

**Tuesday November, 4
10.30am – 12.00pm
Poster Session 2
Modeling Disease
Posters P45- P90**

S5/P45 – INVESTIGATION OF MYOTILIN AS A MODIFIER GENE IN A MOUSE MODEL OF CARDIOMYOPATHY

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S4/P46 – A LOCUS ON CHROMOSOME 7 DETERMINES INFARCT VOLUME IN THE FOCAL CEREBRAL ISCHEMIA MOUSE MODEL OF STROKE

Sehoon Keum, Douglas Marchuk

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P47 ATRIAL NATRIURETIC PEPTIDE AND OSTEOPONTIN ARE USEFUL MARKERS OF CARDIAC DISORDERS IN MICE

Frank Schoensiegel¹, Raffi Bekeredjian¹, Anja Schrewe², Dieter Weichenhan¹, Norbert Frey¹, Hugo A Katus¹, Boris T Ivandic¹

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S8/P48 - IN THE MP MOUSE, MUTANT FIBRILLIN-2 ACCUMULATION IN THE ER OF DEVELOPING CILIARY-BODY CELLS ELICITS THE UNFOLDED PROTEIN RESPONSE AND CAUSES PAN-OCULAR MALFORMATIONS

Joe Rainger, David FitzPatrick, Ian Jackson

MRC Human Genetics Unit, Edinburgh, United Kingdom

S14/P49 – A SYSTEMS GENETICS APPROACH TO IDENTIFY MOLECULAR PATHWAYS THAT MEDIATE GENETIC SUSCEPTIBILITY TO LOW DOSE IONIZING RADIATION

Rachel Lynch¹, Suchita Das¹, Karen Cheng¹, Jim Bogard¹, Sudhir Naswa¹, Stephen Kania², Elissa Chesler¹, Michael Langston², Brynn Voy¹

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P50 USING THE COLLABORATIVE CROSS TO UNCOUPLE THE METABOLIC AND ENDOCRINE FUNCTIONS OF ADIPOSE TISSUE

Maria Namwanje¹, Darla Miller², Suchita Das², Arnold Saxton³, Elissa Chesler², Charles Sullivan¹, Brynn Voy²

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P51 MRC HARWELL: DISEASE MODEL DISCOVERY

Steve Brown, Paul Potter

MRC Harwell, Oxfordshire, United Kingdom

P52 THE HARWELL MOUSE CLINIC AND EUMODIC: A PHENOTYPING FACILITY

Steve Brown, Paul Potter

MRC Harwell, Oxfordshire, United Kingdom

P53 THE EUROPEAN MOUSE MUTANT ARCHIVE (EMMA)

Michael Hagn⁶, Glauco Tocchini-Valentini¹, Yann Herault², Steve Brown³, Urban Lendahl⁴, Jocelyne Demengeot⁵, Martin Hrabè de Angelis⁶, Ewan Birney⁷, Karen Steel⁸, Jean Louis Mandel⁹, Lluís Montoliu¹⁰

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P54 COMMON AND DISTINCTIVE MECHANISMS IN LUNG CANCER, INFLAMMATION AND FIBROSIS

Alexandra Paun, Christina Haston
McGill University, Meakins-Christie Laboratories, Montreal, Quebec, Canada

P55 A PLAN OF JAPANESE MOUSE CLINIC IN RIKEN BRC

Shigeharu Wakana¹, Tomohiro Suzuki¹, Hiroshi Masuya¹, Ikuro Miura¹, Kimio Kobayashi¹, Hideki Kaneda¹, Tamio Furuse¹, Ikuko Yamada¹, Hiromi Motegi¹, Hideaki Toki¹, Maki Inoue¹, Osamu Minowa¹, Nobuhiko Tanaka¹, Tetsuo Noda¹, Toshihiko Shiroishi², Yuichi Obata¹
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P56 ER STRESS-MEDIATED APOPTOSIS IN A NEW MOUSE MODEL OF OSTEOPENIA

Thomas Lisse, Frank Thiele, Helmut Fuchs, Wolfgang Hans, Koichiro Abe, Gerhard Przemec, Martin Hrabec de Angelis
Helmholtz Zentrum München, Neuherberg, Germany

S9/P57 – THE ROLE OF SOX4 IN INSULIN SECRETION AND IMPAIRED GLUCOSE TOLERANCE.

Alison Hough, Michelle Goldsworthy, Roger Cox
Medical Research Council, Harwell, Oxfordshire, United Kingdom

P58 MOUSE INTER-SUBSPECIFIC CONSONIC STRAINS UNCOVERS ADDITIVE AND NON-ADDITIVE GENETIC EFFECTS ON COMPLEX TRAITS

Toyoyuki Takada¹, Akihiko Mita², Akiteru Maeno², Kazuo Moriwaki³, Hiromichi Yonekawa⁴, Toshihiko Shiroishi²
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P59 FREQUENT OCCURRENCE OF MILD OCULAR COLOBOMA WITHOUT MICROPTALMIA IN AN ALBINO MICE STRAIN

Tetsuro Matsuura¹, Naho Tsuji¹, Katsutoshi Kita¹, Kiyokazu Ozaki¹, Kazuyuki Mekada², Atsushi Yoshiki², Isao Narama¹
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P60 GENETIC DISSECTION AND RECONSTITUTION OF TYPE 2 DIABETES PHENOTYPES USING SINGLE AND DOUBLE CONSONIC STRAINS

Naru Babaya¹, Tomomi Fujisawa², Hironori Ueda², Masao Shibata³, Shinsuke Noso¹, Yoshihisa Hiromine¹, Hiroshi Ikegami¹
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P61 COMPARATIVE ANALYSIS OF THE FIBROTIC AND INFLAMMATORY RESPONSES OF ACB/BCA RECOMBINANT CONGENIC STRAINS TO THORACIC IRRADIATION AND BLEOMYCIN TREATMENT

Anne-Marie Lemay, Christina Haston
McGill University, Montreal, Quebec, Canada

P62 GETTING THE MOST OUT OF PHENOTYPES - VIEWS FROM MANY PERSPECTIVES...

Janan Eppig, Anna Anagnostopoulos, Randal Babiuk, Susan Bello, Donna Burkart, Howard Dene, Michelle Knowlton, Terry Meehan, Hiroaki Onda, Beverly Richards-Smith, Cynthia Smith, Monika Tomczuk, Linda Washburn, Jon Beal, Kim Forthofer, Jill Lewis, James Kadin
The Jackson Laboratory, Bar Harbor, Maine, United States

P63 THE JACKSON LABORATORY REPOSITORY: RESOURCE FOR MUTANT STRAINS MODELING HUMAN DISEASE

Deborah Boswell, David Bergstrom, Bo Chang, Muriel Davisson, Leah Rae Donahue, Kenneth Johnson, Cathleen Lutz, Stephen Murray, Laura Reinholdt, Stephen Rockwood, Mike Sasner, the Repository Team
The Jackson Laboratory, Bar Harbor, Maine, United States

P64 IMPROVEMENT OF A TISSUE-SPECIFIC GENE EXPRESSION FOR TRECK METHOD USING A BAC CLONE

Hiromichi Yonekawa¹, Kosuke Shibata¹, Michiko Sekine¹, Kunie Matsuoka¹, Hiroshi Shitara¹, Choji Taya¹, Takashi Amano²
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- P65 HYPOMORPHIC MUTATION IN MOUSE *NPPC* GENE CAUSES RETARDED LONGITUDINAL BONE GROWTH DUE TO IMPAIRED ENDOCHONDRAL OSSIFICATION**
Takehito Tsuji¹, Eri Kondo², Akihiro Yasoda², Masataka Inamoto¹, Chiyo Kiyosu¹, Kazuwa Nakao², Tetsuo Kunieda¹
¹Graduate School of Natural Science and Technology, Okayama University, Okayama, Japan, ²Kyoto University Graduate School of Medicine, Kyoto, Japan
- P66 APOPTIC DEATH OF HAPLOID MALE GERM CELLS IN *PCD*^{3J} MUTANT MICE**
Nameun Kim, Rui Xiao, Haiin Jo, Yunjung Choi, Jinhoi Kim, Chankyu Park
Konkuk University, Seoul, Korea, Republic of
- S10/P67 – MOUSE MODELS FOR FUNCTIONAL ANALYSIS OF FTO**
Christopher Church, Deen Quwailid, Lydia Teboul, Roger Cox
Medical Research Council, Mammalian Genetics Unit, Harwell, Oxfordshire, United Kingdom
- P68 VISUALIZATION OF MITOCHONDRIAL MORPHOLOGY USING MTGFP-TG MICE**
Hiroshi Shitara¹, Midori Shimanuki², Hiromichi Yonekawa¹
¹The Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan, ²University of Tsukuba, Ibaraki, Japan
- P69 MOUSE MODELS OF OTITIS MEDIA**
Michael Cheeseman, Sulzhan Bali, Paul Potter, Martin Fray, Steve Brown
MRC Harwell, Oxfordshire, United Kingdom
- P70 THE POSITIONAL CLONING OF MITOCHONDRIAL NICOTINAMIDE NUCLEOTIDE TRANSHYDROGENASE NNT AS THE BASIS OF INSULIN INSUFFICIENT GLUCOSE INTOLERANCE IN THE C57BL/6J MOUSE HIGHLIGHTS ITS CENTRAL ROLE IN VERTEBRATE HEALTH AND DISEASE**
Ayo A. Toye
University of Leicester, Leicester, United Kingdom
- P71 IDENTIFICATION OF NEW TARGETS PLAYING A ROLE IN METABOLIC DISEASES BY SYSTEMIC ANALYSIS IN THE GERMAN MOUSE CLINIC**
Jan Rozman¹, Birgit Rathkolb², Susanne Neschen³, Nadja Herbach⁴, Sibylle Wagner³, Valérie Gailus-Durner³, Helmut Fuchs³, Martin Klingenspor¹, Bernd Aigner², Eckhard Wolf², Martin Hrabé de Angelis³
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- P72 THE SANGER INSTITUTE MOUSE GENETICS PROGRAMME – AN OVERVIEW**
Niels Adams, Jacqui White, David Sunter, Gordon Dougan, William Skarnes, Seth Grant, Pentau Liu, David Adams, Allan Bradley, Karen Steel
Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom
- P73 THE SANGER INSTITUTE MOUSE GENETICS PROGRAMME – PROGRESS AND RESULTS**
Niels Adams, Jacqui White, David Sunter, Anna-Karin Gerdin, Natasha Karp, Sophie Messenger, Gordon Dougan, William Skarnes, Seth Grant, Pentau Liu, David Adams, Allan Bradley, Karen Steel
Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom
- P74 HIGH THROUGHPUT GENE EXPRESSION ANALYSIS IN MICE**
Jeanne Estabel, Kay Clarke, Yvette Hooks, Jacqui White, David Sunter, Karen Steel, Gordon Dougan, William Skarnes, Seth Grant, Pentau Liu, David Adams, Allan Bradley, Niels Adams
Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom
- P75 STATISTICAL AND EXPERIMENTAL DESIGN CHALLENGES IN HIGH THROUGHPUT PHENOTYPING OF MUTANT MICE**
Natasha Karp, Niels Adams, Jacqui White, David Sunter, Gordon Dougan, William Skarnes, Seth Grant, Pentau Liu, David Adams, Allan Bradley, Karen Steel
Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom

- P76 A SPONTANEOUS MUTATION (DHE) IN THE MOUSE LMNA GENE RESULTS IN HYPOPLASTIC CRANIAL SUTURES AND UNDER-MINERALIZATION OF THE SKELETON**
Leah Rae Donahue¹, Don Liu¹, Michelle Curtain¹, Coleen Marden¹, Carole MacKay², Paul Odgren²
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- P77 A COMPREHENSIVE APPROACH TO ELUCIDATE NOVEL MOLECULAR MECHANISMS IMPLICATED IN DIABETES PATHOGENESIS IN MOUSE MUTANTS**
Susanne Neschen¹, Birgit Rathkolb², Jan Rozman³, Wolfgang Hans¹, Helmut Fuchs¹, Valerie Gailus-Durner¹, Jerzy Adamski¹, Karsten Suhre¹, Eckhard Wolf², Martin Klingenspor³
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 Zheng Chen¹, Mireille Montcouquiol¹, Rene Calderon¹, Nancy Jenkins², Neal Copeland², Matthew Kelley¹, Konrad Noben-Trauth¹
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- P79 POSITIONAL CLONING OF THE WAVED WITH OPEN EYE LIDS 2 (WOE2) LOCUS**
Joseph Toonen, Duska Sidjanin, Joseph Besharse, Lavinia Jackson, Lina Liang
 Medical College of Wisconsin, Milwaukee, WI, United States
- P80 THE REFINEMENT OF PHENOTYPING PROTOCOLS FOR HAEMATOLOGY AND PLASMA BIOCHEMISTRY: A COMPARISON OF DATA GENERATED BY PARTICIPANTS IN THE EUMODIC PROGRAMME**
Tertius A. Hough¹, Christine Podrini², Kan Pai Chiev¹, Jeanne Estabel², Prabhjoat S. Chana², Rachel Kendall¹, Kelly Searles¹, Michael Cheeseman¹, Hilary Gates¹, Sara Wells¹, Jacqui K. White², Niels C. Adams², Steve D.M. Brown¹
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- P81 INTESTINAL CANCER GENE DISCOVERY USING SLEEPING BEAUTY-INDUCED MUTAGENESIS IN APC^{+/+} AND APC^{MIN/+} MICE**
 Timothy Starr¹, Raha Allaei¹, Kevin Silverstein², Rodney Staggs², Tracy Bergemann³, M. Gerard O'Sullivan⁴, Ilze Matise⁴, Adam Dupuy⁵, Lara Collier⁶, Scott Powers⁷, Ann Oberg⁸, Stephen Thibodeau⁸, Lino Tessarollo⁹, Neal Copeland¹⁰, Nancy Jenkins¹⁰, David Largaespada¹, Robert Cormier¹¹
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Clara Moore, Matthew Demczko, Naomi Gottlieb, Lauren Hakkinen
 Franklin & Marshall College, Lancaster, PA, United States
- P83 SPONTANEOUS, MUTAGEN-INDUCED AND GENETICALLY-ENGINEERED MOUSE MODELS OF HUMAN DISEASE IN THE GENETIC RESOURCE SCIENCE GROUP AT THE JACKSON LABORATORY**
David Bergstrom, Muriel Davisson, Jeffrey Lake, Cathy Lutz, Steven Murray, Laura Reinholdt, Stephen Rockwood, Michael Sasner, Kenneth Johnson, Leah Rae Donahue
 The Jackson Laboratory, Bar Harbor, ME, United States

P84 SUPPRESSION OF INTESTINAL ADENOMAS BY A NOVEL GENETIC MODIFIER IN THE APC^{MIN} MOUSE MODEL

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P85 MAPPING OF THE LENS OPACITY 13 (LOP13) LOCUS IN MICE

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P86 INDUCEMENT OF PLASMODIUM BERGHEI ANKA STRAIN RESISTANCE TO PIPERAQUINE, LUMEFANTRINE, AND AMODIAQUINE IN A MOUSE MODEL

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P87 INFRAFRONTIER – THE EUROPEAN INFRASTRUCTURE FOR PHENOTYPING AND ARCHIVING OF MODEL MAMMALIAN GENOMES

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P88 THE COLLABORATIVE CROSS AT ORNL

Elissa J. Chesler¹, Gary A. Churchill³, Cymbeline T. Cuiat¹, William R. Lariviere⁴, Kenneth F. Manly², Darla Miller², Bruce O'Hara⁶, Abraham A. Palmer⁷, David W. Threadgill⁸, Brynn H. Voy¹, Yisong Wang², Robert W. Williams⁹

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P89 IDENTIFICATION OF GENES REGULATED FROM THE DISTAL INTERVAL OF MOUSE CHROMOSOME 16 SYNTENIC TO HUMAN CHROMOSOME 21

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P90 GLOBAL TRANSCRIPTOMES OF ADULT AND EMBRYONIC TISSUES IN MICE WITH 30 MB SEGMENTAL TRISOMY OF CHROMOSOME 17

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ATRIAL NATRIURETIC PEPTIDE AND OSTEOPONTIN ARE USEFUL MARKERS OF CARDIAC DISORDERS IN MICE

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Biomarkers are not established for cardiovascular phenotyping in mice. We compared the use of echocardiography with the determination of N-terminal propeptide of the atrial natriuretic peptide (Nt-proANP) and osteopontin (Opn). We measured plasma Nt-proANP and Opn levels in (1) the inbred strains C57BL/6, BALB/c, C3H/He, DBA/2, FVB/N, 129S1/Sv; (2) a surgical model of nonischemic myocardial infarction; and (3) delta-sarcoglycan (Sgcd) and calsarcin 1 [also known as myozenin 2 (Myoz2)] knockout models of cardiomyopathy. Left ventricular function was assessed as fractional shortening (FS) by echocardiography in conscious mice. Plasma Nt-proANP exhibited marked variability and ranged from 0.31 +/- 0.19 (C57BL/6 male mice) to 1.34 +/- 0.43 nmol/l (DBA/2 female mice), depending on sex, age, and genetic background. Opn was less variable than Nt-proANP and was decreased significantly in C3H/He and DBA/2 throughout the 16 wk of study. Nt-proANP increased temporarily in mice with myocardial injury. In contrast, Opn increased in both operated and sham-treated mice. Nt-proANP was inversely correlated with FS and distinguished controls from Sgcd and Myoz2 mutants with 100% sensitivity and 71% specificity. Opn was increased in Sgcd mutants, which exhibited only mildly reduced FS but marked myocardial degeneration and fibrosis. Both of these histologic features were absent in Myoz2 mutants. Nt-proANP is an early marker of cardiac disease and is suitable for age- and sex-matched comparisons between groups of transgenic and matched control mice. Opn is useful to detect inflammatory and degenerative myocardial disorders that may be missed by echocardiography.

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USING THE COLLABORATIVE CROSS TO UNCOUPLE THE METABOLIC AND ENDOCRINE FUNCTIONS OF ADIPOSE TISSUE

Maria Namwanje¹, Darla Miller², Suchita Das², Arnold Saxton³, Elissa Chesler², Charles Sullivan¹, Brynn Voy²

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The overarching hypothesis behind our work is that heritable variation in the endocrine function of adipose tissue contributes to susceptibility to obesity and its comorbidities. We focus on the renin-angiotensin system (RAS) because we have shown that Angiotensin II (Ang II) regulates adipogenesis, adipocyte metabolism, insulin sensitivity, and expression levels of other key adipokines. In the BXD (C57BL/6J X DBA/2J) recombinant inbred strain panel, adipose angiotensinogen (*Agt*) expression varies approximately 5-fold across strains and is highly heritable, with suggestive eQTLs found on Chr.X Further, while components of the adipose RAS are significantly correlated with adiposity, *Agt* is also part of adipokine coexpression networks that exist independently of fatness. These studies are now being extended into the Collaborative Cross, an emerging population-based mouse model system with genetic variation comparable to that in humans. Using mice from interim generations of the CC, we profile markers of fatness and adipocyte size in parallel with expression of RAS components, adipokines and measures of insulin sensitivity. As expected from the range of fatness and diabetic tendency in the CC parental strains, fat pad weight and glycemia range widely (~ 160 and 6-fold after 6 generations of inbreeding) in interim CC lines. Preliminary data indicate comparable variation in adipokine profiles (e.g., 136-fold difference in *Agt* expression, 10th and 90th percentiles). As genotype data for the CC become available, they will be used to identify the loci that regulate expression of the RAS and other adipokines and to determine how these loci interact with those controlling fatness

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MRC HARWELL: DISEASE MODEL DISCOVERY

Steve Brown, [Paul Potter](#)
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MRC Harwell is at the international forefront of the use of mouse genetics to study the relationship between genes and disease, particularly in the use of ENU mutagenesis to generate novel models of disease. Phenotype driven screens are used to interrogate pipelines of mutagenised mice to identify individual mice with phenotypes of interest. Such screens have successfully generated models of disease in a variety of areas including deafness, diabetes, and circadian rhythm. A further advantage of such screens is the ability to identify novel genes and pathways associated with disease pathologies, because no assumptions are made about the underlying genetic basis of disease; the screens are based purely on phenotype. Additionally, MRC Harwell curates parallel sperm and DNA archives of mutagenised mice enabling researchers to screen specific genes of interest for mutations of interest. The models we create and study, further our understanding of disease processes that occur when a gene is absent or malfunctions. The disease models generated can also be employed for the pre-clinical assessment of new drugs and other therapeutic approaches.

The unit delivers research programmes, facilities, and services in a variety of areas, providing a centre for expertise and services in mouse genetics; from mutagenesis, through phenotyping, to the archiving and dissemination of mouse genetics resources. In addition to the Harwell research groups the unit hosts external research groups and undertakes research collaborative research projects worldwide. The research undertaken aims to advance medicine and knowledge through the discovery and investigation of mouse models of human disease.

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THE HARWELL MOUSE CLINIC AND EUMODIC: A PHENOTYPING FACILITY

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EUMODIC brings together a large consortium of 18 research institutes in 8 European countries who are experts in the field of mouse functional genomics and phenotyping, and will undertake a primary phenotype assessment of up to 650 mouse mutant lines derived from ES cells developed in the EUComm project. Lines showing an interesting phenotype will be subject to a more in depth assessment.

EUMODIC will build upon the comprehensive database of standardised phenotyping protocols, called EMPReSS, developed by the EUMORPHIA project. EUMODIC has developed a selection of these screens, called EMPReSSslim, to enable comprehensive, high throughput, primary, phenotyping of large numbers of mice.

The primary phenotype assessment using EMPReSSslim will be undertaken in four mouse clinics: GSF, Germany; ICS, France; MRC Harwell, UK and the Sanger Institute, UK. A distributed network of centres will develop the more complex, secondary phenotyping screens and apply them to a subset of the mice which have shown interesting phenotypes in the primary screen. The EuroPhenome resource has been developed as a central point for holding phenome data from the large-scale European phenotyping projects using the standardised procedures of EMPReSS.

The phenotyping expertise at the Harwell Mouse Clinic exemplified by the EUMODIC and ENU mutagenesis programs is available to the wider scientific community.

P53**THE EUROPEAN MOUSE MUTANT ARCHIVE (EMMA)**

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The European Mouse Mutant Archive (EMMA) offers the worldwide scientific community a free archiving service for its mutant mouse lines and access to a wide range of disease models and other research tools. A full description of these services can be viewed on the EMMA website at <http://www.emmanet.org>.

The EMMA network is comprised of ten partners who operate as the primary mouse repository in Europe and is funded by the participating institutes and the European Commission Research Infrastructures Programme.

EMMA's primary objectives are to establish and manage a unified repository for maintaining mouse mutations and to make them available to the scientific community. In addition to these core services, the consortium can generate germ-free (axenic) mice for its customers and also hosts courses in cryopreservation.

All applications for archiving and requests for mutant mouse strains are submitted through the EMMA website. Mouse strains submitted for archiving are evaluated by EMMA's external scientific committee. Once approval has been granted depositors are asked to send mice of breeding age to one of the EMMA partners for embryo or spermatozoa cryopreservation. Strains held under the EMMA umbrella can be provided as frozen materials or re-derived and shipped as live mice depending on the customer's needs. However, certain strains that are in high demand are maintained as breeding colonies to facilitate their rapid delivery. All animals supplied by EMMA are classified as SPF in accordance with the FELASA recommendations.

EMMA is a founding member of FIMRe (International Federation of Mouse Resources) and actively cooperates with other leading repositories like TJL and the MMRRRC in the US and BRC RIKEN from Japan.

P54**COMMON AND DISTINCTIVE MECHANISMS IN LUNG CANCER, INFLAMMATION AND FIBROSIS**

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A strong link between inflammation and cancer has long been established and from the perspective of tissue regeneration, cancers are seen as wounds that do not heal. The objective of our study was to compare the molecular mechanisms characterizing lung cancer with those characterizing inflammation or aberrant healing (fibrosis) in order to determine the commonalities and differences between these processes. To this purpose we compared microarray data from models of urethane-induced lung cancer, bleomycin-induced pulmonary fibrosis and radiation-induced inflammation. The majority of differentially expressed genes common to cancer and fibrosis/inflammation are concordantly regulated in the two compared processes (70% for cancer and fibrosis and 62% for cancer and inflammation). Pathway analysis of these concordant genes revealed that immune response and tissue remodelling (represented by pathways such as IL6, IL10, TGF-beta signaling, cell adhesion molecules and ECM-receptor interactions) are common to all three processes. Discordant genes delineate pathways which differentiate lung malignancies from inflammation/fibrosis, such as Fc epsilon RI, insulin, VEGF, natural killer cell signaling and apoptosis. Our study also shows that pathways such as Wnt and Toll-like receptor signaling are representative of the inflammatory aspect of lung carcinomas whereas glycolysis and metabolic processes illustrate the active remodeling taking place in both lung cancer and fibrosis. By revealing common and distinctive mechanisms between cancer and inflammation/fibrosis, our analysis contributes to a better insight of the biology of the disorders which in turn will play a role in the discovery of more effective treatments for these lung diseases.

P55

A PLAN OF JAPANESE MOUSE CLINIC IN RIKEN BRC

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In the RIKEN ENU-mutagenesis project, we have developed a systematic and comprehensive phenotyping platform. As a result of phenotype screening on this platform, we have generated about 400 mutants as animal models for human diseases. Beside, we have developed a high-throughput gene mapping system and a database system for *in silico* exploration of candidate genes of these mutations, in collaboration with Omic bioinformatics data integration team of RIKEN GSC. Using these systems, we have successfully identified causative genes of 64 mutants. All information of these mouse mutants is now open to public through our home page (<http://www.brc.riken.jp/lab/gsc/mouse/indexJ.html>). In this year, we have reconstructed the existing phenotyping platform and rebuilt a new platform. The new system has hierarchical structure, consisting of a basic pipeline that inherits the existing platform and an additional pipeline, which is optimized for more in-depth phenotyping assays. Using this system, we have started to perform more comprehensive and profound phenotyping of mouse mutants. We have opened this system as a Japanese Mouse Clinic to Japanese science community. As was shown from the results of preceding related projects, existing mouse mutants will be revalued as new disease models by identified novel phenotypes detected on the new platform. We also plan to share detailed information about standard operating procedures (SOPs) of our phenotyping analyses with those of other related large-scale projects, such as EUMODIC and GMC. Moreover, we will contribute to international efforts for standardization of mouse phenotype data by sharing annotation of mutant phenotypes, which are made with internationally standardized method, with the other related projects.

P56

ER STRESS-MEDIATED APOPTOSIS IN A NEW MOUSE MODEL OF OSTEOGENESIS IMPERFECTA

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Osteogenesis imperfecta (OI) is a heterogeneous collection of connective tissue disorders typically caused by mutations in the *COL1A1/2* genes that encode the chains of type I collagen, the principle structural protein of bone. Phenotypic expression in OI depends on the nature of the mutation, causing a clinical heterogeneity ranging from a mild risk of fractures to perinatal lethality. Here, we describe a new OI mouse model termed *Aga2* (abnormal gait 2) with a dominant frameshift mutation in the terminal C-propeptide domain of Col1a1 (procollagen type I, alpha 1) that was isolated from the Munich N-ethyl-N-nitrosourea (ENU) mutagenesis program. Heterozygous animals developed severe-to-lethal phenotypes that were associated with markedly increased bone turnover and a disrupted native collagen network. In addition, abnormal pro α 1(I) chains accumulated intracellularly and were poorly secreted extracellularly. This was associated with the induction of endoplasmic reticulum (ER) stress-specific unfolded protein response (UPR) with caspases-12 and -3 activation and apoptosis of osteoblasts both *in vitro* and *in vivo*. Taken together, our studies resulted in the identification of a new model for *Osteogenesis imperfecta*, and identified a role for intracellular modulation of the ER stress-associated UPR machinery towards osteoblast apoptosis during the pathogenesis of disease.

Lisse TS, Thiele F, Fuchs H, Hans W, Przemeck GKH, et al. (2008) ER stress-mediated apoptosis in a new mouse model of Osteogenesis imperfecta. *PLoS Genet* 4(2): e7.

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P58**MOUSE INTER-SUBSPECIFIC CONSONIC STRAINS UNCOVERS ADDITIVE AND NON-ADDITIVE GENETIC EFFECTS ON COMPLEX TRAITS**

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An inbred strain MSM/Ms is derived from Japanese wild mice, *Mus musculus molossinus*. It shows large extent of phenotypic difference in many complex traits, as well as vast amount of genome difference (0.82% SNPs), for a standard laboratory strain C57BL/6J (B6), which is predominantly derived from WestEuropean wild mice, *M. m. domesticus*. We have established a full set of inter-subspecific consomic strains, B6-ChrN^{MSM}, in which each chromosome of B6 is replaced by its counter part of MSM/Ms. We have performed systematic phenotype screening of the B6-ChrN^{MSM} consomic strains as well as the chromosome donor and host strains, MSM/Ms and B6. Currently, we are focusing on complex traits related to reproduction, growth, and energy metabolism. Genetic determinants for some phenotypes are dissected into multiple chromosomes on the B6 background, reflecting their simple additive effects. In contrast, measured values for some quantitative complex traits often far exceed the range between the host strain B6 and the donor strain MSM/Ms. It may be due to segregation of MSM/Ms alleles by chromosome substitution. It is possible that MSM/Ms has alleles on different chromosomes, which have opposite effects on the measured values of the quantitative traits. In that case, substitution of the chromosomes concerned would uncover effects of the MSM/Ms alleles on the relevant consomic strains. Alternatively, it is also possible that chromosome substitution either gives rise to non-additive interactions or disrupts conventional genetic interactions between multiple genes located on the substituted chromosome and remaining chromosomes. In these cases, chromosome substitution would elicit epistatic effects.

P59**FREQUENT OCCURRENCE OF MILD OCULAR COLOBOMA WITHOUT MICROPHthalmIA IN AN ALBINO MICE STRAIN**

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Colobomatous microphthalmia has been reported in some strains of colored mice, however, an inbred line of albino mutant mice with ocular coloboma has not yet been established. We elucidated that albino FLS mice with normal-sized eyes had apparent ocular coloboma. In the present study, we attempted to clarify the detailed time course of morphogenesis of ocular coloboma without microphthalmia in FLS mice in comparison with normally developing eyes in other strain of mice. Five-week-old FLS mice, and the fetuses on gestation day (GD) 11.0-13.0 were used along with age-matched BALB/c mice. After fixation by perfusion, the sizes of both eyeballs (WxHxD) were measured and the fundus was observed under the stereoscopic microscopy. Serial coronal sections of eyes were examined by light and electron microscopy. Morphometrical examination revealed that there was no difference in size of eyeballs between FLS mice with ocular coloboma and normal BALB/c mice. FLS embryos showed normal ocular development up to just before GD 12.0, however both side of inner layer (presumptive retina) and external layer (retinal pigment epithelium) of the optic cup showed incomplete fusion at the optic fissure at GD 12.0-13.0. Neither any hypoplastic changes nor the developmental defects were detected in other component of fetal ocular tissue. These results suggest that the failure in closure of the optic fissure in FLS mice might be rather mild compared to those of other strains with ocular coloboma. Thus, FLS mice are considered to be a suitable model for human mild-type ocular coloboma.

P60

GENETIC DISSECTION AND RECONSTITUTION OF TYPE 2 DIABETES PHENOTYPES USING SINGLE AND DOUBLE CONSONMIC STRAINS

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The NSY mouse is an inbred strain which spontaneously develops type 2 diabetes (T2D) with moderate obesity. We previously mapped two major quantitative trait loci for hyperglycemia on chromosomes (Chr) 11 and 14 by a whole genome scan in (C3H x NSY)F2 mice.

To obtain direct evidence for T2D susceptibility genes on Chr11 and Chr14, and to clarify their function as well as interaction in conferring susceptibility to T2D, we constructed two consomic strains, C3H-11^{NSY} and C3H-14^{NSY} mice, which carry an NSY-derived susceptible Chr11 and Chr14, respectively, on the control C3H background, and also established a double consomic strain, C3H-11^{NSY}14^{NSY}, containing both NSY-Chr11 and NSY-Chr14 in homozygous states. Phenotypes related to T2D were analyzed in those consomic and parental strains.

C3H-11^{NSY} and C3H-14^{NSY} mice showed significantly higher blood glucose level than C3H mice ($p < 0.001$). In NSY-Chr11, both impaired insulin secretion and insulin resistance were observed, whereas insulin resistance, but not impaired insulin secretion, was observed in NSY-Chr14. The degree of hyperglycemia in the C3H-11^{NSY}14^{NSY} was greater than that observed in each single consomic ($p < 0.01$), but was not as severe as that in the parental NSY mouse. C3H-11^{NSY}14^{NSY} mice developed obesity, which was not observed in each single consomic strain.

These data indicate that NSY-derived Chr11 and Chr14 harbor diabetogenic genes, and that the genes on these two chromosomes demonstrate the genetic interaction in causing obesity. The data also indicate the contribution of additional genes on other chromosomes to the full expression of diabetes-related phenotypes in the NSY mice.

P61

COMPARATIVE ANALYSIS OF THE FIBROTIC AND INFLAMMATORY RESPONSES OF ACB/BCA RECOMBINANT CONGENIC STRAINS TO THORACIC IRRADIATION AND BLEOMYCIN TREATMENT

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Bleomycin treatment and thoracic irradiation result in pulmonary fibrosis and lung inflammation in susceptible strains. We hypothesized that a common set of genes could be implicated in the development of pulmonary fibrosis caused by either treatment. We investigated the response of a set of 25 recombinant congenic strains (RCS) derived from A/J and C57BL/6J mice which contain on average 13% of A/J alleles on a C57BL/6J background (named AcB), or 13% of C57BL/6J allele on an A/J background (called BcA). A/J mice are fibrosis resistant while C57BL/6J mice develop fibrosis following both insults. The AcB strains did not develop a fibrotic lung disease in response to either treatment, while some BcA strains developed pulmonary fibrosis. 4 irradiated strains developed significant pulmonary fibrosis and these strains also showed a fibrotic response following bleomycin treatment. 7 bleomycin-treated strains developed fibrosis, but were resistant to injury from radiotherapy. There was no correlation between pulmonary inflammation of bleomycin-treated and irradiated mice. The fibrotic responses of the RCS were used to identify quantitative trait loci (QTL) for this phenotype. Suggestive QTLs were identified on chromosomes 1, 3, 5, 6, 9 and 12 for bleomycin-induced pulmonary fibrosis, and on chromosomes 3 and 4 for radiation-induced fibrosis. The chromosome 3 locus is an overlapping QTL, and a microarray expression study of A/J and C57BL/6J response showed that transforming growth factor, beta receptor I (*Tgfb β 1*) is located in this region and differentially expressed in both inducing treatments.

P62**GETTING THE MOST OUT OF PHENOTYPES - VIEWS FROM MANY PERSPECTIVES...**

Janan Eppig, Anna Anagnostopoulos, Randal Babiuk, Susan Bello, Donna Burkart, Howard Dene, Michelle Knowlton, Terry Meehan, Hiroaki Onda, Beverly Richards-Smith, Cynthia Smith, Monika Tomczuk, Linda Washburn, Jon Beal, Kim Forthofer, Jill Lewis, James Kadin

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To date (July 2008), over 125,000 phenotype-to-genotype associations have been made in MGI, describing genotypes carrying nearly 20,000 different mutant alleles. Nearly 2400 genotypes are annotated as models for over 850 human diseases.

Phenotype and disease data are inherently difficult to robustly capture and standardize, given their diversity in depth and breadth of information, the vagaries of defining genetic backgrounds, and the need to represent both population characteristics (e.g. RI or inbred strains) and phenotype analyses of specific mutations and knockouts in complex genotypes.

MGI (www.informatics.jax.org) has collaboratively built and continues to develop the Mammalian Phenotype Ontology to standardize phenotype descriptive terms. The Mammalian Phenotype Ontology has been widely adopted by mouse and rat communities for annotating phenotype data. This terminology has greatly accelerated our ability to compare, contrast, and understand phenotype and genotype connections.

A suite of tools exists in MGI to navigate these rich phenotype data, and address the multiple perspectives of the user community. Users can

- 1) find alleles or disease models involving mutations in a particular gene from the [Gene Detail Page](#);
- 2) explore genome wide, all alleles that have a particular phenotype using the [Mammalian Phenotype Ontology](#);
- 3) search for extensive details on mutations that have multiple phenotypes, diseases, or other phenotype attributes using the [Phenotype Search Form](#);
- 4) find all mouse models for a human disease by browsing or searching the [Human Disease Vocabulary](#)
- 5) view or search for mutant phenotypic alleles using [Mouse GBrowse](#), showing tracks for mouse alleles and phenotypes in a genome view.
- 6) view the new [phenotype by genotype matrix](#) allowing direct genotype / phenotype comparisons, and the ability to expand or contract phenotype classes depending on the users' interest. This view allows users to zoom in on their phenotype of interest and visually compare how different allelic mutations and genetic backgrounds influence the manifestation of these phenotypes.

We will review the phenotype / disease viewing options in MGI and demonstrate the new matrix view that allows genotype / phenotype comparisons.

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THE JACKSON LABORATORY REPOSITORY: RESOURCE FOR MUTANT STRAINS MODELING HUMAN DISEASE

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The Jackson Laboratory Repository serves as a centralized resource for the scientific community, importing, developing, cryopreserving and distributing mouse strains. Recently acquired strains include models for attention deficit-hyperactivity disorder (ADHD), Diamond Blackfan anemia, Gilles De La Tourette Syndrome, Levi type dwarfism, Rett syndrome, Amyotrophic Lateral Sclerosis and allergic asthma. New additions to the Repository's inducible and conditional mutation mouse strains allow researchers to generate temporal and/or tissue-specific tools for modeling human disease. Equally important are the Cre recombinase-expressing strains that can be used in conjunction with these conditional mutants. Because most of the existing Cre strains have not been fully characterized and 'ectopic' expression of Cre can confound analysis, we have undertaken a project to comprehensively characterize Cre activity in embryonic and adult mouse tissues. We are developing a database of Cre expression data that includes images and expression patterns curated with terms from the Mouse Anatomical Dictionary, and a web interface enabling searches by site of Cre expression at various developmental and adult ages.

The Repository maintains a searchable on-line resource (jaxmice.jax.org/findmice/index.html) for each strain. Donating a strain to the Repository fulfills the requirements for the sharing of mice in accordance with NIH's policy for the sharing of model organisms. Researchers can submit their strains to be considered for inclusion in the Repository by using the on-line form available at: <http://www.jax.org/grc/index.html>.

The Jackson Laboratory Repository is supported by NCCR (RR09781, RR11083, RR16049), The Howard Hughes Medical Institute, The Ellison Medical Foundation and donations from private foundations.

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IMPROVEMENT OF A TISSUE-SPECIFIC GENE EXPRESSION FOR TRECK METHOD USING A BAC CLONE

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We have developed a new method for tissue (or organ)-specific cell ablation named TRECK (Toxin REceptor-mediated Cell Knockout; Saito et al., Nat. Biotech. 19: 746-750, 2001). This method is based on the difference of diphtheria toxin (DT) between mice and humans. Mice are 1,000 – 10,000 times less sensitive to DT than humans. In transgenic mice (hDTR-Tg), in which human DTR gene ligated with a tissue-specific promoter/enhancer is introduced, tissue cells expressing hDTR on the cell surface can be specifically eliminated by DT administration. We previously generated TRECK Tg mice for pancreatic beta cell ablation using rat insulin promoter/enhancer on SCID-genetic background and succeeded in beta cell-specific ablation by DT administration. However, the efficiency of generating TRECK-Tg mice is not very high (~33%). Namely, hyperglycemia was observed in only one out of three lines. To improve transgenesis efficiency, we tried to use BACs to establish transgenic mice. This is because BAC clones are useful to keep long genome regions stably, and, in many cases, the essential regulatory sequences are included in a single BAC. Using homologous recombination system, Recombineering, we modified a 270kb BAC clone (RP23-92L23) containing mouse *ins2* gene which is involved in the insulin structure genes, and its promoter/enhancer region. We finally obtained 3 recombinant BACs in which hDTR gene was replaced with *ins2*-coding region. Then, we have generated Ins-TRECK-Tg mice using a recombinant BAC clone and obtained 5 lines of Ins-TRECK-Tg mice. As expected, all the BAC-Tg lines show the stable expression of hyperglycemia.

P65**HYPOMORPHIC MUTATION IN MOUSE *Nppc* GENE CAUSES RETARDED LONGITUDINAL BONE GROWTH DUE TO IMPAIRED ENDOCHONDRAL OSSIFICATION**

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Long bone abnormality (*lbab/lbab*) is a spontaneous mutant mouse characterized by dwarfism with shorter long bones. The dwarf phenotype of *lbab/lbab* mice was reported to be associated with a missense mutation in the *Nppc* gene, which encodes C-type natriuretic peptide (CNP), but it has not been confirmed whether this mutation is responsible for the dwarf phenotype. In the present study, to verify that the mutation in the *Nppc* gene is responsible for the dwarfism of *lbab/lbab* mice, we first investigated the effect of the targeted expression of CNP in retarded bone growth of *lbab/lbab* mice. By transgenic rescue with the chondrocyte-specific expression of CNP, the dwarf phenotype in *lbab/lbab* mice was completely compensated. Next, we revealed that CNP derived from the *lbab* allele retained only slight activity to induce cGMP production through its receptor (NPRB). Histological analysis of tibial growth plate showed that *lbab/lbab* mice had markedly reduced zone of hypertrophic chondrocytes. These histological features are almost identical to those of CNP-deficient mice. Our results demonstrate that *lbab/lbab* mice have a hypomorphic mutation in the *Nppc* gene that is responsible for retarded longitudinal bone growth caused by impaired endochondral ossification, and *lbab/lbab* mice would be a useful model for the study of human skeletal dysplasias associated with abnormalities in CNP or NPRB function.

P66**APOPTIC DEATH OF HAPLOID MALE GERM CELLS IN *PCD*^{3J} MUTANT MICE**

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The Purkinje cell degeneration (*pcd*) mutant mouse is a famous model regarding to late onset neuronal degeneration with autosomal recessive inheritance. *Pcd* mutant homozygous males also exhibit abnormal sperm development. The major testicular phenotype includes production of misshaped sperm with poor motility. However, the detailed analysis on the testicular abnormality of *pcd* mutant mice has not been reported. We analyzed the structural differences of testes between wild-type and *pcd* mutant mice through hematoxylin/eosin (H&E) staining, TUNEL assays and evaluation of sperm development in a temporal fashion. Epididimal sperm counting and histological analysis of testes showed that the number of sperm in mutants was significantly reduced (~1000 fold less) and, 95% of sperm were characterized by misshaped tails or incomplete head formation. The microscopic examination of the testes of day 12, 15, 18 and adult mice showed that the differences between wild-types and mutants were distinguishable from Day 18. RT-PCR analysis performed with stage specific markers indicated that transcript levels specific to haploid germ cells were decreased. From the TUNEL assay, apoptotic cells were identified from various stages of germ cells from Day 15. Our results suggest that the *pcd* mutant mice have defects in the early stage of spermatogenesis. The abnormal shapes of a small number of presenting sperm itself also indicates that the *pcd* mutant has defects in the late stage sperm morphogenesis, indicating that *pcd* mutant mice can serve as an interesting model to study the mechanisms for sperm development in addition to a model for neuronal degeneration.

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VISUALIZATION OF MITOCHONDRIAL MORPHOLOGY USING MTGFP-TG MICE

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Mitochondria play several important roles in cellular functions; e.g. energy plant, a center of signal transduction cascades, etc., and therefore they cause serious diseases if abnormality arises in their functions. It is believed that mitochondrial functions in cells are directly and closely related to their morphology. However, little has been known about it. Several antibodies against mitochondrial components or mitochondria-specific fluorescent dyes have been widely used to analyze mitochondrial morphology, but these antibodies and dyes have serious drawbacks; limiting use of the antibodies for fixed samples, or quenching of fluorescence by diffusion, photobleaching, etc. To overcome these drawbacks, we have generated a new transgenic mouse strain (mtGFP-Tg mice), the mitochondrial matrix of which is exclusively labeled by EGFP. The mtGFP-Tg mice enable us to observe easily and directly mitochondrial morphology in any tissues of interest under confocal microscope. As a result, extensive difference of mitochondrial morphology was observed among the tissues or organs although the bean-shaped forms of mitochondria have been observed by electron microscopy. Recently, many model mice for human disease have been established. Therefore, it will be possible to examine the morphological changes of mitochondria under the condition of disease *in vivo* using the hybrids of mtGFP-Tg mice and the model mice for human disease.

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MOUSE MODELS OF OTITIS MEDIA

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Two novel MRC-Harwell ENU mutants are the first good animal models of chronic otitis media (OM). *Junbo* carries a mutation in the transcription factor Evi1, while *Jeff* carries a mutation in the Fbxo11 gene. Both genes lie in the TGF- β signalling pathway and may act via its key intracellular signalling molecule, phosphorylated Smad3. Evi1 is a co-repressor of phosphorylated Smad3, while Fbxo11 is a specificity factor for SCF E3 ubiquitin ligase that targets cargoes for proteasomal degradation. One Fbxo11 cargo is Spectrin-b2 a shuttle for phosphorylated Smad3 from the TGF- β receptor to the nucleus. Our hypothesis is that both mutations have a common OM pathway via perturbed TGF- β signalling.

We investigated features of the middle ear environment that may interact with TGF- β signalling and account for an inflammatory condition that is restricted to the middle ear. In particular we have shown that the middle ear of *Junbo* is hypoxic. The interplay between TGF- β signalling and the HIF-1 α pathway governing responses to hypoxia is under investigation in macrophages and neutrophil leukocytes that characterise the cellular exudates in the middle ear. The second gene-environment interaction under study is the role of microbial agents. The middle ear and upper respiratory tract are ordinarily colonised by bacterial commensals. The delayed onset of OM when low health status mice were rederived into SPF conditions indicated a role for nasopharyngeal commensals in OM. Rederivation of *Junbo* into germ free conditions OM now indicates commensal bacteria are not required for OM initiation, but may influence its progression.

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THE POSITIONAL CLONING OF MITOCHONDRIAL NICOTINAMIDE NUCLEOTIDE TRANSHYDROGENASE NNT AS THE BASIS OF INSULIN INSUFFICIENT GLUCOSE INTOLERANCE IN THE C57BL/6J MOUSE HIGHLIGHTS ITS CENTRAL ROLE IN VERTEBRATE HEALTH AND DISEASE

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I first implicated the Nnt gene in type 2 diabetes and by extension metabolic syndrome through genetic mapping and positional cloning of the C57BL/6J mouse gene defect in a diabetes QTL mapping and functional genomics study (Toye et al., 2005) [1]. This provided the first evidence of the hitherto elusive role of Nnt in vertebrate disease [1] thus extending pioneering work over 6 decades in the discovery, and biochemical and biophysical characterisation of Nnt by Kaplan-NO, Rydstrom-J., Mitchell-P, Hatefi-Y, Jackson-BJ, and others [2,3]. I advanced a major extension of knowledge and hypotheses on the fundamental mechanism of Nnt action specifically in diabetes and more widely in health and disease offering a paradigm shift in core understanding of vertebrate cell biology - This is now substantiated by further experimental research [2,3]. Nnt is a central hub in mitochondrial metabolism with broad ranging effects on vital organismal function in health and disease.

I present a synthesis of existing knowledge, new insights on the role of Nnt in health and disease, reagents for further studies, and a roadmap for future work.

References

1. Toye A.A., Lippiat J.D., Proks P., et al. (2005). *Diabetologia*, 48:675-86.
2. Toye A.A. (2008). Proceedings of the 3rd International Mitochondria Minisymposium: Mitochondria and their proteomics. Natcher Conference Center (Building 45), NIH, Bethesda, Maryland, USA. January 9–11, 2008. Page 121.
3. Toye A.A. (2008). Proceedings of the BARI International Symposium on Mitochondrial Physiology and Pathology. University of Bari, Bari, Italy. 22 -26 June 2008.

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IDENTIFICATION OF NEW TARGETS PLAYING A ROLE IN METABOLIC DISEASES BY SYSTEMIC ANALYSIS IN THE GERMAN MOUSE CLINIC

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We have established the German Mouse Clinic (GMC) for systemic phenotyping of mutant mouse lines to model genetic human diseases. Up to now, more than 85 mutant lines have been analyzed in the primary screen of the GMC (320 key parameters in 14 different disease areas), and in 95 % of the lines new or additional phenotypes have been identified. With a special focus on phenotypes related to dysfunctional body mass regulation, the energy metabolism screen successfully identified 7 mutant lines with increased body mass and almost 30 underweight mouse mutant lines. A broad phenotypic characterization of the over- and underweight mutants could help to establish new animal models for disturbed energy homeostasis regulation and to elucidate novel pathways involved in the pathogenesis of metabolic diseases such as the metabolic syndrome and diabetes. We are currently including genotype-environment-interactions in the analysis of mutant lines and will switch from a constant to a variable environment by establishing “environmental platforms” with different standardized challenge experiments. Within the genome-wide screen for abnormalities in plasma glucose concentrations, 9 diabetic mutant lines were established in the Munich ENU-Mouse Mutagenesis Screen (e.g. Herbach et al., 2007), that will undergo further characterization the GMC. The Mouse Clinic concept enables us to study the pleiotropic effects of gene-environment-interactions and the systemic features of complex diseases like diabetes.

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

Brown, Chambon, Hrabé de Angelis and the Eumorphia Consortium; (2005) *Nat Genet*. 37(11), 1155.

Herbach et al., 2007 *Diabetes*

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THE SANGER INSTITUTE MOUSE GENETICS PROGRAMME – AN OVERVIEW

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Using current technology we cannot easily predict the function of genes by sequence alone; each gene needs to be examined in the context of a whole living organism. The Mouse Genetics Programme aims to make a significant contribution to 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 mouse ES cells produced at the Sanger Institute by selecting 250 each year to generate new mouse mutants. Mutants will be subjected to a standardized battery of phenotyping tests.

We are one of four primary phenotyping clinics in the EC-funded EUMODIC programme, each year studying a wide range of phenotypic measures in 40 new mutant lines. The remaining ~210 lines per year will be phenotyped using core funding. The philosophy of this core-funded phenotyping is to include only tests where we have a collaborator who is willing to take on mutants with the feature of interest for further definitive study, and to reduce the number of mice to the minimum required to allow detection of a robust phenotype. We also aim to include as many challenges as possible to maximize our chances of detecting phenotypes. We are soliciting suggestions from the academic community for screens to include in this battery of tests.

Phenotyping data, expression data and mice are freely available to the scientific community. Visit the Sanger Mouse Resource Portal (<http://www.sanger.ac.uk/cgi-bin/modelorgs/mgc/index.cgi>) for details.

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THE SANGER INSTITUTE MOUSE GENETICS PROGRAMME – PROGRESS AND RESULTS

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At the Wellcome Trust Sanger Institute we run a series of phenotyping pipelines that encompass an array of primary screens designed to pull out abnormalities in various disease relevant readouts as a consequence of gene deletion. The screens employed include a range of tests and assays for the measurement of parameters relevant for many key disease areas including cardiovascular disease, diabetes and obesity, immune disorders, hearing and vision disorders, kidney and renal dysfunction, pain and motor function, fertility and DNA instability. The data resulting from the primary screens will further the understanding of the interplay of genes in disease and will provide an insight into various underlying biological pathways. We are planning to phenotype 250 mutant lines per year. Phenotyping data, expression data and mice are freely available to the scientific community. Visit the Sanger Mouse Resource Portal (<http://www.sanger.ac.uk/cgi-bin/modelorgs/mgc/index.cgi>) for details.

We will present an overview of the phenotyping results collected to date within the programme. A more detailed description of data collected from a sub-set of mutant lines will also be given.

P74**HIGH THROUGHPUT GENE EXPRESSION ANALYSIS IN MICE**

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Mouse and human genes are highly conserved and appear to serve similar functions to the extent that changes in the equivalent gene in the two species often lead to similar disease manifestations. Therefore we can use the mouse as a model for human diseases. One key element is identifying the expression pattern of genes during development and in adults.

The use of a bacterial reporter gene encoding β -Galactosidase (β -Gal), expressed under the control of the endogenous promoter of the target gene makes rapid expression profiling of multiple tissues at various developmental stages in the mouse possible. Expression of β -Gal is revealed by a simple and stable reaction in the presence of X-Gal. This X-Gal-based expression screen has been adapted to the adult mouse. The entire animal is screened for the presence of β -Gal at high resolution, without the need for generating serial sections.

This expression screen will be performed on all targeted knockout lines of mice generated by the WTSI Mouse Genetics Programme. For each mutant line, 6 week old heterozygous mice and litters from defined developmental stages are stained. Data will be presented to demonstrate the power of this approach.

Expression data is complemented by histological analysis performed on adult homozygous null mice. A defined set of tissues is collected from each line to study morphology by H&E staining, and cellular expression by immunohistochemistry for β -Gal. All the images are available on the WWW via the Sanger Mouse Resources Portal (<http://www.sanger.ac.uk/cgi-bin/modelorgs/mgc/index.cgi>).

P75**STATISTICAL AND EXPERIMENTAL DESIGN CHALLENGES IN HIGH THROUGHPUT PHENOTYPING OF MUTANT MICE**

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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. This high throughput study of numerous phenotypic characteristics across many mutant lines produces large quantities of data and raises issues regarding data interpretation. We will present the approaches that we have adopted to optimise data analysis encompassing confidence testing, effect size and power analysis.

Typically, confidence tests are used to detect significant changes between groups of wildtype and mutant animals. However, each time a significance test is used, a false positive can occur, and these accumulate over a large number of tests which is called the multiple testing problem. We have compared methods to address this multiple testing problem. Specifically we have assessed the affect on the number of changes identified as statistically significant and the associated false positive rate. Once changes are identified as statistically significant, the measure of effect size can be used to indicate if the change is biologically relevant. Finally, power analysis can be used to optimise the experiment, ensuring that there is sufficient power to detect phenotypic changes. Focusing on these issues will allow robust conclusions to be drawn from the data and will facilitate optimisation of future studies.

P76

A SPONTANEOUS MUTATION (*DHE*) IN THE MOUSE *LMNA* GENE RESULTS IN HYPOPLASTIC CRANIAL SUTURES AND UNDER-MINERALIZATION OF THE SKELETON

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The *Lmna* gene encodes the nuclear lamins A and C, which, along with lamin B, constitute the proteinaceous nuclear envelope. *Lmna* mutations are associated with connective tissue disorders, including cardiomyopathies, muscular dystrophies, lipodystrophies, progeria and bone abnormalities. We discovered a new mutation in mouse *Lmna* that demonstrates a critical role for *Lmna* in cranial suture development and skeletal mineralization. *Dhe*, (*D*ominant *h*air and *e*ars) is a semi-dominant mutation in exon 1 of *Lmna* (L52R). *Dhe*/+ mice exhibit a sparse coat, small ear pinnae, hypoplastic cranial sutures, and under-mineralization of the skeleton. To assess suture formation we used X-ray, histological, and in situ analyses. Skeletal mineralization was measured by DEXA and X-ray. DEXA showed that areal BMD is lower in *Dhe*/+ than in controls (*Dhe*/+ 0.037; +/+ 0.045 g/cm²). Under-mineralization can be seen in radiographs of axial and appendicular skeleton. In X-rays of *Dhe*/+ skulls, the premaxillary/maxillary and cranial vault sutures, and the entire parietal bone, are clearly visible and radiolucent, indicating severe hypomineralization. Microscopic examination revealed severely hypomorphic sutures in *Dhe*/+ skulls. The bony plates fail to overlap, the cells and connective tissue connecting the bones are loosely organized and hypoplastic, and suture material is poorly attached. Thus, *Lmna* is critical to normal cranial bone and suture formation and to skeletal mineralization.

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A COMPREHENSIVE APPROACH TO ELUCIDATE NOVEL MOLECULAR MECHANISMS IMPLICATED IN DIABETES PATHOGENESIS IN MOUSE MUTANTS

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Diabetes is among the most frequent chronic metabolic diseases. To develop effective strategies for diabetes prevention and treatment, novel approaches for the elucidation of disease-relevant molecular pathomechanisms are required.

To explore diabetes etiology it will be crucial to study intricate biological systems - as these consider multiple interactions of genes, pathways, and tissues - throughout disease progression. Thus, in mouse models associations of genes or single point mutations (e.g. transgene/knockout mice, mutants from Munich ENU mutagenesis program) [1-3] with clinical phenotypes will allow for systemic correlations and determination of co-susceptibilities between diabetes and other diseases. To achieve this goal mutant mice will be subjected to comprehensive, standardised phenotyping in the German Mouse Clinic (GMC) covering 14 diseases areas [4-6] combined with specialised diabetes screens, such as glucose clamps for localisation of primary, organ-specific defects (e.g. pancreatic β -cell dysfunction, blunted insulin action in insulin target tissues). Pleiotropic interactions between a genetic disposition and the environmental context (e.g. nutritive, stress, exercise challenges) modulating the onset and progression of diabetes will be assessed in the recently established GMC II. Acquired, multidimensional informations in context with alterations in spatio-temporal and quantitative metabolomic patterns, assessed at the Genome Analysis Center (GAC), will be used to identify novel pathways implicated in the progression from a healthy to a diseased state. Based on the complexity of genetic and environmental interactions that determine diabetes susceptibility, onset, and severity our approach will further advance the understanding of underlying biomolecular pathomechanisms thus, contributing to more effective diagnostic, preventive and personalized therapeutic strategies.

References

- 1 Hrabé de Angelis and Balling; 1998, Mutat Res
- 2 Hrabé de Angelis et al., 2000, Nat Genet
- 3 Apelqvist et al., 1999, Nature
- 4 Gailus-Durner, Fuchs et al., 2005, Nat Meth
- 5 Barco Barrantes et al., 2006, Mol Cell Biol
- 6 "Standards of Mouse Model Phenotyping", M. Hrabé de Angelis, Ed.

P78

MUTATIONS IN JXC1/SOBP - ENCODING A NUCLEAR FCS TYPE ZINC FINGER PROTEIN - CAUSE ORGAN OF CORTI PATTERNING DEFECTS IN THE JACKSON CIRCLER (JC) MOUSE

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The mouse cochlea emerges from the ventral pole of the otocyst to form a one and three-quarter coil. Little is known about the factors that control the growth of the cochlea. Jackson circler (*jc*) is a recessive mutation causing deafness due to a growth arrest of the cochlea duct at day 13.5 of embryonic development. Here we identify a novel gene (*Jxc1*) in the *jc* locus. *Jxc1* encodes a nuclear protein that has two FCS-type zinc finger domains (PS51024), bears nuclear localization signals and highly conserved sequence motifs. Transiently expressed wildtype protein localized to the nucleus but mutant isoforms were mislocalized in the cytoplasm. In *jc* mutants, the cellular patterning of the organ of Corti is severely disrupted exhibiting supernumerary hair cells at the apex, showing mirror-image duplications of tunnel of Corti and inner hair cells, and expressing ectopic vestibular-like hair cells within Kölliker's organ. *Jxc1* mRNA was detected in inner ear sensory hair cells, supporting cells, and the acoustic ganglia. Expression was also found in the developing retina, olfactory epithelium, trigeminal ganglion and hair follicles. Collectively, our data support a role for *Jxc1* in controlling a critical step in cochlear growth, cell fate, and patterning of the organ of Corti.

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POSITIONAL CLONING OF THE WAVED WITH OPEN EYE LIDS 2 (WOE2) LOCUS

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Waved with open eyelids 2 (*woe2*) is an autosomal recessive mouse mutation that arose spontaneously on the C57BL/6J X 129 F1 background. Phenotypically, *woe2* mice exhibit open eyelids at birth, a wavy coat, microphthalmia/anophthalmia, heart defects and corneal opacities. Histological analysis of *woe2* eyes showed corneal neovascularization, anterior synechiae, cataracts, retinal rosettes, and optic nerve hypoplasia. Mapping of the *woe2* locus was conducted by backcrossing homozygote *woe2* mice to the C3A.BLiA-*Pde6b*⁺/J strain. The *woe2* locus was mapped using microsatellite markers to the 6.8 cM critical region between *D7Mit340* and *D7Mit1*. The evaluation of the *woe2* critical region identified Protein Phosphatase 1, Regulatory (inhibitor) Subunit 13 Like (*Ppp1r13l*) as a candidate gene. *Ppp1r13l* is composed of 13 exons resulting in 2475 bp long cDNA. Sequence analysis of the *woe2* genomic DNA identified a 1308 bp deletion encompassing *Ppp1r13l* exons 9, 10, and 11. cDNA analysis from *woe2* mice showed that deletion results in an alternatively spliced *Ppp1r13l* transcript lacking exons 9-11 resulting in a premature stop codon. Currently we are evaluating consequences of the *woe2* deletion for the stability of the Ppp1r13l protein. Our hypothesis is that *woe2* is a Ppp1r13l loss of function mutation. Ppp1r13l (also known as iASPP) has been implicated in inducing apoptosis by blocking NF-kappaB or inhibiting apoptosis by blocking p53. Thus suggesting Ppp1r13l likely plays an essential role in molecular mechanisms associated with cell survival, proliferation, and migration. Evaluation of the role of Ppp1r13l in the eye development is currently underway.

P80

THE REFINEMENT OF PHENOTYPING PROTOCOLS FOR HAEMATOLOGY AND PLASMA BIOCHEMISTRY: A COMPARISON OF DATA GENERATED BY PARTICIPANTS IN THE EUMODIC PROGRAMME

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The EUMODIC consortium is committed to the phenotypic assessment of ~650 mouse knockout lines developed on standardised backgrounds in the EUCOMM project. EUMODIC has refined a comprehensive database of standardised phenotyping protocols, called EMPReSSslim, to enable comprehensive high throughput primary phenotyping of these knockout lines. Additional tests will be performed on lines with interesting phenotypes identified by primary screening. Terminal blood samples are collected at the end of both the primary screening pipelines allowing for various blood based tests. Haematology tests include a full blood count and differential WBC count while the plasma biochemistry involves a 22 test profile incorporating liver, kidney, bone and lipid parameters. The standardisation of protocols between participating phenotyping centres has been a major challenge for the programme. Diet, age, gender, strain, sample collection and processing protocols as well as the diagnostic equipment and exact reagents used are all variables that potentially affect results. Here we present a pilot comparison of baseline data for selected parameters generated from inbred strains at the MRC Harwell and the Wellcome Trust Sanger Institute. Both centres subscribe to the same external quality assurance scheme (UK NEQAS). Despite minor differences in value means, the data generated from selected inbred strains indicate comparable ranking of parameters between the institutes. The elimination of experimental variables is an ongoing effort with the regular review of data serving as indicators of the progress of harmonisation. These refined protocols are important for future multi-centre phenotyping of mouse models of disease and for therapeutic studies.

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INTESTINAL CANCER GENE DISCOVERY USING SLEEPING BEAUTY-INDUCED MUTAGENESIS IN APC^{+/+} AND APC^{MIN/+} MICE

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Colorectal cancer involves the somatic acquisition of a suite of gene mutations and other genomic alterations that develops through a characteristic pathway from benign adenoma to metastatic adenocarcinoma. However, the full constellation of genetic changes and how they interact in specific stages of cancer development remain to be elucidated. To address this need we have developed an unbiased *Sleeping Beauty* (SB)-based screen for the discovery of somatic mutations that cause intestinal cancer in wildtype mice or modify malignancy after initiation by specific gene mutations such as in the *Apc* gene. Our tripartite system consists of: 1) an SB transposase allele containing a floxed-stop (Isl) cassette "knocked-in" to the *Rosa26* locus (RSB11); 2) a *villin*-Cre transgene; and 3) a mutagenic SB transposon, T2/Onc. Using this triple transgenic system in *Apc*^{+/+} mice we observed tumorigenesis in the great majority of mice and we identified more than 18,000 transposon insertion sites and 109 candidate genes/loci at common insertions sites (CIS) that were found to altered by insertion at a frequency higher than expected by chance. In parallel we introgressed the three transgenes into the *Apc*^{Min/+} strain of mice to discover genes that modify the tumor phenotype in a susceptible genetic background. We found that SB-mutagenesis caused a significant increase in Min tumorigenesis and we identified more than 13,000 transposon insertions and 21 candidate genes/loci that were found at CIS. These 21 genes include several that overlap with the *Apc*^{+/+} dataset but most of these CIS were unique to the *Apc*^{Min/+} strain background.

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DEVELOPMENT OF CARDIOVASCULAR DEFECTS IN THE MURINE TS65DN DOWN SYNDROME MODEL

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The Ts65Dn mouse model for Down syndrome inherits a triplication of the distal region of Mus musculus chromosome 16 (MMU 16) with more than half the orthologs of human trisomy 21. We have focused on the developmental disruptions that result in perinatal lethality and cardiovascular defects in Ts65Dn mice. Defects in the segmental trisomic mice include muscularized valves, septal defects, and aortic arch anomalies that may be due to abnormalities in endocardial cushion formation or differentiation and altered bloodflow during development. Formation of the branchial arch arteries is delayed in trisomic embryos at embryonic day 10.5 compared to littermates, suggesting a mechanism by which the great thoracic arteries may be affected. As septation of the heart chambers occurs, altered levels of apoptosis are detectable in the endocardial cushions of trisomic vs. euploid embryos. We are analyzing the spatial and temporal localization of candidate genes to identify pathways critical to cardiogenesis that are disrupted by trisomy. MMU 16 candidate genes include DSCR1 (RCAN1) and DYRK1A that both act synergistically to regulate NFATc1 function known to be critical in proper endocardial cushion development.

P83

SPONTANEOUS, MUTAGEN-INDUCED AND GENETICALLY-ENGINEERED MOUSE MODELS OF HUMAN DISEASE IN THE GENETIC RESOURCE SCIENCE GROUP AT THE JACKSON LABORATORY

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Mouse models of human genetic illness are powerful tools for exploring gene function, characterizing deviant phenotypes, assessing disease progression and exploring therapeutic strategies in an ethically acceptable context. Such disease models may arise as spontaneous mutations, be captured among diverse groups of inbred strains, be induced as the result of mutagenesis, or be developed through genetic engineering.

Individual research interests and resource development efforts within the Genetic Resource Science (GRS) group at The Jackson Laboratory (JAX) are involved in each of these areas. The JAX Mouse Mutant Resource (MMR) has a long and fruitful history in identifying, collecting, characterizing, mapping and distributing valuable mouse models of human disease that may arise spontaneously within JAX production colonies. Additionally, individual research interests are providing molecular and phenotypic insights into both genetically diverse inbred strains, as well as mutant strains that have arisen through JAX mutagenesis programs. Finally, recent initiatives are being directed at the development of specific disease models through genetic engineering approaches.

Here, we will summarize recent additions to the group-wide MMR collection of spontaneously-arising mouse models, and provide specific examples of focused research efforts directed at exploring such diverse areas as the roles of NADPH oxidases in vestibular dysfunction and Sox genes in skeletal development; as well as mouse models of human chronic granulomatous disease and facio-cutaneo-skeletal (Costello) syndrome.

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SUPPRESSION OF INTESTINAL ADENOMAS BY A NOVEL GENETIC MODIFIER IN THE *APC^{MIN}* MOUSE MODEL

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Familial adenomatous polyposis (FAP) is an autosomal dominant disorder marked by hundreds to thousands of benign adenomas in the colon, which if left untreated, may progress to malignancy. The mutant adenomatous polyposis coli (*Apc^{Min}*) mouse is an effective model to study biological mechanisms which, when altered, lead to the initiation, growth, and progression of intestinal and colorectal tumors. Genetic background greatly influences adenoma number, size, and location in *Apc^{Min}* mice. Modifier genes have been shown to alter these phenotypes. Our laboratories showed that the *Pla2g2a* and *Atp5a1* genes are responsible for the protective *Modifier of Min 1* (*Mom1*) and *Mom2* phenotypes, respectively. Hybrid progeny from C3H/HeJ (C3H) females crossed to C57BL/6J (B6) *Apc^{Min/+}* males showed an ~80% decrease in adenoma number compared to B6 *Apc^{Min/+}* mice. A related cross involving *Mus castaneus* (CAST) mice showed a similar decrease in adenoma number. These findings indicate the presence of additional potent resistant modifier loci (distinct from *Mom1* and *Mom2*) in the C3H and CAST genomes. We have conducted several crosses to limit the boundaries of a new modifier locus (called *Mom4*). We describe the genetic strategies being used to identify the gene(s) responsible for these protective effects, which will lead to a better understanding of the molecular and biochemical pathways involved in intestinal homeostasis and disease. Discovery of modifier genes will affect the prevention, diagnosis, and treatment of human colorectal cancer. Research supported by NCI grants to LDS and AMB, and by a Professor Fredric Reiders Ph.D. Scholarship to SCN.

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MAPPING OF THE *LENS OPACITY 13 (LOP13)* LOCUS IN MICE

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Lens opacity 13 (*lop13*) is a novel congenital autosomal recessive cataract locus that arose spontaneously in the 129/sv-ter strain. The *lop13* mice exhibit nuclear cataracts and compromised wound healing of skin fissures surrounding the eyes and the neck. A primary goal of this study is to identify the gene harboring the mutation responsible for the *lop13* phenotype and to establish mouse/human homology of the *lop13* locus. In addition, work is being done to establish which molecular processes are compromised in the *lop13* lens. The *lop13* mice were backcrossed to wild type C3H/HeJ mice and 144 F2 progeny were generated. Genomic DNA was isolated from collected spleens and polymorphic microsatellite markers throughout the mouse genome were sequenced. The linkage map established the *lop13* critical region as being between the genes *Serhl* and *Csdc2* on mouse chromosome 15. Evaluation of the *lop13* critical region identified 21 genes within the 1.1 Mb critical region. A single C→T base pair substitution was identified in nucleotide 3112 of Sterol Regulatory Element Binding Protein 2 (*Srebp-2*). This mutation results in the substitution of an evolutionarily conserved arginine to cysteine at amino acid 1038. *Srebp-2* plays an essential role in activating the transcription of several genes involved in cholesterol biosynthesis. Studies are currently in progress to evaluate the role of *Srebp-2*^{Arg1038Cys} in the *lop13* phenotype. Elucidation of the compromised molecular processes will provide insight into the role of *Srebp-2* and cholesterol in lens development, maintenance of lens transparency and wound healing.

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INDUCEMENT OF *PLASMODIUM BERGHEI* ANKA STRAIN RESISTANCE TO PIPERAQUINE, LUMEFANTRINE, AND AMODIAQUINE IN A MOUSE MODELKiboi DANIEL¹, Nganga JOSEPH¹, Nzila G², BELL ANGUS¹

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Artemisinin based combination therapies are the next strategy against fast emerging drug resistant *Plasmodium falciparum*. However, selection pressure exerted by long-half life antimalarial drugs Piperaquine (PQ), lumefantrine (LM) and amodiaquine (AQ) remains a challenge especially in high transmission areas. Using rodent malaria model current study forecasts emergence of PQ, LM and AQ resistance and provides resistant lines to explore mechanism of resistance underlying these drugs. *Plasmodium berghei* ANKA strains resistant to PQ, LM and AQ were selected in mice by exposing the strain to drug selection pressure. Effective doses at 99% (ED₉₉) of PQ, LM and AQ against the parent line were 8.10, 4.48 and 5.05 mg/kg.day respectively. By exposing this parent line to increasing concentration PQ, a strain with an index of resistance (I₉₉) [ED₉₉ of PQR line/ ED₉₉ of parent line] of 25.93 was selected after 28 passages. Experience with the use of LM led to the selection of a resistant strain attaining an I₉₉ of 6.48 in 28 passages. An I₉₉ of 4.10 in AQ resistance was recorded within 36 passages. The I₉₉ of the PQ resistance phenotype remained almost unchanged, 20.85 after growing the parasite in absence of drug for 5 passages a clear indication of the stability of the resistant phenotype. The study reports for the first time selection of stable *P. berghei* lines resistant to PQ. PQ resistance could emerge rapidly than resistance to AQ and LM reducing therapeutic life of PQ. PQ resistance needs to be monitored closely to guard against its complete loss to resistance.

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INFRAFRONTIER – THE EUROPEAN INFRASTRUCTURE FOR PHENOTYPING AND ARCHIVING OF MODEL MAMMALIAN GENOMES

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Mouse models are essential tools for the functional analysis of the mammalian genome and the molecular basis of human diseases. The European research community and international collaborative efforts such as the International Mouse Knockout Consortium (IMKC) will produce a large number of mouse disease models over the next years. The bottleneck for the exploitation of this valuable resource will be access to systematic functional and molecular characterisation. In addition, mouse models should be made available to the entire European mouse genetics, biomedical and translational research community which strongly depends on access to novel mouse disease models. The current resources to achieve this goal are limited. Existing facilities across Europe can only offer capacity for the systemic phenotype analysis, archiving and dissemination of a few hundred disease models per year.

To solve this problem, the Infrafrontier project will organise and establish an efficient distributed infrastructure for the systemic phenotyping, archiving and distribution of mouse models on a well-concerted, large-scale and pan-European level. Infrafrontier will organise two complementary and linked European infrastructure networks: Phenomefrontier for large scale and comprehensive phenotyping in a cross-laboratory effort (European mouse clinics); Archivefrontier for archiving and distribution of mouse mutant lines (organised by EMMA, the European Mouse Mutant Archive). Taken together, Infrafrontier will bring the systemic phenotyping, archiving, and dissemination of mouse disease models to the next level and will contribute to maintaining Europe's leading role in the functional annotation of the mouse genome. Infrafrontier has been included in the roadmap of the European Strategy Forum for Research Infrastructures (ESFRI) and receives preparatory phase funding by the European Commission.

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THE COLLABORATIVE CROSS AT ORNL

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The Collaborative Cross is an international effort to develop a large panel of recombinant inbred strains from eight widely divergent progenitor lines. Production and characterization of the Collaborative Cross continues at the Oak Ridge National Laboratory, where several hundred lines have been initiated in two phases. The first and second sets of incipient CC lines have reached 13 and 6 generations of inbreeding, respectively. The breeding history of each line is documented, and DNA samples from all retired breeders have been collected and stored. In a minor modification to the breeding protocol, additional breeding pairs are being maintained at later generations to improve retention of lines. Genotyping efforts are underway, in parallel with collaborative phenotyping efforts that span reproductive, metabolic, morphological and behavioural domains over several generations. Estimates of heritability for these traits collected across generations support the developing power of the CC for mapping causative genetic variation. Interim CC generations are also being used to dissect gene-environment interactions that underlie susceptibility to the effects of ionizing radiation and to social stress. Mice from the breeding population are available on a collaborative basis for further characterization.

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IDENTIFICATION OF GENES REGULATED FROM THE DISTAL INTERVAL OF MOUSE CHROMOSOME 16 SYNTENIC TO HUMAN CHROMOSOME 21

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The phenotypic abnormalities observed in Down syndrome are caused by dysregulated expression of genes located either on Chromosome 21 or elsewhere in the genome, but regulated from Chromosome 21. To identify the genes regulated by mouse orthologs of human Chromosome 21 genes, we constructed a subconsomic strain C57BL/6J-Chr16d^{PWD} and compared its brain transcriptome profile with the parental C57BL/6J strain. The two mouse strains are genetically identical with the exception of the telomeric 23 megabases on Chromosome 16 that was introgressed from the PWD/Ph inbred strain of *Mus m. musculus* subspecies. Any reproducible phenotypic difference between both strains, including the mRNA levels of brain expressed genes, are encoded in this 23 Mb interval, syntenic with Human Chromosome 21. The results of brain transcriptome analysis using Affymetrix GeneChips Mouse Gene 1.0 ST will be discussed.

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GLOBAL TRANSCRIPTOMES OF ADULT AND EMBRYONIC TISSUES IN MICE WITH 30 MB SEGMENTAL TRISOMY OF CHROMOSOME 17

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The phenotypes associated with Down syndrome (DS) include those seen also in unrelated aneuploidies, such as lower viability, growth and mental retardation, cardiovascular or craniofacial abnormalities, as well as more specific clinical features. After decades of studies, it is still unclear how an extra copy of a non-mutated chromosome 21 causes these anomalies. Recent whole-genome transcriptome studies revealed gene-dosage effect for most of the triplicate genes in DS cerebellum or in tissues of the mouse DS models.

Here we analyzed the expression profiles of mice with segmental trisomy Ts43H/Ph¹, which carries a proximal part of chromosome 17 (MMU17) in three copies (approximately 30.1 Mb, >300 genes). We compared the global transcriptomes of liver and brain in adult male mice and the head part in 14.5-day embryos using the Affymetrix GC Mouse 430 2.0 arrays. The expression levels of most genes in brains, livers and embryos were increased ~1.5 fold in the trisomic region when compared to the diploid mouse controls. Nine pair-wise trisomic/euploid and 3 trisomic/trisomic comparisons of expression data will be reported and the results compared to the unrelated trisomic mouse models, Ts65Dn and Ts1Cje.

¹ Vacik T., Ort, T., Gregorova S., Strnad P., Blatny R., Conte N., Bradley A., Bures J., Forejt, J.: PNAS, 102 (2005): 4500-4505

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