

**MUTAGENESIS
ORAL PRESENTATION****Monday October, 29****14.35 – 14.50pm****O3-1****LARGE SCALE SEQUENCING OF ENU-INDUCED MUTATIONS ON MOUSE CHROMOSOME 11**

Melissa Boles^{1,2,3}, Bonney Wilkinson^{1,2}, Andrew Salinger², Jane Rogers⁴, Sarah Hunt⁴, Fiona Hughes⁴, Tony Cox⁴, Allan Bradley⁴, David Adams⁴, and Monica J. Justice^{2,3}

¹These authors contributed equally to the work, ²Dept. of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, ³Interdepartmental Program in Cell and Molecular Biology, Baylor College of Medicine, Houston, TX, ⁴Burroughs-Wellcome Sanger Institute, Hinxton, UK

Mouse mutagenesis with N-ethyl-N-nitrosourea (ENU) reveals gene functions unique to mammals, and many mutants model human diseases. To examine the function of genes conserved between the mouse and human, a high-efficiency ENU mutagenesis screen using a balancer chromosome was targeted to mouse Chromosome 11, which is highly conserved with human chromosome 17. This screen identified 92 mutant lines that have a wide range of phenotypes, including craniofacial abnormalities, neurological defects, infertility, impaired growth, and lethality. Each of these mutations lies within a defined molecular interval of mouse Chromosome 11 between Trp53 and Wnt3. All exons within the 34-Mb region, containing about 740 genes with over 14,000 exons, are being sequenced for each mutant to identify the molecular lesions. Currently, 40 mutant lines have been sequenced to identify 80 rare variants. Of the rare variants, 21 occurred in an exon, 34 in an intron, 15 either in the 5' or 3' UTR, and 10 either upstream or downstream of a gene. The mass sequencing of so many mutant lines, combined with molecular mapping data, has allowed for the rapid identification of causative lesions. The mutations reveal functions of unknown genes, as well as new phenotypes in characterized genes. As an example, we have identified a potential hypomorphic allele of *disheveled*, a well-characterized gene whose elimination results in perinatal lethality. Unlike the knock-out mice, the ENU-mutant mice are alive at weaning, though smaller than littermates. Further functional confirmation of many of the mutant lines is being carried out.

**MUTAGENESIS
ORAL PRESENTATION**

Monday October, 29

14.50 – 15.05pm

O3-2

THE SANGER INSTITUTE MOUSE GENETICS PROGRAMME

Karen P Steel, Gordon Dougan, Bill Skarnes, Seth Grant, David Tannahill, Lorraine Everett, Pentao Liu, David Adams, Jacqui White, Niels Adams, Allan Bradley
Wellcome Trust Sanger Institute

The physiological function of a gene can not be predicted from its sequence, thus we need to examine each gene in the context of a whole living organism. The Mouse Genetics Programme aims to make a significant impact on our understanding of the function of genes and their role in disease by generating large numbers of mutant mice and screening them for characteristic features of disease. We plan to exploit the growing resource of targeted mutations in C57BL6/N mouse ES cells produced at the Sanger Institute by selecting 250 each year to generate new mouse mutants. Mutant cohorts will be subjected to a standard battery of phenotyping tests. Mice and data will be freely available to the scientific community.

We are soliciting suggestions from the academic community for genes to prioritise and screens to include in our battery of tests. We are one of the four main phenotyping centres in the EC-funded EUMODIC programme, studying a wide range of phenotypic measures in 40 new mutant lines each year. However, the philosophy of the core-funded phenotyping battery is to include only tests where we have a collaborator who is willing to take on for further definitive study the mutants with the feature of interest and to reduce the number of mice required to a minimum consistent with detecting a robust phenotype. We also aim to include as many challenges as possible to maximize our chances of finding new phenotypes.

**MUTAGENESIS
ORAL PRESENTATION****Monday October, 29****15.05 – 15.20pm****O3-3****RECENT PROGRESS IN THE RIKEN ENU-MUTAGENESIS PROJECT**

Noda T, Motegi H, Inoue M, Toki H, Minowa O, Sakuraba Y, Fukumura R, Murata T, Makino, Takahasi KR, Nakai Y, S, Miura I, Kobayashi K, Kaneda H, Furuse T, Suzuki T, Masuya H, Gondo Y, Wakana S and Shiroishi T
RIKEN GSC Functional Genomics Research Group

RIKEN mouse mutagenesis program aims to develop mouse mutants by genome-wide screening for various phenotypes of ENU-mutagenized mice for studying the functions of genes, and to establish animal models for human diseases. We have primarily conducted dominant and recessive phenotype screening focusing on late-onset phenotypes for developing models for human common diseases. For this purpose, we extended the observation period to more than one year and a half. Besides these screenings, we have carried out in-depth characterization of phenotypes of selected mutants, and identified the causative genes by a high-throughput gene mapping and a bioinformatics tool that we established. So far, we established totally 384 mutants (<http://www.gsc.riken.go.jp/Mouse/index.html>), in which a number of them appeared to be suitable animal models for common diseases. For examples, models for diabetes, hyperlipidemia, cancer, mental disease and osteoarthritis (OA) have been developed, and their causative genes were identified. In parallel with the phenotype-base screening, we have developed a gene-driven screening system to detect mutations of target genes of interest. Size of our frozen sperm and genomic DNA archive has run up to 8,000 G1 mice. We have obtained more than 400 point mutations from screening the archive, including coding sequences of various genes (e.g., *Disc1* and *Drd4*) as well as noncoding sequences (e.g., *Shh* remote enhancer). To enhance accessibility to these mutant resources, we developed a website termed "PhenoSITE" (<http://www.gsc.riken.go.jp/Mouse/>) in which integrated viewer of the mutants under standardized phenotype vocabularies is now available. These mouse mutants are now available through RIKEN BioResource Center, Tsukuba (<http://www.brc.riken.jp/lab/animal/en/>).

**MUTAGENESIS
ORAL PRESENTATION****Monday October, 29****15.20 – 15.35pm****O3-4****SYSTEMIC ANALYSIS AT THE GERMAN MOUSE CLINIC-OVERVIEW OF 75 MUTANT MOUSE LINES**

Martin Hrabé de Angelis and the German Mouse Clinic Consortium
GSF/Institute of Experimental Genetics, Neuherberg, Germany

We established the German Mouse Clinic as the first mouse phenotyping platform worldwide with the logistics of systemic, standardized phenotypic analysis and interpretation, with open access for the scientific community (Gailus-Durner, Fuchs *et al.* 2005). We will present an schematic overview of 75 mutant mouse lines (knock-outs, ENU mutants, gene traps, humanized) systemically analysed in the areas of allergy, behavior, clinical chemistry, cardiovascular analyses, dysmorphology, energy metabolism, eye development and vision, host-pathogen interactions, immunology, lung function, molecular phenotyping, neurology, nociception, and pathology. We have detected for more than 90% of the mutant lines novel phenotypes.

The GMC is one of the four large-scale phenotyping centers of the EUMODIC consortium which will undertake a primary phenotype assessment of up to 650 mutant mouse lines made available by the EUCOMM project. Therefore, we have established recently a new GMC primary workflow with two phenotyping pipelines and a doubled capacity.

To explore the complex relationship between environmental changes and genetic factors, we set up standardized challenge platforms for mouse phenotyping - the German Mouse Clinic II (GMC II). By mimicking specific environmental exposures or life styles that have a strong impact on human health, we want to determine their effects on disease etiology and progression, uncovering the physiological and molecular mechanisms of genome-environment interactions. We have chosen five areas - diet, air, stress, exercise and immunity - representing the major interfaces of the organism with the environment (gut, lung/skin, brain/sense organs, muscle/bone and immune system).

Gailus-Durner, Fuchs *et al.* (2005) *Nat Methods*. 2(6), 403-4.

This work is supported by the NGFN.

**MUTAGENESIS
ORAL PRESENTATION****Monday October, 29****16.00 – 16.15pm****O3-5****THE FUNCTIONAL ANNOTATION OF THE MOUSE GENOME - THE CHALLENGE OF PHENOTYPING**

Steve D.M. Brown and the EUMORPHIA and EUMODIC Consortia
MRC Mammalian Genetics Unit, Harwell, OX11 ORD, UK

With the completion of the mouse genome sequence, a key goal for functional genomics is the creation of a series of mutant alleles for every mammalian gene. An even greater challenge will be the determination of phenotypic outcomes for each mutation. A vital element of this endeavour will be to develop standardised phenotyping platforms that allow for reproducibility of test outcome over both time and place. The EUMORPHIA programme, funded by the European Commission, comprised a consortium of 18 research institutes from across Europe working on establishing new approaches to phenotyping with a focus on improving and standardising phenotyping platforms for the mouse. A major achievement has been the development of a new robust primary screening strategy, EMPReSS (European Mouse Phenotyping Resource for Standardised Screens). This primary screen incorporates over 150 SOPs, many validated on a cohort of inbred strains across a number of laboratories. EMPReSS covers all of the major body systems, as well as generic approaches in imaging, pathology and gene expression. The availability of standardised screens and associated informatics structures and tools will be a vital underpinning for a systematic and rational functional annotation of the mouse genome. Representing phenotypic information in a standardised way presents further challenges. Development of phenotype ontological structures that take into account assay protocol, genetic background and environment will be crucial. In addition, the mining of phenotypic characters for correlations indicative of underlying processes will require the availability of databases of raw phenotype data. In the EUMODIC programme, we are using a version of EMPReSS, EMPReSSslim, to begin the process of primary phenotyping of large numbers of mouse mutants generated through the EUComm mouse mutagenesis programme. 4 mouse clinics within the EUMODIC consortium will undertake comprehensive phenotyping using EMPReSSslim of up to 650 mouse mutant lines. A proportion of mutants with interesting phenotypes will undergo more detailed secondary/tertiary phenotyping at other centres within the EUMODIC consortium. All phenotype data will be made publicly available through the EuroPhenome database. EUMODIC is a first step towards tackling the need for comprehensive large-scale phenotyping in the mouse and the study of mammalian gene function.

**MUTAGENESIS
ORAL PRESENTATION**

Monday October, 29

16.15 – 16.30pm

O3-6

**THE KNOCK OUT MOUSE PROJECT DATA COORDINATION CENTER (KOMP-DCC):
ACCELERATING THE FUNCTIONAL CHARACTERIZATION OF THE MOUSE GENOME**

Carol Bult, Janan Eppig, James Kadin, Jeremy Mason, and Martin Ringwald
The Jackson Laboratory

The NIH Knockout Mouse Project is a large-scale mutagenesis initiative to produce a public resource of mouse embryonic stem cells containing a null mutation in every gene in the mouse genome. Participants in KOMP include The Jackson Laboratory, Regeneron Pharmaceuticals, Children's Hospital Oakland Research Institute, the University of California at Davis, the Sanger Institute, the University of Pennsylvania and the Samuel Lunenfeld Research Institute. The KOMP initiative leverages the availability of the annotated reference mouse genome sequence and recent advances in molecular genetics technologies that allow for large-scale approaches to inducing genetic mutations in specific genes. The goal of KOMP and similar initiatives (e.g., EUCOMM and NorCOMM) is to enhance the utility of the laboratory mouse as a model system of human disease through systematic functional analysis of mouse genes.

The KOMP Data Coordination Center (DCC) is the central clearinghouse of data and information regarding the status of the KOMP project and resources. The DCC supports the mission of the KOMP initiative by integrating mouse genome annotations with knowledge about existing mutations in mouse genes, functional annotations, and associations with known human disease genes. We will present the current status of the KOMP initiative, review the genes selected for KOMP relative to other similar functional genomics initiatives, and demonstrate how to track the status of genes in the KOMP pipeline and search for resources generated by the KOMP program.

Regularly updated information about KOMP gene targeting efforts and resource distribution is available to the scientific community at <http://www.knockoutmouse.org>.

**MUTAGENESIS
ORAL PRESENTATION****Monday October, 29****16.30 – 16.45pm****O3-7****ACTIVITIES OF FEDERATION OF INTERNATIONAL MOUSE RESOURCES (FIMRe)**

FIMRe Board of Directors

FIMRe (<http://www.fimre.org> <<http://www.fimre.org/>>) is an international association of organizations whose members, in a manner consistent with the governmental obligations and legal responsibilities of each, pledge to

- facilitate the use of, and sharing among, mouse resource centers across national boundaries and barriers;
- commit to cooperative, standardized approaches to selection, archiving, protection, safe management, and distribution of mouse models;
- establish and follow commonly shared principles of operation as regards animal health, genetics, environmental management and quality control;
- work cooperatively to secure access to, and utilization of, available resources, services, and expertise in all aspects of archive management and distribution of mouse models;
- achieve a common ground on approaches to insure efficient, effective, and economical access to mouse models and services by the biomedical research community.

FIMRe's goal is to facilitate the use of mouse models of human disease, behavior and development for the benefit of researchers who are investigating the function of each gene in the mouse genome.

Mouse strains available from all the FIMRe resource centers are listed in the International Mouse Strain Resource (<http://www.imsr.org> <<http://www.imsr.org/>>), and their individual web sites. The bi-institutional Agreement for International Recovery of Cryopreserved Mouse Strain from Repositories has been signed among the FIMRe members. Most of the strains in the FIMRe resource centers are cryopreserved as embryos, gametes and ES cells. Researcher can choose a regional FIMRe member as the site of recovery of cryopreserved mice.