

COST

Domain Committee "BMBS"

COST Action (BM0901)

Start Date (13.11.2009)

European systems genetics network for the study of complex genetic human diseases using mouse genetic reference populations (SYSGENET)

MONITORING PROGRESS REPORT

Reporting Period: from April 2011- April 2012

This Report is presented to the relevant Domain Committee.
It contains three parts:

- I. Management Report*** prepared by the COST Office/Grant Holder
- II. Scientific Report*** prepared by the Chair of the Management Committee of the Action
- III. Previous versions of the Scientific Report; i.e., part II of past reporting periods***

The report is a "cumulative" report, i.e. it is updated annually and covers the entire period of the Action.

Confidentiality: the documents will be made available to the public via the COST Action web page except for chapter *II.D. Self evaluation*.

Based on the monitoring results, the COST Office will decide on the following year's budget allocation.

Executive summary (max.250 words):

The Action is now running for two and a half year and has considerably increased to 45 MC and MC substitute members from 18 different countries. Two MC meetings took place in 2011. The first MC meeting in Helsinki FI, on June 10, 2011 reviewed on-going activities and discussed the plans for the remainder of the year. The second MC meeting took place in London, UK, December 9, 2011, to review the last year activities and discuss the actions and budget plan for the coming year. Three WG meetings were held: The bioinformatics WG3 got together in Groningen, NL, July 6th-7th to review different tools for complex trait mapping and genotyping and to perform feasibility studies to integrate data from different databases. The WG4 held two meetings, to build European/International networks. The first one was on January 24, 2011 in Frankfurt DE together with partners from the US to discuss future strategies for the distribution of Collaborative Cross mouse strains in EU. The second meeting was held on September 21, 2011 in Frankfurt DE, with only European partners about the first steps to establish activities in Europe for phenotyping and distribution of CC mice. Furthermore, SYSGENET organised two scientific workshops. A work shop in Helsinki FI, on June 9, 2011, brought together clinicians and mouse researchers to discuss the mouse model cross-species research on schizophrenia. The second workshop on October 23-24, 2011 in Tel-Aviv IL, brought together researchers in Europe to exchange their results in the area of complex genetics in infection and inflammation. Eight STSMs were funded and four trainees were supported for participation at the 11th MRY SGDP Centre Summer School at the King's College London, UK.

I. Management Report prepared by the COST Office/Grant Holder



I.A. COST Action Fact Sheet

- **COST Action BM0901** - European systems genetics network for the study of complex genetic human diseases using mouse genetic reference populations (SYSGENET)
- **Domain BMBS**

- **Action details:**

CSO Approval: (26/05/2009)

End date: (12/11/2013)

Entry into force: (07/07/2009)

Extension: NA

- **Objectives**

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. The main benefit of establishing SYSGENET will be at the scientific level. SYSGENET will allow researchers in different European countries to devise common research programs and infrastructures which will give them access to various mouse genetic reference populations (GRP) resources from different European laboratories and to future GRP world-wide resources. 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.

- **Parties:** list of countries and date of acceptance

Austria 03/08/2009	Greece 10/03/2010	Poland 07/07/2009
Belgium 13/10/2010	Hungary	Portugal
Bulgaria	Iceland	Romania
Croatia	Ireland	Serbia
Cyprus	Israel 07/07/2009	Slovakia
Czech Rep. 22/09/2010	Italy 04/08/2009	Slovenia
Denmark 28/10/2009	Latvia	Spain 11/07/2009
Estonia 10/09/2009	Lithuania	Sweden
Finland 07/01/2010	Luxembourg 08/02/2010	Switzerland 31/07/2009
FYR of Macedonia	Malta	Turkey 16/09/2009
France 10/09/2009	Netherlands 07/07/2009	United Kingdom 07/07/2009
Germany 07/07/2009	Norway 06/02/2012	

- **Intentions to accept:**

- **Other participants:**

Prof. Grant Morahan, Western Australian Institute of Medical Research, Perth, AU

Chair: Klaus Schughart, Helmholtz Centre for Infection Research, Inhofenstr. 7, 38124 Braunschweig, +49-531-6181-1100, kls@helmholtz-hzi.de

DC Rapporteur: Felicity Rose, University of Nottingham, Room B57, Centre for Biomolecular Sciences, University Park Nottingham, NG7 2RD, United Kingdom, +44-115-8467856
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- **Action Web site:** <http://www.helmholtz-hzi.de/sysgenet>
- **Grant Holder Representative:** Prof. Klaus Schughart, kls@helmholtz-hzi.de
- **Working Groups**

WG	Name	Country	Institution	Function
WG1	Guus Smit	NL	Vrije Universiteit Amsterdam	chair
	Xavier Montagutelli	FR	Institute Pasteur	co-chair
WG2	Paul Franken	CH	University of Lausanne	chair
	Leonard Schalkwyk	UK	King's College London	co-chair
WG3	Ritsert Jansen	NL	Groningen Bioinformatics Centre	chair
	Richard Mott	UK	WTC for Human Genetics	co-chair
WG4	Fuad Iraqi	IL	Tel Aviv University	chair
	Martien Kas	NL	University Medical Centre Utrecht	co-chair
WG5	Wim Crusio	FR	University of Bordeaux and CNRS	chair
	Gudrun Brockmann	DE	Humboldt University Berlin	co-chair

I.B. Management Committee member list

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I.C. Overview activities and expenditure

Meetings

Meeting Type	Date	Place	Cost	Total
WG4: Strategic meeting to discuss CC distribution in EU and US	24/01/2011	Frankfurt, Germany	3372.71	
4th SYSGENET MC meeting/Joint WG Meetings	10/06/2011	Helsinki, Finland	5815.16	
2nd SYSGENET Bioinformatics Working Group 3 meeting	06/07/2011-07/07/2011	Groningen, Netherlands	6403.21	
Other COST relevant meeting: International Workshop on Metabolomics, CICbioGUNE, Bilbao	12/09/2011	Bilbao, Spain	659.95	
WG4: SYSGENET - CC EU distribution and phenotyping strategy meeting	21/09/2011	Frankfurt, Germany	3487.55	
5th SYSGENET MC and working group meeting	09/12/2011	London, United Kingdom	11235.38	30973.96

STSM

Beneficiary	Date	Place	Cost	Total
Konstantina Dimitrakopoulou	06/09/2010-06/11/2010	Helmholtz Centre for Infection Research	810.00	
Luci Chevallier	01/11/2010-31/12/2010	Helmholtz Centre for Infection Research	600.00	
Caroline Durrant	12/05/2011-26/05/2011	Sackler Faculty of medicine, Tel-Aviv University	1350.00	
Rabea Hall	22/05/2011-27/05/2011	Medical University Graz	540.00	
Fuad Iraqi	09/07/2011-29/07/2011	Wellcome Trust Centre for Human genetics, University of Oxford	1800.00	
Elena Terenina	03/10/2011-09/10/2011	Polish Academy of Sciences, Krakow	630.00	
Laura Palomo Diaz	01/10/2011-31/10/2011	Helmholtz Centre for Infection Research	1500.00	
Sebastian Heise	01/11/2011-22/12/2011	University Medical Centre, Utrecht, NL	1500.00	8730.00

Workshops

Beneficiary	Date	Place	Cost	Total
Workshops/Conferences: SYSGENET Workshop: Human and mouse cross-species research on schizophrenia	09/06/2011	Helsinki, Finland	14207.26	
Workshops/Conferences: SYSGENET Infection and Inflammation Workshop	23/10/2011-24/10/2011	Tel-Aviv, Israel	14470.60	28497.86

Schools

Title	Date	Place	Cost	Total
11 th MRC SGDP Centre Summer School	23/10/2011-24/10/2011	King's College London, UK	2840.00	2840.00

Dissemination

Title	Date	Name of Publisher	Cost	Total
SYSGENET a meeting report from anew European network for systems genetics	31/05/2011	Mammalian Genome, Springer	2000.00	2000.00

Others

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FSAC: Financial and Scientific Administration and Coordination	Max 15%	of scientific Expenditure	9400.00
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II. Scientific Report

SYSGENET represents a network of scientists in Europe who use mouse genetic reference populations (GRP) to identify complex genetic factors influencing phenotypic traits. Studies with GRPs are expected to contribute to the discovery of principal biological processes and gene networks that are involved in disease phenotypes. The findings will be translated to human diseases and represent the basis for understanding disease etiology and developing new treatment strategies. These gene networks can be extended to other species, as well.

The researchers in SYSGENET are using various GRPs as model systems to investigate the biological mechanisms and gene regulatory networks involved in disease phenotypes. The SYSGENET network partners are studying phenotypes relevant to infectious diseases, inflammatory disorders, metabolic diseases, cancer, neurological and psychiatric disorders, and infertility. The GRPs presently exploited by the network laboratories include inbred strains, consomic strains, recombinant inbred strains, congenic strains, interspecific recombinant congenic strains, outbred populations, and the upcoming large recombinant inbred strain collection known as the collaborative cross.

SYSGENET integrates the different national, European, and world-wide research programs in the field of complex genetics, systems biology, and the development of sophisticated experimental model systems. SYSGENET also reaches out to systems genetics programs in the United States and Australia.

II.A. Innovative networking

- *Innovative knowledge resulting from COST networking through the Action.*

A workshop meeting in Groningen brought together three groups who work in the field of bioinformatics analyses of complex traits. The Groningen group (Ritsert Jansen) and the Memphis group (Rob Williams) both developed tools for complex trait analysis and provide them together with large data sets to the scientific community via the internet. At the meeting, future strategies to integrate the tools and databases were discussed. In addition, first pilot studies were performed to move data from one data base to the other were performed. This is an important advancement in the field because it will allow more researchers to profit from the developments at both sites.

A second workshop was held at Tel-Aviv University to present and discuss variety of approaches for dissecting host susceptibility to infectious diseases using mouse genetic reference populations. A total of 23 scientists participated at the workshop and 13 presentations were given. The newest, mostly unpublished results obtained from mouse models for infectious diseases with various pathogens, Rift Valley Fever, malaria, streptococci, pseudomonas, pneumococci, influenza A virus, were presented. Also, new mapping tools and related studies in human populations were discussed. In addition, the first phenotyping studies of the Collaborative Cross population for a new model of induced periodontitis were presented.

Two strategic meetings were held to work out the details of the future distribution of mice from the Collaborative Cross (CC) resource to scientists in the EU, and especially, to SYSGENET partners. The first meeting in Frankfurt, 24.1.2011, was held together with researchers from the US to coor-

dinate efforts in Europe and US and to discuss issues related to MTAs. The second meeting, in Frankfurt on the 21.9.2011, was held between SYGENET partners who will have funds to receive and phenotype CC mice. A strategy was developed which should allow receipt of mice, their distribution between the partners and the subsequent distribution to the European research community.

- *Significant scientific breakthroughs as part of the COST Action.*

Several publications in high impact journals were produced by SYGENET participants, they are listed below. The complete list is provided in Annex 2.

H. Yamamoto, E.G. Williams, L. Mouchiroud, C. Canto, W. Fan, M. Downes, C. Heligon, G.D. Barish, B. Desvergne, R.M. Evans, K. Schoonjans, J. Auwerx. NCoR1 is a conserved physiological modulator of muscle mass and oxidative function. *Cell*, 2011, 147, 827-839.

Yalcin B, Wong K, Agam A, Goodson M, Keane TM, Gan X, Nellåker C, Goodstadt L, Nicod J, Bhomra A, Hernandez-Pliego P, Whitley H, Cleak J, Dutton R, Janowitz D, Mott R, Adams DJ, Flint J. Sequence-based characterization of structural variation in the mouse genome. *Nature*, 2011; 477:326-9.

Keane TM, Goodstadt L, Danecek P, White MA, Wong K, Yalcin B, Heger A, Agam A, Slater G, Goodson M, Furlotte NA, Eskin E, Nellåker C, Whitley H, Cleak J, Janowitz D, Hernandez-Pliego P, Edwards A, Belgard TG, Oliver PL, McIntyre RE, Bhomra A, Nicod J, Gan X, Yuan W, van der Weyden L, Steward CA, Bala S, Stalker J, Mott R, Durbin R, Jackson IJ, Czechanski A, Guerra-Assunção JA, Donahue LR, Reinholdt LG, Payseur BA, Ponting CP, Birney E, Flint J, Adams DJ. Mouse genomic variation and its effect on phenotypes and gene regulation. *Nature*, 2011, 14; 477: 289-94.

Conrad DF, Keebler JE, DePristo MA, Lindsay SJ, Zhang Y, Casals F, Idaghdour Y, Hartl CL, Torroja C, Garimella KV, Zilversmit M, Cartwright R, Rouleau GA, Daly M, Stone EA, Hurler ME, Awadalla P; 1000 Genomes Project. Variation in genome-wide mutation rates within and between human families. *Nat Genet*. 2011; 43: 712-4. Hans Lehrach is member of the 1000 Genomes Project.

Mills RE, Walter K, Stewart C, Handsaker RE, Chen K, Alkan C, Abyzov A, Yoon SC, Ye K, Cheetham RK, Chinwalla A, Conrad DF, Fu Y, Grubert F, Hajirasouliha I, Hormozdiari F, Iakoucheva LM, Iqbal Z, Kang S, Kidd JM, Konkel MK, Korn J, Khurana E, Kural D, Lam HY, Leng J, Li R, Li Y, Lin CY, Luo R, Mu XJ, Nemesh J, Peckham HE, Rausch T, Scally A, Shi X, Stromberg MP, Stütz AM, Urban AE, Walker JA, Wu J, Zhang Y, Zhang ZD, Batzer MA, Ding L, Marth GT, McVean G, Sebat J, Snyder M, Wang J, Ye K, Eichler EE, Gerstein MB, Hurler ME, Lee C, McCarroll SA, Korbel JO; 1000 Genomes Project. Mapping copy number variation by population-scale genome sequencing. *Nature*, 2011, 470: 59-65. Hans Lehrach is member of the 1000 Genomes Project.

Guillem K, Bloem B, Poorthuis RB, Loos M, Smit AB, Maskos U, Spijker S, Mansvelter HD. Nicotinic acetylcholine receptor $\beta 2$ subunits in the medial prefrontal cortex control attention. *Science* 2011; 333: 888-91.

Aylor DL, William Valda, Wendy Foulds-Mathes W, Buus RJ, Ricardo A. Verdugo RA, Ralph S. Baric RS, Ferris MT, Frelinger FA, Heise M, Frieman MB, Gralinski LE, Bell TA, Didion JP, Hua K, Nehrenberg DL, Powell CL, Steigerwalt J, Xie Y, Kelada SNP, Collins FS, Yang IV, Schwartz DA, Branstetter LA, Chesler EJ, Miller DR, Spence J, Liu EY, McMillan L, Sarkar A, Wang J, Wang W, Zhang Q, Broman KW, Korstanje R, Durrant C, Mott R, Iraqi FA, I Pomp D, Threadgill D, de Villena FPM, Churchill GA (2011) Genetic Analysis of Complex Traits in the Emerging Collaborative Cross. *Genome Research* 21(8): 1213-1222. (*Genetics & Heredity* 6/156, IF 13.588).

Durrant C, Tayem H, Yalcin B, Cleak J, Goodstadt L, Pardo-Manuel de Villena F, Mott R, Iraqi FA, (2011) Mapping QTL associated with host susceptibility to *Aspergillus fumigatus* infection in the Collaborative Cross mouse resource population. *Genome Research* 21(8): 1239-1248. (*Genetics & Heredity* 6/156, IF 13.588).

Duprez, L., Takahashi, N., Van Hauwermeiren, F., Vandendrische, B., Goossens, V., Vanden Berghe, T., Declercq, W., Libert, C., Cauwels A., and Vandenabeele, P., RIP1/RIP3-dependent necroptosis drives lethal TNF-induced systemic inflammatory response syndrome (SIRS). *Immunity*, 2011, 35(6):908-18. (ISI-IF=24,22)

- *Tangible medium term socio-economic impacts achieved or expected.*

The Action represents an activity in basic research. The main socio-economic impact will be the gaining of new knowledge and its dissemination through the publication of scientific results.

- *Spin off of new EC RTD Framework Programme proposals/projects.*

Several SYSGENET participants were funded by international programs that are listed below and in Annex 3.

Xavier Montagutelli - Agence Nationale de la Recherche (ANR), Programme Blanc, SVSE 6 – Génomique, génétique, bioinformatique, biologie systémique, 2012-2014, Identification of the plague resistome in the mouse using genetic and systems biology approaches. COST network colleague: Fuad Iraqi.

Joan Campbell-Tofte - Development of Phyto-solutions for the innovative treatment of type 2 diabetes: inhibiting tissue degenerative processes, targeting underlying causes and mechanisms Proposal acronym: PHYTOSOL-T2D. SME-targeted Collaborative Project (small-scale focused research project). Call: HEALTH.2012.2.1.2-1: Systems medicine: SME-driven research applying systems biology approaches to address medical and clinical needs. FP7-HEALTH-2012- INNOVATION-1. Coordinator Jepser Mehlsen (Chief Medical Consultant) Leader and Head of Research, Innova Center (Research Unit, Frederiksberg, Hospital) COST network colleague: Juan Manuel Falcón Pérez.

Martien Kas - ERC starting grant on complex trait genetics. COST network colleague: Fuad Iraqi.

Alessandra Bragonzi - Genetic dissection of cystic fibrosis host susceptibility to *Pseudomonas aeruginosa* infections using a highly genetically diverse mouse resource population, the Collaborative Cross mice, Telethon (<http://www.telethon.it/en>). COST network colleague: Fuad Iraqi.

Feride Severcan - SBAG-BMBF-6 (108S264), Inten-C project, Coordinator, Project name: Genetic and Biophysical Investigation of the Relation between Muscle Characteristics and Obesity. 01.04.2009 - 01.04.2012. In collaboration with Gudrun Brockmann.

Juan Manuel Falcón Pérez - META JTC2011 LIVEROMICS Integrated Research on Genomics and Pathophysiology of the Metabolic Syndrome and the Diseases arising from it. COST network colleague: Frank Lammert.

Juan Manuel Falcón Pérez - FP7-SME-2012. Validating & Optimizing the Rauvolfia-Citrus Therapy, an Innovative Treatment for Type-2 Diabetes that Prevents Tissue Degenerative Processes. COST network colleague: Joan Campbell-Tofte.

Hans Lehrach, coordinator - ITFoM "IT Future of Medicine", EU Cooperation ICT Flagship. COST network colleagues: Kurt Zatloukal, Rudi Balling.

- *Spin off of new National Programme proposals/projects.*

SYSGENET scientists applied for several national programmes. The complete list is presented in Annex 3.

One example is a grant from the Swiss National Science Foundation awarded to Paul Franken, Johan Auwerx and colleagues to study metabolic pathways controlling glycaemia, sleep, and aging.

II.B. Inter-disciplinary networking

- *Additional knowledge obtained from working with other disciplines within the COST framework.*

A workshop was held in Helsinki where mouse and human researchers met who are working in the field of schizophrenia research. At the meeting, the most relevant clinical questions related to the disease were presented and mouse models of schizophrenia phenotypes were presented. From this meeting, a publication (Kas et al., 2011, Science Translational Medicine) resulted which reported about the meeting, the discussion points and proposed potential future areas where mouse research may contribute substantially to advance the understanding of the human disease.

- *Evaluation of whether the level of inter-disciplinarity is sufficient to potentially provide scientific impacts.*

The results of the inter-disciplinary meeting in Helsinki were published in an internationally renowned journal, Science Translational Medicine.

Kas MJ, Kahn RS, Collier DA, Waddington JL, Ekelund J, Porteous DJ, Schughart K, Hovatta I. Translational neuroscience of Schizophrenia: seeking a meeting of minds between mouse and man, Sci Transl Med. 2011 Sep 28;3 (102):102mr3.

- *Evaluation of whether the level of inter-disciplinarity is sufficient to potentially provide socio-economic impacts.*

The continuous efforts of the Action should contribute to bridge the border between experimental and clinical researchers. First successes were the meeting in Helsinki and additional similar meetings are planned for 2012.

II.C. New networking

- *Additional new members joining the Action during its life.*

No new countries

- *Total number of individual participants involved in the Action work.*

Presently, 45 individual participants (30 MC members and 14 MC substitute members and the Chair of the Action) are involved in the Action. Several additional members joined different Action meetings and workshops. 24.4% of the MC members involved in the Action are female, and six Early Stage Researchers are MC or MC substitute members.

- *Involvement of Early Stage Researchers in the Action, in particular with respect to STSMs, networking activities, and Training Schools. In addition, justification should be provided if less than 4 STSMs were carried out during the year.*

The COST Action supported eight STSMs in 2011.

Konstantina Dimitrakopoulou from University Patras, GR group of Anastasios Bezerianos visited Klaus Schughart at Helmholtz Centre of Infection Research, Braunschweig, DE. Her STSM Topic

was: Comprehending microarray data from experiments focusing the transcriptome profiling of T cells.

Lucie Chevallier from Pasteur Institute, Paris, FR group of Xavier Montagutelli visited Klaus Schughart at Helmholtz Centre of Infection Research, Braunschweig, DE. Her STSM Topic was: Analysis of gene expression data of resistant and sensitive mouse strains to *Yersinia pestis*.

Caroline Durrant from Oxford University, UK group of Richard Mott visited Fuad Iraqi at Tel Aviv University TAU, IL. Her STSM Topic was: Analyses of survival phenotypes in Collaborative Cross mice

Rabea Hall from Saarland University Hospital, Homburg, DE group of Frank Lammert visited Kurt Zatloukal at Medical University Graz, AT. Her STSM Topic was: Bile duct ligation in mice and phenotypic characterisation of biliary fibrosis.

Fuad Iraqi as MC member from Tel-Aviv University, IL visited Richard Mott at Wellcome Trust Centre for Human genetics, University of Oxford, UK. His STSM Topic was: Analysis of recorded phenotype data on the Collaborative Cross mice using QTL mapping methods developed.

Laura Palomo Diaz from CIC bioGUNE, Derio, ES group of Juan M Falcon visited Klaus Schughart at Helmholtz Centre of Infection Research, Braunschweig, DE. Her STSM Topic was: Phenotyping serum-derived exosomes from mouse models for infectious diseases.

Elena Terenina from INRA- Laboratoire de Genetique Cellulaire, Toulouse, FR group of Pierre Mormede (WG5) visited Michal Korostynski at Polish Academy of Sciences, Krakow, PL. Her STSM Topic was: Identification of promoter site related to genetic variation in glucocorticoid receptor efficiency in mice.

Sebastian Heise from Humboldt University Berlin, DE, group of Gudrun Brockmann visited Martien Kas NL University medical Centre, Utrecht, NL. His STSM Topic was: *In situ* hybridization of candidate genes in a major QTL region for obesity in BFM1860 mice.

Seven recipients were Early Stage Researchers (ESR). Six ESRs are permanent MC/MC substitute members of the Action and participate regularly in the MC meetings. In addition, three ESRs participated in different Working Group meetings.

- *Involvement of researchers from outside of COST Countries.*

As non-official country, Australia joined the Action, and is represented by Prof. Grant Morahan.

The additional member Rob Williams from the University of Tennessee Health Science Centre (UTHSC) in Memphis, USA, is a leader in the field of complex trait analysis. He participated at the WG3 meeting in Groningen, NL.

Tom Weaver, director of the MRC mouse clinic at Harwell, UK, and Michael Hagn, director of EMMA, joined the Action during the strategic meeting in Frankfurt where the future CC distribution of Collaborative Cross mice was discussed. In addition, representatives of centres in the USA (Jackson Laboratory Bar Harbor (Karen Svenson), University of North Carolina (Darla Miller, Fernando Pardo-Manuel De Villena), North Carolina State University (David Threadgill) were participating at this strategic meeting.

- *Advancement and promotion of scientific knowledge through publications and other outreach activities.*

The SYSGENET Action was presented at several scientific meetings. The complete list is provided in Annex 4. Examples are given below. Furthermore, SYSGENET researchers published many papers that are listed in Annex 2.

Klaus Schughart - SYSGENET COST Action BM901. A model organism for the study of complex traits. Metabolomics workshop, Bilbao, September 12-14, 2011.

Fuad Iraqi - AHSA workshop on Using Biotechnology for the Fight against AIDS and Infectious Diseases. The Sackler Faculty of Medicine, Tel-Aviv University, Israel. April 3rd, 2011.

Fuad Iraqi - Annual meeting of European Mouse Mutant and Archive (EMMA). Stockholm, Sweden, April 14-15, 2011.

Fuad Iraqi - 25th International Mammalian Genome Conference (IMGC), Washington DC, USA, June 22-26, 2011.

- *Activities and projects with COST network colleagues.*

The Action members were very productive and the Action stimulated new collaborations between them. Many MC members have now collaborations with other MC members. The on-going collaborations are listed in Annex 1. Joint publications between scientists from different laboratories are listed in Annex 2.

Some examples of SYSGENET collaborations that resulted in publications are given below. Fuad Iraqi and Klaus Schughart participated in the Collaborative Cross initiative. Rudi Balling and August Smit participated at an important workshop on the future prospects of biology for health research. Tassos Bezerianos and Klaus Schughart collaborated on the analysis of large scale transcriptome data to develop new approaches to identify gene-gene interaction networks.

Collaborative Cross Consortium (Iraqi FA, Mahajne M, Salaymah A, Sandovsky H, Tayem, Vered K, Balmer L, Hall M, Manship G, Morahan G, Pettit K, Scholten J, Tweedie K, Weerasekera L, Cleak J, Durrant C, Goodstadt L, Mott R, Yalcin B, Aylor DL, Baric R, Bell TA, Bendt KM, Brooks JD, Buus RJ, Crowley JJ, Calaway JD, Calaway ME, Cholka A, Darr DB, Didion JP, Dorman A, Everett E, Ferris MT, Mathes WF, Fu CP, Gooch TJ, Goodson SG, Gralinski LE, Hansen SD, Heise M, Hoel J, Lee S, Lenarcic AB, Liu EY, McMillan L, Magnuson TR, Manly KF, Miller DR, O'Brien DA, Odet F, Pan W, Pardo-Manuel de Villena F, Perou C, Pomp D, Quackenbush CR, Robinson NN, Sharpless N, Shaw GD, Spence JS, Sullivan PF, Sun W, Tarantino LM, Valdar W, Wang J, Wang W, Welsh CE, Whitmore A, Wiltshire T, Wright F, Xie Y, Yu Z, Zhabotynsky V, Zhang Z, Zou F, Powell C, Steigerwalt J, Threadgill DW, Chesler EJ, Churchill GA, Gatti DM, Svenson KL, Yang H, Shusterman A, Nashef A, Weiss EI, Houri-Haddad Y, Soller M, Schughart K, French JE, Collins FS, Crawford N, Hunter K, Kelada SNP, Peck BCE, Reilly K, Tavarez U, Bottomly D, Hitzeman R, McWeeney SK, Frelinger J, Phillippi J, Spritz RA, Benson AK, Kim J, Legge R, Low SJ, Ma F, Martinez I, Walter J, Williams RW, Aicher L, Katze M, Rosenzweig E and Broman KW (2011) The Genome Architecture of the Collaborative Cross Mouse Genetic Reference Population. *Genetics*, 2012; 190(2):389-401.

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- *The capacity of the Action members to raise research funds.*

All Action members are very actively raising funds to support their research. The details of present funding and grant applications are listed in Annex 3. In two cases, funding can only be obtained

because members are part of the SYSGENET Action (see below).

Jan Cendelin. Neurotransplantation therapy in the mouse model of spinocerebellar ataxia type 2

It is a national grant of the Ministry of Education, Youth and Sports of the Czech Republic. Project

duration: 2012-2013. *The membership in the COST Action was a condition for the application.*

Feride Severcan - Code: SBAG-110S235, COST project, Coordinator, Project name: Characterization of structure, function and content of different adipose tissues in inbred obese mice models.

01.02.2011- 01.08.2013. In collaboration with Gudrun Brockmann. *The membership in the COST*

Action was a condition for the application.

ANNEX 1

Activities and projects with COST network colleagues from another country

Feride Severcan, Gudrun Brockmann - BMBF (TUR 08/I02) "TubiTek", Genetic and biophysical investigations of the relationship between muscle characteristics and fat deposition.

Frank Lammert, Juan Falcón Pérez - META JTC2011 LIVEROMICS Integrated Research on Genomics and Pathophysiology of the Metabolic Syndrome and the Diseases arising from it.

Joan Campbell-Tofte, Juan Falcón Pérez - FP7-SME-2012. Validating & Optimizing the Rauwolfia-Citrus Therapy, an Innovative Treatment for Type-2 Diabetes that Prevents Tissue Degenerative Processes.

Jean-Jacques Panthier, Klaus Schughart - Project for international scientific cooperation (PICS), Centre National de la Recherche Scientifique (CNRS), Identification de cibles pour de nouvelles thérapies antivirales, 2010-2013, PI: Jean-Jacques Panthier.

Jean-Jacques Panthier, Fuad Iraqi - Workshop on Host Susceptibility to Infectious diseases, organized by Fuad Iraqi, October 23th -24th 2011, Tel-Aviv, Israel. Seminar on Host genetic control of Rift Valley fever in mice.

Jean-Jacques Panthier, Fuad Iraqi - Domaine d'Intérêt Majeur (DIM), Région Ile-de-France, Maladies Infectieuses, Parasitaires, et Nosocomiales émergentes", project Title: Zoonoses émergentes non parasitaires, Identification de mécanismes de résistance au virus de la fièvre de la Vallée du Rift chez les Mammifères.

Jean-Jacques Panthier, Fuad Iraqi - Agence Nationale de la Recherche (ANR), Programme Blanc, SVSE 3 – Microbiologie, immunologie, infectiologie, 2012-2014, Identification of key cellular pathways and genes involved in the pathogenicity and resistance to Rift Valley Fever virus.

Hans Lehrach, Kurt Zatloukal, Rudi Balling - ITFoM "IT Future of Medicine", EU Cooperation ICT Flagship, coordinator.

Hans Lehrach, Kurt Zatloukal - BBMRI "European Biobanking and Biomolecular Resources Infrastructure", EU Capacities, partner.

Feride Severcan, Gudrun Brockmann - SBAG-BMBF-6 (108S264), Inten-C project, Coordinator, Project name: Genetic and Biophysical Investigation of the Relation Between Muscle Characteristics and Obesity. 01.04.2009 - 01.04.2012.

Guus Smit, Juan Falcón Pérez –DNA methylation states related to Major Depression models.

Guus Smit, Rudi Balling - Computational modeling of proteomics data.

Klaus Schughart, Jean-Jacques Panthier - Genetic susceptibility to infectious diseases in mouse genetic reference populations.

Klaus Schughart, Juan Falcón Pérez – Metabolomics in collaborative cross parental mouse strains.

Klaus Schughart, Tassos Bezerianos - Identification of gene interaction networks in transcriptomes of lungs from mice infected with influenza A virus.

Klaus Schughart, Rudi Balling - Neurological phenotypes in collaborative cross parental lines

ANNEX 2

Publications from partners related to SYSGENET research in high impact factor journals

H. Yamamoto, E.G. Williams, L. Mouchiroud, C. Canto, W. Fan, M. Downes, C. Heligon, G.D. Barish, B. Desvergne, R.M. Evans, K. Schoonjans, **J. Auwerx**. NCoR1 is a conserved physiological modulator of muscle mass and oxidative function. *Cell*, 2011,147, 827-839.

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ANNEX 3

European grants with participation of SYSGENET partners

Hans Lehrach, Kurt Zatloukal, Rudi Balling - ITFoM “IT Future of Medicine”, EU Cooperation ICT Flagship, coordinator: **Hans Lehrach**.

Hans Lehrach - ESGI, “European Sequencing and Genotyping Infrastructure”, EU Capacities, coordinator.

Hans Lehrach - OncoTrack, “Methods for systematic next generation oncology biomarker development”, EU IMI managing entity.

Hans Lehrach - livSYSiPS, “The systems biology of network stress based on data generated from in vitro differentiated hepatocytes derived from individual-specific human iPS cells” EU ERANET, ERASySBio, coordinator.

Juan Manuel Falcón Pérez - FP7-SME-2012. Validating & Optimizing the Rauvolfia-Citrus Therapy, an Innovative Treatment for Type-2 Diabetes that Prevents Tissue Degenerative Processes. COST network colleague: **Joan Campbell-Tofte**.

Joan Campbell-Tofte - Development of Phyto-solutions for the innovative treatment of type 2 diabetes: inhibiting tissue degenerative processes, targeting underlying causes and mechanisms Proposal acronym: PHYTOSOL-T2D. SME-targeted Collaborative Project (small-scale focused research project). Call: HEALTH.2012.2.1.2-1: Systems medicine: SME-driven research applying systems biology approaches to address medical and clinical needs. FP7-HEALTH-2012- INNOVATION-1. Coordinator Jepsen Mehlsen (Chief Medical Consultant) Leader and Head of Research, Innova Center (Research Unit, Frederiksberg, Hospital) COST network colleague: **Juan Manuel Falcón Pérez**.

Rudi Balling – ESF, Project: CoGIE, Coordinator: Holger Lerche, Tübingen, DE.

Rudi Balling – FP7, Project: EpiPGX, Coordinator: Sanjay Sisodiya, London, UK.

Grants from national programs which were only supported because the PIs are SYSGENET members

Jan Cendelin. Neurotransplantation therapy in the mouse model of spinocerebellar ataxia type 2. National grant of the Ministry of Education, Youth and Sports of the Czech Republic. Project duration: 2012-2013. **The membership in the COST action was a condition for the application.**

Feride Severcan - Code: SBAG-110S235, COST project, Coordinator, Project name: Characterization of structure, function and content of different adipose tissues in inbred obese mice models. 01.02.2011-01.08.2013. In collaboration with **Gudrun Brockmann**. **The membership in the COST action was a condition for the application.**

International grants with participation of SYSGENET partners from different countries

Xavier Montagutelli - Agence Nationale de la Recherche (ANR), Programme Blanc, SVSE 6 – Génomique, génétique, bioinformatique, biologie systémique, 2012-2014, Identification of the plague resistome in the mouse using genetic and systems biology approaches. COST network col-

league: **Fuad Iraqi**.

Martien Kas - ERC starting grant on complex trait genetics. COST network colleague: **Fuad Iraqi**.

Alessandra Bragonzi - Genetic dissection of cystic fibrosis host susceptibility to *Pseudomonas aeruginosa* infections using a highly genetically diverse mouse resource population, the Collaborative Cross mice, Telethon (<http://www.telethon.it/en>). COST network colleague: **Fuad Iraqi**.

Feride Severcan - SBAG-BMBF-6 (108S264), Inten-C project, Coordinator, Project name: Genetic and Biophysical Investigation of the Relation between Muscle Characteristics and Obesity. 01.04.2009 - 01.04.2012. In collaboration with **Gudrun Brockmann**.

Juan Manuel Falcón Pérez - META JTC2011 LIVEROMICS Integrated Research on Genomics and Pathophysiology of the Metabolic Syndrome and the Diseases arising from it. COST network colleague: **Frank Lammert**.

Projects funded from national programs related to SYSGENET themes

Gudrun Brockmann - DFG Br 1285/8 "Identification of QTL for water holding capacity", Nature of differential muscle characteristics, in particular water holding capacity, in selected mouse strains.

Gudrun Brockmann - DFG Graduate College (DFG 1208) "Molecular Endocrinology", Mechanisms for hormonal adaptation in the Berlin Fat Mouse Line (Project in the DFG-funded Graduate College Molecular Endocrinology).

Iiris Hovatta - Academy of Finland: Neurogenomics of anxiety (2008-2013).

Iiris Hovatta - Peter and Patricia Gruber Foundation: The Rosalind Franklin Young Investigator Award (2010-2012).

Iiris Hovatta - Sigrid Jusélius Foundation: Genetic and molecular regulation of anxiety disorders (2009-2012).

Iiris Hovatta - ERC Starting Independent Investigator Award: A cross-species neurogenomics approach to anxiety (2012-2016).

Kurt Zatloukal, Leopold Fröhlich - IMGuS - Systems Biology of Steatohepatitis" funded from 2008 to 2011 by the AWS (=Austria Wirtschaftsservice). Participants from University of Heidelberg, MPI for Molecular Genetics, Berlin, University of Vienna and Graz, Biocrates Innsbruck.

Claude Libert - ZFN knockout of the *Mus spretus* GILZ-encoding gene. Sigma-Aldrich.

Claude Libert - A detailed study of the role of SRC1A and SRC2 in TNF-induced glucocorticoid resistance. Bijzonder Onderzoeksfonds.

Claude Libert - Resolving the glucocorticoid resistance of severe asthma. Maro Fonds (Koning Boudewijnstichting).

Claude Libert - The interactions between the brain and MMP3 and MMP8 in systemic inflammation. FWO onderzoeksproject G.0054.12.

Paul Franken, Johan Auwerx, Bernard Thorens, and Ioannis Xenarios: 2011 – 2014 Sinergia grant of the Swiss National Science Foundation (136201), 'A systems genetics approach towards identification of metabolic pathways controlling glycemia, sleep, and aging' (PI and coordinator Paul Franken; Thorens UNIL, Auwerx EPFL, Xenarios SIB/Vital-IT); 3 years.

Hans Lehrach - BMBF: NGFNplus, "Modifiers of Intestinal Tumor Formation and Progression", partner. (terminated in 2011).

Hans Lehrach - AWS (Österreichische Nationalstiftung für Forschung, Technologie und Entwicklung): IMGUS Project: "Systems biology of prostate cancer", partner. (terminated in 2011). COST network colleague: **Kurt Zatloukal**.

Hans Lehrach - AWS (Österreichische Nationalstiftung für Forschung, Technologie und Entwicklung): IMGUS Project: "Systems Biology of Steatohepatitis", partner. (terminated in 2011).

Annamari Ranki - funded by EU project MAARS (www.maars.eu).

Klaus Schughart - FluResearchNet - national network funded by German Ministry for Research and Education (BMBF): Host susceptibility to influenza virus infections in mammalian species.

Klaus Schughart - Helmholtz Russian Joint Research Group - national network funded by Helmholtz Association: Genetic susceptibility to tuberculosis.

Andreas Lengeling - Wellcome Trust Project Grant WT087610MA: Genetic dissection of Streptococcus pyogenes induced macrophage necrosis (2010-2012).

Guus de Smit - NeuroBasic PharmaPhenomics consortium (2011-2015). 12-partner consortium on mouse behavioral traits and the effects of psycho-active compounds.

Grant proposals submitted related to SYSGENET themes rejected or not yet approved

Joan Campbell-Tofte - Validating & Optimizing the Rauvolfia-Citrus Therapy, an Innovative Treatment for Type-2 Diabetes that Prevents Tissue Degenerative Processes. Proposal acronym: RC4T2D. Research for SMEs Call identifier: FP7-R4SME -2012.

Iris Hovatta - Academy of Finland: Neurogenomics of anxiety (2008-2013).

Iris Hovatta - Peter and Patricia Gruber Foundation: The Rosalind Franklin Young Investigator Award (2010-2012).

Iris Hovatta - Sigrid Jusélius Foundation: Genetic and molecular regulation of anxiety disorders (2009-2012) ERC Starting Independent Investigator Award: A cross-species neurogenomics approach to anxiety (2012-2016).

Fuad Iraqi - DFG-Trio- Identifying genetic factors underlying the host susceptibility to Periodontitis in human and a highly genetically diverse reference mouse population, the Collaborative Cross. Applicants: University of Kiel, Germany; Tel-Aviv University, Israel; Hadassah Dental School, Israel; and Al-Quds University, Palestinian National Authority.

Fuad Iraqi - DFG-Trio - Mapping Genetic factors underlying host susceptibility to the development of type-2 diabetes. Applicants: University of Dresden, Germany; Tel-Aviv University, Israel; Red Crescent and Al-Quds University, Palestinian National Authority.

Fuad Iraqi - Israeli Science Foundation (ISF) (Dissecting the genetic based of hosts susceptibility to priondntitis in mice Applicants: Tel-Aviv University and Hadassah Dental School, Israel.

Fuad Iraqi - Israeli Science Foundation (ISF) - Identifying the genetic factors determining host susceptibility to Type-2 Diabetes in mice) Applicants: Tel-Aviv University and Felsenstein Medical Research Centre, Israel.

Fuad Iraqi - Bi-national Israel-USA foundation (BSF) (Development of a high-throughput platform for genetic analysis of host susceptibility to bacterial infections using the Collaborative Cross mouse genetic reference population). Applicants: Tel-Aviv University, Israel and North Carolina State University, USA.

Fuad Iraqi - 6. Bi-national Israel-USA foundation (BSF) (Dissecting the genetics of inflammation resolution using a highly genetically-diverse mouse population: identification of candidate genes). Applicants: Tel-Aviv University, Israel; Hadassah Dental School, Israel and The Forsyth Institute, Cambridge, USA.

Fuad Iraqi - Israeli Science Foundation (ISF)-JDRF - Mapping genetic factors underlying host susceptibility to Type-1 Diabetes. Applicants: Tel-Aviv University and Felsenstein Medical Research Centre, Israel.

Fuad Iraqi - EU-FP7 Infrastructure (INFRAFRONTIERscale) Applicants: 24 members from the EU

Fuad Iraqi - Wellcome Trust-UK - Developing the collaborative Cross mice as a resource for dissecting complex traits Applicants: Oxford University, UK; Tel-Aviv University, Israel; Harwell research centre, UK

Hans Lehrach - MELODI "Molecular Effects of Lifestyle on Obesity and Diabetes", EU Cooperation, partner. (rejected in stage2).

Jean-Jacques Panthier - Fondation pour la Recherche Médicale, Appel d'Offres de la Fondation pour la Recherche Médicale « Équipes FRM 2012 », Vulnérabilité aux agents infectieux émergents et sévérité des infections dans des populations génétiques de références

Richard Mott - Pre-application to the Wellcome trust in October 2011 for continuation for CC funding, entitled "The Collaborative Cross Genetic Reference Population of Mice".

Wim Crusio - 2005-2012: Genetic regulation of hippocampal anatomy and learning. R01 MH072920-01, National Institute of Mental Health, Bethesda, MD, USA (PI)

Hans Lehrach - MELODI "Molecular Effects of Lifestyle on Obesity and Diabetes", EU Cooperation, partner. (rejected in stage2)

Leonard Schalkwyk - US NIH (NIMH) with Abraham Palmer (Chicago).

Leonard Schalkwyk - *Genome wide association study of behavior & gene expression in heterogeneous mice*, investigator initiated R01 under **PA-10-067**.

Leonard Schalkwyk - UK BBSRC, Brain tissue methylome and genome wide survey for allele-skewed DNA methylation" project grant application.

Guus de Smit - NIH, NIDA, RO1 (National Institute for Drug Abuse), 2011.

Rudi Balling – FP7, Project: SymChron, Coordinator: Jean Bousquet, Montpellier, FR.

Rudi Balling – IMI, Project: ETRIKS, Coordinator: Yike Guo, London, UK.

ANNEX 4

Presentation of SYSGENET and SYSGENET-related research projects at meetings

Klaus Schughart - SYSGENET COST Action BM901. A model organism for the study of complex traits. Metabolomics workshop, Bilbao, September 12-14, 2011.

Fuad Iraqi - A joint USA-EU meeting to discuss the disruption of Collaborative Cross (CC) populations in Europe and USA. Frankfurt, Germany, January 23-24, 2011.

Fuad Iraqi - AHSA workshop on Using Biotechnology for the Fight against AIDS and Infectious Diseases. The Sackler Faculty of Medicine, Tel-Aviv University, Israel. April 3rd, 2011.

Fuad Iraqi - Annual meeting of European Mouse Mutant and Archive (EMMA). Stockholm, Sweden, April 14-15, 2011.

Fuad Iraqi - European Conference on Clinical Microbiology and Infectious Diseases (ECCMID). Milan, Italy, May 6-10, 2011.

Fuad Iraqi - 3rd SYSGENET meeting, Helsinki, Finland, June 9-19, 2011.

Fuad Iraqi - 25th International Mammalian Genome Conference (IMGC), Washington DC, USA, June 22-26, 2011.

Fuad Iraqi - International Symposium celebrating Prof. Moshe Soller's 80th Birthday. Hebrew University, Jerusalem, Israel. June 30th, 2011.

Fuad Iraqi - Annual meeting of Infrafrontier EU consortium. Rome, Italy, July 4-5, 2011.

Fuad Iraqi - Annual Meeting of European Mouse Mutant Archive (EMMA). Moterotondo, Italy, October 13-14, 2011.

Fuad Iraqi - SYSGENET workshop on host susceptibility to infectious diseases. The Sackler Faculty of Medicine, Tel-Aviv University, Israel. October 23-24, 2011.

Paul Franken - Reverse genetics of sleep and EEG traits in mice. EUMODIC Final meeting, Geneva 21-22, November 2011.

Caroline Durrant - 10th Annual Meeting of the Complex Trait Community in Washington, DC USA (June 22-25, 2011).

Richard Mott - SYSGENET workshop on host susceptibility to infectious diseases. The Sackler Faculty of Medicine, Tel-Aviv University, Israel. October 23-24, 2011.

Müllenbach R, Hall R, Ilkayets I, Dooley S **Lammert F**. Modulatoren der hepatozellulären Antwort auf EtOH in genetischen Referenzpopulationen. Jahrestagung der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten (DGVS), Leipzig 2011: Arbeitsgruppe: Alkohol und Folgekrankheiten.

Anton Terasmaa, Punapart M., Sütt S., **Köks S.**, Soomets U., Vasar E., **Schalkwyk L.** - Chronic treatment with valproic acid upregulates PPAR-delta in wild type but not Wfs1 knock-out mice. Meeting of Society for Neuroscience, Washington, DC.

III. Previous scientific report(s)

First scientific report

II. Scientific Report

SYSGENET represents a network of scientists in Europe who use mouse genetic reference populations (GRP) to identify complex genetic factors influencing phenotypic traits. The findings will be translated to human diseases and represent the basis for understanding disease etiology and developing new treatment strategies. The researchers in SYSGENET are using various GRPs as model system to investigate the biological mechanisms and gene regulatory networks involved in disease phenotypes. The SYSGENET network partners are studying phenotypes relevant to infectious diseases, inflammatory disorders, metabolic diseases, cancer, neurological and psychiatric disorders and infertility. The GRPs presently exploited by the network laboratories include inbred strains, consomic strains, recombinant inbred strains, congenic strains, interspecific recombinant congenic strains, outbred populations and the upcoming large recombinant inbred strains collection known as the collaborative cross.

II.A. Innovative networking

- *Innovative knowledge resulting from COST networking through the Action.*

A scientific meeting was held in Braunschweig, DE, April 7-9, 2010. During this meeting, all participating partners presented their ongoing scientific projects. This meeting allowed all partners of the Action to share information on highly sophisticated phenotype analysis in mice and new scientific approaches to study mouse models for human diseases. For the latter, new discoveries in the field of psychiatric diseases, circadian rhythms and metabolic diseases were presented.

- *Significant scientific breakthroughs as part of the COST Action.*

Klaus Schughart published a report about the SYSGENET objectives and the first scientific meeting of the Action: SYSGENET: a meeting report from a new European network for systems genetics (*Mammalian Genome* (2010) 21:331-336). In addition, several publications in high impact journals were produced by SYSGENET partners. Below, three examples are given, the complete list is provided in the Annex 2.

The X chromosome in immune functions: when a chromosome makes the difference, Libert, C., Dejager, L., Pinheiro, I. **Nature Rev. Immunol.** 10, 594-604, 2010.

New life for anti-diabetic drugs. R.H. Houtkooper, J. Auwerx. **Nature**, 2010, 466, 443-44.

Metabolic networks of longevity. R.H. Houtkooper, R.W. Williams, J. Auwerx. **Cell**, 2010, 142, 9-14.

- *Tangible medium term socio-economic impacts achieved or expected.*

The Action represents an activity in basic research. The main socio-economic impact will be the gaining of new knowledge and its dissemination through publications of scientific results.

- *Spin off of new EC RTD Framework Programme proposals/projects.*

Several SYSGENET partners were involved in EU projects and grant proposal for FP7 projects. The complete list is provided in Annex 3.

- *Spin off of new National Programme proposals/projects.*

Several SYSGENET partners applied for several national programmes, a selection of which is listed below. The complete list is provided in Annex 3. Paul Franken and Johan Auwerx, both members of the SYSGENET action submitted a grant to the SWISS National Science Foundation to phenotype BXD RI mice for metabolic phenotypes. This grant has not yet been evaluated. Klaus Schughart has successfully applied for funding from the German ministry (BMBF) to perform host genetic studies on susceptibility to influenza A infections (FluResearchNet). Feride Severcan has successfully applied for a National project in Turkey. Code: SBAG-110S235, Characterization of structure, function and content of different adipose tissues in inbred obese mice models. Kurt Zatloukal received funding for the IMGuS project: Systems Biology of Steatohepatitis and for a ERA-SySBio project :LivSYSiPS: The systems biology of network stress based on data generated from *in vitro* differentiated hepatocytes derived from individual-specific human iPS cells. Frank Lammert has successfully applied for two national DFG projects: DFG LA 997/5-1 Modulators of hepatic response to TGF- $\alpha\beta$ mediated cellular injury in inbred mice: Identification of modifiers of fibrosis susceptibility. DFG LA 997/6-1 Identifizierung und Charakterisierung von zellulären Mechanismen und genetischen Determinanten der kardialen und systemischen Fibrogenese.

II.B. Inter-disciplinary networking

- *Additional knowledge obtained from working with other disciplines within the COST framework.*

So far, no specific activities have been performed to work with other disciplines in the COST program. However, specific work shops have been planned in 2011 to discuss the use of the mouse models with human clinical researchers and to initiate joint projects. Also, the action is currently putting together a writing group to review the use of mouse models for a better understanding of human diseases.

Furthermore, Klaus Schughart introduced the SYSGENET consortium at the CTC (Complex Trait Community) meeting in Chicago, USA (May 7-10, 2010). Also, Klaus Schughart and Martien Kas presented SYSGENET and the importance of GRPs at the Casimir meeting in London, UK (May 2010). In order to integrate the SYSGENET activities with the mouse knock-out phenotyping activities, Fuad Iraqi presented SYSGENET at the Infrafronter (The European Infrastructure for phenotyping and archiving of model mammalian genomes) annual meeting in Munich, DE (June 10-11, 2010).

- *Evaluation of whether the level of inter-disciplinarity is sufficient to potentially provide scientific impacts.*

Our plans to closely interact with human clinically should provide a good basis to cross the gap between experimental basic research and applied clinical research. This is a very difficult task and will be approached in 2011. Both the previewed joint meeting on neuropsychiatric diseases and the writing of a review on mouse models together with clinicians are expected to have a positive impact.

Following up on discussion between members of the SYSGENET consortium and US partners at the IMPC-meeting in Crete, GR (October 2010), a small meeting was initiated in Frankfurt, DE (January 24, 2011). At this meeting strategies for the future distribution of CC strains in EU and the US were discussed and next steps initiated.

- *Evaluation of whether the level of inter-disciplinarity is sufficient to potentially provide socio-economic impacts.*

The continuous efforts described above should contribute to bridge the border between experimental and clinical researchers. If successful, this will have an impact on raising the awareness for the mouse model which is important for biomedical research and eventually to human health.

II.C. New networking

- *Additional new members joining the Action during its life.*

Four new COST-countries (BE, GR, IT, TR) joined the Action.

- *Total number of individual participants involved in the Action work.*

Presently, 42 individual participants (29 MC members and 13 MC substitute members) are involved in the Action work. Several additional members joined different meetings and workshops from the action. 21.4% female MC members are involved in the Action, and five Early Stage Researchers are MC or MC substitute members.

- *Involvement of Early Stage Researchers in the Action, in particular with respect to STSMs, networking activities, and Training Schools. In addition, justification should be provided if less than 4 STSMs were carried out during the year.*

The COST Action BM0901 supported two STSMs in 2010. Both recipients were Early Stage Researchers (ESR). Five ESRs are permanent MC/MC substitute members of the Action and participate regularly in the MC meetings. In addition, nine ESRs participated in different working group meetings.

- *Involvement of researchers from outside of COST Countries.*

As an outside COST country, Australia joined the Action, being represented by Prof. Grant Morahan. He also participated at the first scientific MC and Working Group meeting in Braunschweig, DE, April, 2010. Also, two of the world leaders in the field of systems genetics, Prof. Dr. Rob Williams and Prof. David Threadgill, both US, actively participated in meetings of the Action.

- *Advancement and promotion of scientific knowledge through publications and other outreach activities.*

The SYSGENET researchers published several papers in high impact journals. The most relevant publications for 2010 are listed in Annex 2. In addition, SYSGENET was introduced at several meetings (see above).

- *Activities and projects with COST network colleagues.*

The Members of the Action were very productive and the Action stimulated new collaborations between partners. Many MC members have now collaborations with other MC members. The ongoing collaborations are listed in Annex 1. As one example, the SYSGENET MC member Sulev Koks has on-going collaboration with the COST network colleagues Dr. Stephan Weidinger, TU-Munich, DE, from the COST Action BM0903, SKINBAD.

- *The capacity of the Action members to raise research funds.*

All Action members are very actively raising funds to support their research, but we did not monitor this specifically. One FP7 application resulted from new interactions of partners in the Action, but it was not granted.

*2010 Annex 1
Collaborations of the SYSGENET network 2010*

Feride Severcan, TR	Gudrun Brockmann, DE
Gudrun Brockmann, DE	Martien Kas, NL
Hans Lehrach, DE	Gudrun Brockmann, DE
Hans Lehrach, DE	Leonard Schalkwyk, UK
Hans Lehrach, DE	Jiri Forejt, CZ
Hans Lehrach, DE	Kurt Zatloukal, AT
Eero Vasar, EE	Iiris Hovatta, FI
Sulev Koks, EE	Iiris Hovatta, FI
Leonard Schalkwyk, UK	Sulev Koks, EE
Leonard Schalkwyk, UK	Martien Kas, NL
Martien Kas, NL	August B Smit, NL
Klaus Schughart, DE	Gudrun Brockmann, DE
Klaus Schughart, DE	Frank Lammert, BE
Klaus Schughart, DE	Anastasio Bezerianos, GR
Klaus Schughart, DE	Xavier Montagutelli, FR
Klaus Schughart, DE	August B Smit, NL
Xavier Montagutelli, FR	Jiri Fortje, CZ
Claude Libert, BE	Xavier Montagutelli, FR
Jean-Jacques Panthier, FR	Klaus Schughart, DE
Rudi Balling, LU	HZI / Klaus Schughart, DE
Juan M Falcon, ES	August B Smit, NL
Joan Campel-Tofte, DK	Juan M Falcon, ES
Paul Franken, CH	Johan Auwerx, CH

2010 Annex 2
Publication List of the SYSGENET network 2010

Publications resulting from collaborations of partners within the Action:

SYSGENET: a meeting report from a new European network for systems genetics. **Schughart K; SYSGENET consortium.** *Mamm Genome.* 2010 Aug;21(7-8):331-6. Epub 2010 Jul 11

XGAP: a uniform and extensible data model and software platform for genotype and phenotype experiments. Swertz, M.A.; Velde, K.J.; Tesson, B.M.; Scheltema, R.A.; Arends, D.; Vera, G.; Alberts, R.; Dijkstra, M.; Schofield, P.; **Schughart, Klaus***; Hancock, J.M.; Smedley, D.; Wolstencroft, K.; Goble, C.; de Brock, E.O.; Jones, A.R.; Parkinson, H.E.; **Jansen, R.C.**; (2010). *Genome Biology: Volume: 11 Issue: 3, S-Page: R27*

Gene expression changes in the host response between resistant and susceptible inbred mouse strains after influenza A infection. Alberts, R.; Srivastava, B.; Wu, H.; Viegas, N.; Geffers, Robert*; Klawonn, F.; Novoselova, N.; Zaverucha, do, V; **Panthier, J.J.**; **Schughart, Klaus***; (2010). *Microbes and Infection: Volume: 12 Issue: 4, S-Page: 309-E-Page: 318*

The KRAB-containing zinc-finger transcriptional regulator ZBRK1 activates SCA2 gene transcription through direct interaction with its gene product, ataxin-2. Hallen L, Klein H, Stoschek C, Wehrmeyer S, Nonhoff U, Ralser M, Wilde J, Röhr C, Schweiger MR, **Zatloukal K**, Vingron M, **Lehrach H**, Konthur Z, Krobitsch S. *Hum Mol Genet.* 2011 Jan 1;20(1):104-14. Epub 2010 Oct 6.

Somatic mutation profiles of MSI and MSS colorectal cancer identified by whole exome next generation sequencing and bioinformatics analysis. Timmermann B, Kerick M, Roehr C, Fischer A, Isau M, Boerno ST, Wunderlich A, Barmeyer C, Seemann P, Koenig J, Lappe M, Kuss AW, Garshasbi M, Bertram L, Trappe K, Werber M, Herrmann BG, **Zatloukal K**, **Lehrach H**, Schweiger MR. *PLoS One.* 2010 Dec 22;5(12):e15661.

Somatic Mutation Profiles of MSI and MSS Colorectal Cancer Identified by Whole Exome Next Generation Sequencing and Bioinformatics Analysis. Timmermann B, Kerick M, Roehr C, Fischer A, Isau M, Boerno ST, Wunderlich A, Barmeyer C, Seemann P, Koenig J, Lappe M, Kuss AW, Garshasbi M, Bertram L, Trappe K, Werber M, Herrmann BG, **Zatloukal K**, **Lehrach H**, Schweiger MR. *PLoS One.* 2010 Dec 22;5(12):e15661.

A new mouse model reveals a critical role for host innate immunity in resistance to Rift Valley fever. do Valle TZ, Billecocq A, Guillemot L, Alberts R, Gomet C, Geffers R, Calabrese K, **Schughart K**, Bouloy M, **Montagutelli X**, **Panthier JJ.** *J Immunol.* 2010 Nov 15;185(10):6146-56. Epub 2010 Oct 11

"4D Biology for health and disease" workshop report. Abrahams JP, Apweiler R, **Balling R**, Bertero MG, Bujnicki JM, Chayen NE, Ch@ne P, Corthals GL, DylfÖg T, F∂rster F, Heck AJ, Henderson PJ, Herwig R, Jehenson P, Kokalj SJ, Laue E, Legrain P, Martens L, Migliorini C, Musacchio A, Podobnik M, Schertler GF, Schreiber G, Sixma TK, **Smit AB**, Stuart D, Svergun DI, Taussig MJ. *N Biotechnol.* 2010 Oct 15.

Finding and sharing: new approaches to registries of databases and services for the biomedical sciences. Smedley D, Schofield P, Chen CK, Aidinis V, Ainali C, Bard J, **Balling R**, Birney E, Blake A, Bongcam-Rudloff E, Brookes AJ, Cesareni G, Chandras C, Eppig J, Flicek P, Gkoutos G, Greenaway S, Gruenberger M, Hériché JK, Lyall A, Mallon AM, Muddyman D, Reisinger F, Ringwald M, Rosenthal N, **Schughart K**, Swertz M, Thorisson GA, Zouberakis M, Hancock JM. *Database (Oxford).* 2010 Jul 6;2010:baq014. Print 2010

EMMA – mouse mutant resources for the international scientific community. Wilkinson, P., Sengerova, J., Matteoni, R., Chen, C.K., Soulat, G., Ureta-Vidal, A., Fessele, S., Hagn, M., Massimi, M., Pickford, K., Butler, R.H., Marschall, S., Mallon, A.M., Pickard, A., Raspa, M., Scavizzi, F., Fray, M., Larrigaldie, V., Leyritz, J., Birney, E., Tocchini-Valentini, G.P., **Brown, S.D.M.**, **Herault, Y.**, Montoliu, L., De Angelis, M.H. And Smedley, D. (2010) *Nucl. Acids Res.* 38: 570-6.

Peripheral blood RNA gene expression profiling in illicit methcathinone users reveals effect on immune system. Sikk K, **Köks S**, Soomets U, **Schalkwyk LC**, Fernandes C, Haldre S et al. *Movement Disorders* 2010; 25(7): S226-S226.

The stromal gene encoding the CD274 antigen as a genetic modifier controlling survival of mice with gamma-radiation-induced T-cell lymphoblastic lymphomas. **Santos J**, González-Sánchez L, Villa-Morales M, Ors I, López-Nieva P, Vaquero C, González-Gugel E, Fernández-Navarro P, Roncero AM, Guenet JL, **Montagutelli X** and Fernández-Piqueras J. *Oncogene* (2010), Volume: 29, Pages: 5265-5273,

Publications from partners related to SYSGENET research in high impact factor journals

New life for anti-diabetic drugs. R.H. Houtkooper, **J. Auwerx**. *Nature*, 2010, 466, 443-44.

A map of human genome variation from population-scale sequencing. **1000 Genomes Project Consortium**, Durbin RM, Abecasis GR, Altshuler DL, Auton A, Brooks LD, Durbin RM, Gibbs RA, Hurles ME, McVean GA. *Nature*. 2010 Oct 28;467(7319):1061-73. Hans Lehrach is member of the 1000 Genomes Project.

Diversity of human copy number variation and multicopy genes. Sudmant PH, Kitzman JO, Antonacci F, Alkan C, Malig M, Tsalenko A, Sampas N, Bruhn L, Shendure J; **1000 Genomes Project**, Eichler EE. *Science*. 2010 Oct 29;330(6004):641-6. **Hans Lehrach** is member of the 1000 Genomes Project.

The X chromosome in immune functions: when a chromosome makes the difference, **Libert, C.**, Dejager, L., Pinheiro, I. *Nature Rev. Immunol.* 10, 594-604, 2010.

Genes and cognition. S. Pietropaolo and **W.E. Crusio**. *Wiley Interdisciplinary Reviews: Cognitive Science*, in press, 2010.

Metabolic networks of longevity. R.H. Houtkooper, R.W. Williams, **J. Auwerx**. *Cell*, 2010, 142, 9-14.

Interleukin-6 signaling in liver-parenchymal cells suppresses hepatic inflammation and improves systemic insulin action. Wunderlich, T., Stroehle, P., Koerner, C., **Libert, C.**, Gruber, S., Tovar, S., Ringeisen, G., *Cell Metabolism*, 2010, 12, 237-249.

A hearing and vestibular phenotyping pipeline to identify mouse mutants with hearing impairment. Hardisty-Hughes, R.R., Rarker, R. and **Brown S.D.M.** (2010). *Nature Protocols* 5: 177-90.

Reviews from partners related to the SYSGENET research field

The neurobiology of repetitive behavior: Of mice... Langen M, **Kas MJ**, Staal WG, van Engeland H, Durston S. *Neurosci Biobehav Rev.*, in press

Interaction proteomics of synapse protein complexes . Li KW, Klemmer P, **Smit AB**. *Anal Bioanal Chem.* 2010 Aug;397(8):3195-202. Review.

Murine models of acute and chronic lung infection with cystic fibrosis pathogens. Bragonzi A. *Int J Med Microbiol.* 2010 Dec;300(8):584-93.

Crosstalk between TNF and Glucocorticoid Receptor Signaling Pathways . Van Bogaert, T., De Bosscher, K., **Libert, C.**, Cytokine and Growth Factor Reviews, 2010, 21, 275-286

Regulatory crosstalk of the metabolic network. Grüning NM, **Lehrach H**, Ralser M. Trends Biochem Sci. 2010 Apr;35(4):220-7.

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Data-driven assessment of eQTL mapping methods. Michaelson, J.J.; Alberts, R.; **Schughart, Klaus***; Beyer, A.; (2010). BMC GENOMICS: Volume: 11, S-Page: 502

Towards the integration of mouse databases - definition and implementation of solutions to two use-cases in mouse functional genomics. Gruenberger, M.; Alberts, R.; Smedley, D.; Swertz, M.; Schofield, P.; **Schughart, Klaus***; (2010). BMC Research Notes: Volume: 3 Issue: 1, S-Page: 16

TMPRSS2 and TMPRSS4 facilitate trypsin-independent spread of influenza virus in Caco-2 cells. J Bertram, S.; Glowacka, I.; Blazejewska, P.; Soilleux, E.; Allen, P.; Danisch, S.; Steffen, I.; Choi, S.Y.; Park, Y.; Schneider, H.; **Schughart, Klaus***; Pohlmann, S.; (2010). Journal of Virology: Volume: 84 Issue: 19, S-Page: 10016-E-Page: 10025

Genes and cognition. S. Pietropaolo and **W.E. Crusio**. *Wiley Interdisciplinary Reviews: Cognitive Science*, in press, 2010.

Increased glucocorticoid receptor expression and activity mediate the LPS resistance of SPRET/EI mice. Dejager, L., Pinheiro, I., Puimège, L., Fan Y.-F., **Libert, C**, *J. Biol. Chem.*, (2010) 285, 31073-86

Genetic inactivation of KCNJ16 identifies Kir1.5 as an important determinant of neuronal PCO2/pH sensitivity. D'adamo, M.C., Shang, L., Imbrici, P., **Brown, S.D.M.**, Pessia, M., Tucker, S.J. (2010) *J. Biol. Chem.*, in press.

Mus spretus SEG/Pas mice resist virulent Yersinia pestis, under multigenic control. C. Blanchet, J. Jaubert, E. Carniel, C. Fayolle, G. Milon, M. Szatanik, **J.J. Panthier, X. Montagutelli** (2010). *Genes Immun*. In press.

Behavioral pattern analysis and dopamine release in quinpirole-induced repetitive behavior in rats. de Haas GG, Nijdam A, Westra T, **Kas MJ**, Westenberg HG. *J. Clinical Psychopharmacology*, in press

Cross-species behavioural genetics: A starting point for unravelling the neurobiology of human psychiatric disorders. de Mooij-van Malsen AJ, Vinkers CH, Peterse DP, Olivier B, **Kas MJ**. *Prog Neuropsychopharmacol Biol Psychiatry*, in press

The parent-of-origin of the extra X chromosome differentially affects psychopathology in Klinefelter syndrome Bruining H, van Rijn S, Swaab H, Giltay J, Kates W, **Kas MJ**, van Engeland H, Sonnevile L. *Biological Psychiatry*, in press

Gene Set Enrichment; a problem of pathways. Davies M, Meaburn EL, **Schalkwyk LC** (2010). *Briefings in Functional Genomics* in press.

A reliable and validated technique for phenotyping otitis media in the mouse. Bhutta, M.F., Hedge, E.A., Parker, A., Cheeseman, M.T. and **Brown, S.D.M.** (2010) *Otoendoscopy: Hearing Research*, in press.

Unraveling the genetics of otitis media – from mouse to human and back again. Rye, M.S., Bhutta, M.F., Cheeseman, M.T., Burgner, D., Blackwell, J.M., **Brown, S.D.M.**, Jamieson, S.E. (2010). *Mammalian Genome*, in press.

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2010 Annex 3

Spin off of new EC RTD Framework Programme proposals/projects.

- Johan Auwerx FP7 - ERC : title " Sirtuins: Phenogenomics of the sirtuin corepressor family". NO. 231.138.
- August B Smit Coordinator of large scale network FP7 Health Neurocypres www.neurocypres.eu
Coordinator of large scale network FP7 Health SynSys www.synsys.eu
Partner in large scale network FP7 Health EU-FP7 MEFOPA www.mefopa.eu
Partner in ITN FP7 CerebNet www-3.unipv.it/dsffcm/pagine/labs/dangelo/cerebnet.html
Partner in ITN FP7 BrainTrain www.brain-train.nl
- Paul Denny Member of the FP7-funded consortium, PNEUMOPATH
- Ritsert Jansen involved in various FP7 EU projects: EURATRANS (rats)
PANACEA (worms)
EUROMOTOR (humans)
- Hans Lehrach/Kurt Zatloukal BBMRI "European Biobanking and Biomolecular Resources Infrastructure", EU Capacities - partner
ESGI, "European Sequencing and Genotyping Infrastructure", EU Capacities, coordinator
OncoTrack, "Methods for systematic next generation oncology biomarker development", EU IMI managing entity
MELODI (applied, successful in stage 1) "Molecular Effects of Lifestyle on Obesity and Diabetes", EU Cooperation, partner
livSYSiPS, "The systems biology of network stress based on data generated from in vitro differentiated hepatocytes derived from individual-specific human iPS cells" EU ERA-NET, ERASySBio, coordinator
- Hans Lehrach/Kurt Zatloukal/Rudi Balling: ITFoM "IT Future of Medicine", EU Cooperation ICT Flagship, coordinator.
- Hans Lehrach/Jiri Forejt/Yann Hérault: AnEUploidy, "Understanding gene dosage imbalance in human health using genetics, functional genomics and systems biology", EU FP6 Integrated Project, partner - includes mouse genetics using the B6.PWD chromosome substitution strains.
- Fragiskos Kolisis: 2009-2012 : e-Laboratory for Interdisciplinary Collaborative Research in Data Mining and Data-Intensive Sciences (e-LICO).
EnviroGenomarkers. A European FP7 research project aiming at the development and application of a new generation of biomarkers to study the role of environmental agents in human disease.
- Jean-Jacques Panthier Member of the Arbo-zoonet Network. Arbo-Zoonet is the International Network for Capacity Building for the Control of Emerging Viral Vector Borne Zoonotic Diseases Coordination Action funded by the European Union (EU) under FP7 and was launched in May 2008.
FP7 Cooperation: Theme 2 Food, Agriculture and Fisheries, and Biotechnology Call identifier FP7-KBBE-1-3-06
- Gudrun Brockmann bodyfat content of B6.PWD-consomics (only B6.PWD-Chr5-strain)

Spin off of new National Programme proposals/projects.

- Klaus Schughart Funding from the German ministry (BMBF) to perform host genetic studies on susceptibility to influenza A infections (FluResearchNet).
- Johan Auwerx Application: Swiss National Fund, Sinergia, title "A systems genetics approach towards identification of metabolic pathways controlling glycemia, sleep and aging", collaborative Grant with Paul Franken and Bernard Thorens - Submitted: No:136201.
- Feride Severcan Code: SBAG-110S235, COST project, Project name: Characterization of structure, function and content of different adipose tissues in inbred obese mice models. Duration: 01.02.2011- 01.08.2013.
Code: SBAG-BMBF-6 (108S264), Inten-C project, This is a joint project with Germany, Project name: Genetic and Biophysical Investigation of the Relation Between Muscle Characteristics and Obesity. Duration: 01.04.2009 - 01.04.2012.
- Frank Lammert DFG LA 997/5-1 Modulators of hepatic response to TGF- $\alpha\beta$ mediated cellular injury in inbred mice: Identification of modifiers of fibrosis susceptibility.
DFG LA 997/6-1 Identifizierung und Charakterisierung von zellulären Mechanismen und genetischen Determinanten der kardialen und systemischen Fibrogenese.
- Hans Lehrach BMBF: NGFNplus, "Modifiers of Intestinal Tumor Formation and Progression", partner.
- Hans Lehrach/Kurt Zatloukal AWS (Österreichische Nationalstiftung für Forschung, Technologie und Entwicklung): IMGuS Project: "Systems biology of prostate cancer", partner.
AWS (Österreichische Nationalstiftung für Forschung, Technologie und Entwicklung): IMGuS Project: "Systems Biology of Steatohepatitis", partner - includes mouse genetics using the B6.A/J and the B6.PWD chromosome substitution strains
- Paul Franken Funding from EUMODIC as a secondary phenotyper.
- August B Smit Dutch: NeuroBasic Mouse PharmaPhenomics Consortium
- Paul Franken/Johan Auwerx Submitted grant: Swiss National Science Foundation. Phenotype the BXD RI mice for metabolic phenotypes.