disease in humans are not modulated by single gene mutations but are affected by complex interactions of several genes and their allelic variants, together with diverse environmental factors. Well known examples are infections, metabolic, cardio-vascular and neurological diseases. Therefore, to understand the effect of combinations of alleles to a given phenotype is an important step towards an efficient diagnosis and therapy of human diseases.
At present, we are just beginning to appreciate the complexity of genotype-phenotype associations in humans, but more detailed and comprehensive analyses in basic research are urgently needed. Although studies in humans are essential, they are limited because of the size of cohorts, strong but often unknown environmental influences, poor diagnosis, and lack of repeatability. Therefore, animal models are absolutely essential to complement human studies. They allow investigating principle biological mechanisms in well controlled experimental systems.

In particular, the mouse is an ideal model system for studying genetic factors that contribute to disease because genetic reference populations (GRPs) with a large number of allelic variants in many genes are available. Several GRPs are currently available, and more are currently being produced in the US and Australia. Examples for GRPs are Recombinant Inbred Strains (RIS), Consomic Substitution Strains (CSS) and Interspecific Recombinant Congenic strains (IRCS). Currently, the largest set of RIS is the BXD strain collection. They represent a set of about 70 different strains in which two parental genomes, C57BL/6J and DBA/2J are segregating. Thus, instead of an individual mouse variant being the model, the model actually is the whole population of related RI strains.

By performing phenotype analysis on a GRP, one can immediately map the genomic regions that contribute to the phenotypic variations. More importantly, RI strains allow multiple research groups to work in parallel on the same genetically identical set of strains and collect many mutually reinforcing data sets. These data sets can then be compared at multiple levels across many biological systems. In addition to classical phenotyping, *e.g.* diabetes, infection susceptibility or behaviour, which allows detecting Quantitative Trait Loci (QTLs), genome-wide gene expression levels can also be analysed in GRPs. The latter approach permits to identify so-called expression-QTLs (eQTLs). eQTLs describe potential regulatory gene-gene interactions and relating may eQTLs to each other will eventually allow identifying whole gene regulatory networks.

This new systematic approach of assessing data from multiple phenotypes on many individuals in segregating GRPs has been termed Systems Genetics.

B.2 Current state of knowledge

Numerous research groups in Europe are performing complex genetics analyses. For this purposes several GRPs have been generated and are currently being maintained by different national research networks and institutions in Europe. Examples are:

1. The GeNeSys network in Germany and the Dutch Mouse Phenomics Consortium (MPC) in the Netherlands has set up a central RIS resource of about 40 BXD strains.
2. In the UK and Israel 200 RIS strains were generated from eight parental mouse inbred strains and are currently maintained in Tel Aviv. This activity is part of the world-wide Collaborative Cross initiative.

3. In France, about 50 Interspecific Recombinant Congenic Strains (IRCS) have been established where segments of the *Mus spretus* strain SEG/Pas have been introgressed onto the laboratory mouse strain C57BL/6J.
4. In Prague, a set of 27 Consomic Substitution and subconsomic Strains (CSS) has been established where whole chromosomes of the strain PWD/Ph have been introgressed onto a C57BL/6J mouse background.
5. In The Netherlands, a set of 21 consomic strains (CSS) are currently maintained. They are derived from C57BL/6J (host strain) and A/J (donor strain). This panel was originally generated by the group of Joseph Nadeau (University of Cleveland, USA),

All the above described activities are funded by national or bi-national programmes and are not yet integrated. Therefore, the main objective of the proposed SYSGENET network will be to bring together the different expertise, resources and existing national activities in the field of systems genetics in Europe and to integrate them into a world-wide effort to understand complex genetics of human diseases using mouse GRPs.

B.3 Reasons for the Action

The proposed network will play an important role in integrating mouse genetics activities in the field of complex genetics in Europe and into international networks. The most important one is the integration of European activities into the Collaborative Cross (CC).
The international Complex Trait Consortium (http://complextrait.org/) has designed the Collaborative Cross (CC) as a novel innovative GRP. The CC aims at the generation of about 1500 recombinant inbred strains from eight parental mouse inbred strains and is currently ongoing in the US and in Australia, and at a smaller scale in Israel (see above). The partners of the proposed network are all active participants in the CTC and intensively involved in the design, scientific concept and progress of the CC. However, concepts for usage of the CC and implementing it as a resource on European grounds have not been developed, mainly because there is no European network which unites scientists in the EC in this field. Thus, SYSGENET will represent a consortium and an infrastructure which will allow a strong European presence in this endeavour and give European researchers access to this novel resource, when it is ready in the coming next 3-4 years.

B.4 Complementarity with other research programmes

SYSGENET aims to integrate activities in the field of complex genetics. In this way, it will be highly complementary to already ongoing research programmes in the EU on single gene genetics (Mendelian genetic traits) in Europe. Modelling human diseases using Mendelian mouse genetics, *e.g.* gene trap and gene targeting approaches, is being supported by several EU research Framework Programmes, *e.g.* EUCOMM and EUMODIC. However, there are no comprehensive research programmes that would address modelling of human diseases for complex genetic diseases. Establishing a COST network across Europe in the field of systems genetics would thus represent an ideal and important complementation to existing ongoing research programmes in the field of functional genetics.

C. OBJECTIVES AND BENEFITS

C.1 Main/primary objectives

The main objective of SYSGENET is to contribute to the discovery of gene networks that are involved in the development of complex genetic diseases in human. SYSGENET will allow researchers in different European countries to devise common research programmes and infrastructures which will give them access to various GRP resources from different European laboratories and to future GRP resources world-wide. The results from these research activities will provide the basis for a better understanding of human diseases and allow the development of new strategies for their prevention and therapy. In addition, SYSGENET will create a data sharing pan-European platform where the results of multiple phenotypic studies can be combined and new associations between phenotypes, gene networks and genotypes can be identified, allowing entering into the new area of systems genetics.

C.2 Secondary objectives

The operational goal of this Action is to create a network of scientists with expertise in systems genetics to integrate the different national, European and world-wide research programmes in this field. In addition, SYSGENET will provide a platform for short term scientific missions (STSM) and train young researchers in the field of systems genetics.

C.3 How will the objectives be achieved?

SYSGENET will be built on already existing and ongoing nationally funded research projects in the different partner countries. The COST framework represents an ideal instrument in the European framework which allows bringing together the many groups and experts across Europe in the field of systems genetics, to prepare future infrastructures needed for the maintenance and development of GRPs, and to create an environment where young researchers can develop a career in this newly emerging field.

The objectives of SYSGENET will be realised by:

1. Coordination of ongoing and future projects in Europe in the field of systems genetics
2. Establishing an infrastructure which allows to set up a European mouse breeding colony and distribution system GRPs, and in particular the Collaborative Cross
3. Sharing expertise in the analysis of QTLs, eQTLs, candidate gene search and analysis
4. Sharing expertise in phenotype analysis
5. Establishing a data sharing platform for combined analysis of multiple phenotypes
6. Association with ongoing mouse genomics projects involved in the analysis of Mendelian genetic traits in the EU
7. Association with ongoing systems genetics projects in the US and Australia
8. Contribution to the establishment of standards (genetic quality control, phenotyping)

The instruments used to achieve these goals are:

1. Network meetings, scientific meetings and work shops
2. Working Groups
3. Short Term Scientific Missions
4. Training courses

The deliverables are:

1. Establishing a Management Committee and Working Groups
2. Generation of scientific results in the field of systems genetics contributing to the understanding of molecular and genetic mechanisms of human diseases

3. Developing a concept for coordination of phenotyping and standardization of recording and sharing the results
4. Developing a concept for establishing and sharing GRP resources in Europe
5. Developing a concept for the integration of European research activities into international activities
6. Organisation of network meetings, Management Committee and Working Group meetings, scientific work shops and meetings
7. Organisation of training schools
8. Establishing a platform for exchange visits for the career development of young researchers and women

C.4 Benefits of the Action

The long-term benefit of SYSGENET will be the identification of genes and gene networks that contribute to human diseases. Fundamental principles of, *e.g.* host-pathogen interactions, gene-environment interactions, gene regulatory networks will be studied and the molecular basis identified. These discoveries will allow the European research community to make a major scientific contribution to the field of complex genetics, systems biology and generation of experimental model systems for human diseases. The knowledge created will allow a better understanding of the biological mechanisms that cause disease and thus, to devise new strategies for the diagnosis, prevention and therapy of human diseases.

The establishment of a common phenotype database will allow new types of genotype-phenotype relationships at a new level of more comprehensive and yet unprecedented complexity. New tools will be developed that will aid the analysis of human diseases in human cohort and case-control studies.

An important aspect of the future work in complex genetics is the establishment of a common database and an infrastructure for providing mice from the different GRPs. At present, there is no European network that is addressing this issue. Without such a network, the European research community will miss out the opportunity to make a significant contribution in the field of systems genetics and the analysis of complex diseases in human.

Furthermore, SYSGENET will contribute to the education of young researchers in the field of systems genetics by offering special training schools.

C.5 Target groups/end users

The SYSGENET activity will target all major scientific groups in Europe which work in the field of systems genetics and use GRPs as a resource. These groups will be the end users for which SYSGENET aims to create a common platform for the distribution of mouse strains from various GRPs and bioinformatics resources and tools to analyze complex genetic traits.
Furthermore, through its international outreach activities, SYSGENET will also target the scientific community world-wide and contribute to shaping future research infrastructures and programmes.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The principle scientific approach of the SYSGENET research projects will be to phenotype mice from different GRPs, to collate the data in a central database and to analyse them for QTLs and draw conclusion about associations between different diseases. The most innovative aspect of this approach is to commonly exploit the currently available and future GRP resources across many laboratories.

D.2 Scientific work plan - methods and means

The following research areas will be addressed. However, SYSGENET will be open to include other areas of experimental approaches to complex genetics in mouse GRPs.
Infectious diseases: Infections have a major impact on human health; about ¼ of all deaths world-wide are caused by infections. Many antibiotic-resistant pathogens are emerging, modern medical treatments and an ageing population increase the overall risk for infections in immune-compromised people and the global trade and travelling is spreading newly emerging diseases rapidly across the globe. This research area is aiming to understand the basic mechanisms of host pathogen-interactions at the molecular, genetic, and cellular and organism level by using infection models well established in the partner laboratories. More importantly, a systems genetics approach will not only allow to identify susceptibility/resistance genes, but also to evaluate additional risk factors for the development of other common diseases, *e.g.* cancer or cardio-vascular diseases.

Metabolic disease: These diseases depend to a large extend on gene-environment interactions. For example, obesity is determined by food intake, food quality but also to a large extend by the genetic background. In recent years, studies in experimental mouse models have contributed to the discovery of genes that contribute to the obese phenotype. Epidemiological observations in humans indicate an association between malnutrition and susceptibility to infection on the one hand, and obesity and autoimmune diseases on the other hand. However, very little is known about the molecular mechanisms that influence the effect of obesity and other genetic risk factors to other common diseases, like immune defects, allergies, cardio-vascular diseases. A systems genetics approach will allow unravelling associations across phenotypes and genotypes influencing these traits.

Liver diseases**:** Organ fibrosis, or scarring, is a leading cause of morbidity and mortality world-wide. Specifically, liver fibrosis is the common end-stage of all chronic liver diseases, in particular chronic viral infections, and represents a major economic challenge to our health care systems. Activated myofibroblasts are the key players driving the process of *de novo* deposition of abnormal extracellular matrix, which is modulated by complex interactions between cytokines, receptors, and matrix components. Several studies demonstrated that the course and progression of the fibrogenic response to chronic liver injury display significant variability among individual patients. Host genetic factors are critical but are yet to be identified systematically. Some genetic determinants of liver fibrogenesis have been identified by quantitative trait locus analysis in experimental mouse model systems and shown to also contribute to disease in humans. Using GRPs will allow determining genetic factors and identifying causal gene networks contributing to liver fibrogenesis. The genetic determinants that contribute to steatohepatitis and fibrosis will be studied. In humans, steatohepatitis develops either as a consequence of alcohol abuse, or as a metabolic disease, resulting from obesity, insulin resistance, or a combination of these. However, the disease develops only in a subgroup of individuals with the respective risk factors, indicating a strong influence of genetic background. A similar phenomenon is observed in mouse models, where different inbred mouse strains show distinct susceptibilities to the disease.

Cancer**:** In 2008 about 148.000 new cases of colorectal cancer have been diagnosed in the United States and about 50.000 deaths were reported by the National Cancer Institute. The individual genetic background has a major impact on the life-time risk of developing cancer and on cancer progression. Modifiers that influence intestinal tumour formation will be identified by crossing an established mouse model of human colon carcinogenesis (the *Apc*$^{min/+}$ mouse) to the B6.PWD chromosome substitution strains.

Behaviour: Psychiatric illnesses are a major health problem worldwide, for example unipolar major depression is among the top ten sources of disease burden in both low and middle income countries and high income countries. There is an urgent need for better understanding of underlying genetic and environmental factors. Especially for behavioural studies the mouse is an essential complement to human studies because the environment can be well controlled and it is possible to access the brain tissues. Because of the difficulty of measuring behaviours precisely, GRPs consisting of inbred strain panels are particularly valuable. But even more so, the future GRPs that will be generated as an international effort offer the advantages of an RI panel with single gene resolution, and this will be a revolution in behaviour genetics.

Regeneration**:** The regeneration of adult tissues and the use of stem cells has become a major interest in biomedical research. For example, in the brain, the hippocampus generates lifelong new neurons. Adult hippocampal neurogenesis is discussed as an important factor in the development of neuropsychiatric disorders such as Alzheimer disease and major Depression. Similarly, the haematopietic system generates new blood cells from a very small pool of stem cells during the entire life of an organism. In both cases, the gene regulatory pathways which govern the maintenance of the stem cell population and their differentiation into progenitor lineages are not well known. Systems genetics with GRPs will help to identify and understand the molecular pathways that are common and specific to different regeneration processes and the development of stem cells.

Reproduction: During the past decades, decline of human male and female fertility has been repeatedly reported in different countries of the developed world. The mouse models will help to distinguish the genetic and environmental part of the phenotype. Genetic regulatory networks controlling the male gametogenesis will be studied as their knowledge is urgently needed for developing rational probes to diagnose the causal mechanisms of declining male fertility.

Bioinformatics and database**:** At present, a number of tools to analyze data from GRP phenotyping data have been developed and are publicly available. However, the expertise to explore this vast amount of data in a proper way is not widely present across European laboratories. Therefore, establishing SYSGENET will provide a larger community in Europe with the necessary expertise and state-of-the-art software tools. Furthermore, phenotype data will need to be collected in a common database and in a standard format. SYSGENET will provide the necessary environment of experts in the field and major stake holders to build a commonly accepted and valuable data resource. These activities use and further develop the existing tools in GeneNetwork which has been developed at the University of Tennessee Health Science Center in Memphis and incorporates already a wide range of genotype and phenotype data sets for GRPs.

E.ORGANISATION

E.1 Coordination and organisation

In SYSGENET, the participating laboratories will provide their expertise and contribute through their national funding programmes to promote research in the area of systems genetics.
SYSGENET will establish a general management structure which consists of the Management Committee and Working Groups. The instruments applied will be scientific meetings and workshops, training schools and Short Term Scientific Missions.
At least one member from each participating country will be represented in the Management Committee (MC)**.** In addition, each Working Group will have one representative in the MC. The MC will elect a chair from its members who will be responsible for the general organisation of the Action and represent the Action towards the EU commission and the public. The MC will meet at least twice per year as the committee which organizes and decides about the various activities of the Action. The MC will decide about the distribution of funds according to the scientific needs of the Action. Also, the MC will prepare the annual reports and the final report. The first MC meeting will serve as a kick-off meeting, to discuss and finalize the general objectives, goals and deliverables of the Action, and to inaugurate the Working Groups.

The different activities of SYSGENET will be organized in five Working Groups (WGs)**.** Each WG will be headed by one scientist who will develop the aims of the Working Groups together with the participating scientists, and in close interaction with the MC. The leading scientist will report the progress to the MC. The Working Groups will continuously meet during the funding period, but at least twice per year.

Plenary Symposia and/or Workshops will be held once per year. In year 2 and 4, the symposia will be held jointly with international partners. These actions will be open to the general scientific community.

Training Schools will be established for young researchers (PhD student level and early postdoctoral level). They are envisaged for a period of 3-5 days, with experts from the SYSGENET network, their associated international research groups, and experts in the field of systems genetics.

An exchange programme will be developed as Short Term Scientific Missions (STSMs**)** to allow young researchers to visit other groups from the participating laboratories and to learn a specific method or get acquainted to another research area which is relevant for their studies.

For optimally economizing costs and time, the annual meetings, joint international meetings and MC meetings will be combined and performed at the same location and adjacent or same days (see time table).

E.2 Working Groups

WG1 "GRP Resources"

The objective of this Working Group is to define the needs for the European research community in terms of types of different genetic reference populations (GRPs) and their powers for studying systems genetics, numbers of animals to be generated and studied, and origin of strains. The WG will also collect information of already existing GRPs in Europe. In addition, the WG will identify the best concept and locations to maintain GRP resources in Europe and design business models to sustain them. Furthermore, the logistics of distributing mice across the different European research teams, as well as standards for quality control and health status of animals at the different sites of the consortium will be specified.

WG2 "Phenotyping & Genotyping"

The objective of this Working Group will be to describe ways for standardization of phenotype analysis across the different European research teams, descriptions of assays and results, and define criteria for data capture in close interaction with WG3. In addition, resources and infrastructures for genotyping of GRPs should be worked out in collaboration with ongoing international activities. For the discussions on genotyping and phenotyping analysis close interaction with WG 4 will be important to integrate these into other non-European programmes. Furthermore, these activities will be performed in cooperation with already existing EU-projects, like EUMODIC, EUCOMM, *etc.* which now address mainly the phenotyping of mouse knock-out and gene-trapped mutants.

WG3 "Bioinformatics"

The objective of this Working Group is to establish a common database in which phenotyping data will be entered and to provide tools for the community to analyze complex traits and trait correlations. These activities will be performed in close interactions with already existing databases and analysis tools at the Wellcome Trust Center for Human Genetics and the GeneNetwork database developed at the University of Memphis.

WG4 "International Outreach"

The objective of this Working Group is to establish relationships to other related activities in non-European countries. In particular, the WG will identify and describe the best ways to interact with the initiatives for the Collaborative Cross in the United States and Australia. A major task will be to work out access to these mouse strains and the coordination with already existing activities in Europe. Also, meetings with other non-European groups in the field of phenotyping and genotyping will be held to ensure that future activities are not duplicated but performed in the most integrative way.

WG5 "Training & Mobility"

The objective of this Working Group will be to identify the needs for training of young researchers in the field of systems genetics, phenotyping and genotyping tools, develop concepts for training courses in the different Institutes involved in the consortium and identify suitable training experts. These activities will be performed in close interaction with WGs 2, 3 & 4. In addition, this WG will oversee the STSM: review of applications, selection of candidates and activities to be funded.

E.3 Liaison and interaction with other research programmes

National programmes

In each participating European country, the partners are funded through national research programmes. The goal of SYSGENET is to integrate these national activities.

In the UK**,** the Wellcome Trust Centre for Human Genetics, Oxford has several Wellcome Trust-funded programmes in mouse complex genetics: (i) a five-year programme grant to use commercially available outbred populations of mice for mapping complex traits. (ii) a five-year programme grant to develop statistical methods in mouse complex genetics.

In Israel and the UK**,** 200 RIS strains were generated from eight parental mouse inbred strains and are currently maintained in Tel Aviv. First phenotyping studies have been initiated in Tel Aviv and Oxford. This activity is part of the Collaborative Cross and funded by the Wellcome Trust.

The Dutch Mouse Phenomics Consortium (MPC) in The Netherlands has set up a central recombinant inbred strain resource of 40 BXD, strain and a consomic panel derived from C57BL/6J (host strain) and A/J (donor strain) is currently being maintained. National funding has been obtained to study the these strains, *e.g.* from The Netherlands Organisation for Scientific Research (NWO).

In France, Interspecific Recombinant Congenic Strains (IRCS) have been established where short-sized segments of the *Mus spretus* mouse strain SEG/Pas have been introgressed onto a laboratory mouse genetic background, C57BL/6J. This programme is funded by the Institut Pasteur and by grants for collaborations with several laboratories in France and Europe.

In Switzerland, in the National Centres of Competence for Research (NCCR) a programme is initiated in which the Center of Phenogenomics of the EPFL will use GRPs to elucidate genetic mechanisms contributing to the control of metabolism and aging.

In Germany, the GeNeSys programme represents a network of ten research laboratories which shares a common BXD recombinant inbred strain set for the analysis of traits influencing infections (*S. aureus*, Influenza A, *L. monocytogenes*, *M. tuberculosis*, *Y. enterocolytica*, Leishmania, septic shock), diabetes, liver fibrogenesis, and adult neurogenesis.

EU programmes

At the European level, SYSGENET will seek close collaborations and interactions with already existing research programmes in mouse genetics. Examples are:
EuroMouse is an initiative to unite all activities in mouse research at the European level (http://www.prime-eu.org/euromouseiiprojects.htm).
The EU-funded programme EUCOMM aims to establish an ES cell resource in which a total of 13.000 mouse genes will be mutated (http://www.eucomm.org/).
EUMODIC represents an EU-funded programme with the objective to phenotype up to 650 mutant mouse lines (http://www.eumodic.eu/).
Infrafrontier aims to establish a European infrastructure for large scale phenotyping and archiving of mouse mutants and lines (http://www.infrafrontier.eu/).

International programmes

The international Complex Trait Consortium (CTC) (http://complextrait.org/) has designed the Collaborative Cross (CC) as a novel innovative GRP.

E.4 Gender balance and involvement of early-stage researchers

This COST Action will respect an appropriate gender balance in all its activities and the Management Committee will place this as a standard item on all its MC agendas. The Action will also be committed to involve early-stage researchers. This item will also be placed as a standard item on all MC agendas.
Female Scientists**:** In order to achieve an equitable gender balance in the proposed Action, we especially encourage highly qualified women to participate. Several of the participating universities and research institutes offer mentoring programmes and support or provide day care facilities for children of all age groups. The most important measure to take will be to encourage and support the career progression of the women already in each of our teams and view female applicants for the activities supported by this Action favourably.
Young researchers**:** A special exchange and training school programme will be established for young researchers. It will target PhD students in their final years and early stage researchers at the postdoctoral level. More details have been described above.

F. TIMETABLE

The life time of the Action is four years, with continued activity beyond that period via collaborations, website, and anticipated programme funding. The Action is initiated with a kick-off meeting. Below is a schematic time schedule for the different actions during the running period.

Action Item	Year1	Year2	Year3	Year4
Kick-off meeting, 1st SYSGENET general meeting (all participants)	Q1			
Inauguration of MC				
Inauguration of WG (leader, group members, objectives, goals)				
WG meetings (definition of tasks, deliverables and milestones)	Q2-4			
MC meeting (report WGs, final definition of tasks, etc.)	Q3			
Deliverables no 1 WGs	Q4			
WG meetings		Q1-4		
2nd annual SYSGENET general meeting		Q2		
MC meeting (report WGs, deliverables)				
Outreach meeting with international scientific community				
Deliverables no 2 WGs		Q3		
MC meeting (report WGs, deliverables)		Q4		
Deliverables no 3 WGs			Q1	
WG meetings			Q1-4	
3rd annual SYSGENET general meeting			Q2	
MC meeting (report WGs, deliverables)				
Deliverables no 5 WGs			Q3	
MC meeting (report WGs, deliverables)			Q4	
WG meetings				Q1-3

Final annual SYSGENET general meeting				Q3
Outreach meeting with international scientific community				
MC meeting (report WGs, deliverables)				
Deliverables no 5 WGs				Q3
Final report and publication				Q4

Q: quarter of year

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: AT, CZ, FR, DE, IL, NL, CH, TR, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 36 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

The participating scientists will publish their results on phenotyping and genotyping of mouse GRPs. These scientists have a well proven track record in scientific research and are experts in the field of complex genetics.
Furthermore, the MC and the Working Groups will work out a dissemination plan to publish the specific results of their meetings. This plan will be part of the deliverables and milestones.

H.2 What?

The main results of SYSGENET will be new findings by the participating scientific groups on the contribution of genomic factors to disease related phenotypes. These results are expected to provide new insights into the molecular mechanisms of diseases in humans.

Another important aspect of SYSGENET is to identify the needs for a European infrastructure and to make suggestions for its implementation. For this part, the MC will work out a dissemination plan to present the results of the Working Groups' discussions to the scientific community.
Each of the Working Groups will develop a dissemination plan for the results of their work. These will be contained in publications in scientific journals and the final report to the EC.
Each of the Working Groups will develop a dissemination plan for the results of their work. These will be contained in publications in scientific journals and the final report to the EC.

H.3 How?

The scientific results of the SYSGENET network will be published in scientific journals and presented at scientific meetings.
A final report will be created to the EC containing suggestions for future funding programmes to support the establishment of an infrastructure for mouse GRPs in Europe and for a large scale phenotyping programme.
In addition, a website will be set up where the objectives, goals and progress of the SYSGENET network will be presented.