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MEETING REPORT

Mouse genetics 2011: meeting report

John K. Simmons · Jessica C. Amlin-Van Schaick · Thomas R. Geiger · Karlyne Reilly · Kent Hunter · Beverly A. Mock

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Introduction

Mouse Genetics 2011 was organized by the Genetics Society of America in Washington, DC, as a joint meeting of the 25th International Mammalian Genome Conference and the 10th Complex Traits Community Meeting.[1]

While celebrating the incredible progress made by the field in the last 25 years, this year's joint meeting illuminated the incredible possibility for the future. As genome-level studies have revolutionized the pace for discovering the genetic underpinnings of human disease, an unprecedented opportunity exists for integrating those findings with model organism genetics to achieve the common goals of both understanding and improving human disease. The keynote address, Verne Chapman Lecture, plenary presentations, and numerous platform talks all described work highlighting advances where the interface of mouse models and human genetics has led to an extraordinary understanding of the mechanisms of a disease or propelled a discovery into clinical development.

J. K. Simmons · T. R. Geiger · K. Hunter · B. A. Mock
Laboratory of Cancer Biology and Genetics, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

J. C. Amlin-Van Schaick · K. Reilly
Mammalian Genetics Cancer Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Frederick, MD, USA

B. A. Mock (✉)
Laboratory of Cancer Biology and Genetics, Bldg. 37, Rm. 3146, 37 Convent Drive, MSC 4258, Bethesda, MD 20892-4258, USA
e-mail: bev@helix.nih.gov

Overarching themes: highlights from the keynote address and Verne Chapman Lecture

Francis Collins, director of the US National Institutes of Health, delivered the keynote address entitled "Mickey, Mendel, and the Medical Magic of Mouse Genetics." In his talk, Collins provided a brief overview of the current large NIH-sponsored efforts related to mouse models for understanding human disease and biology, including the $47.2 million Knockout Mouse Project (KOMP, komp.org), which had to date already generated 8,199 knockout embryonic stem (ES) cells; the newly announced $110 million phenotyping project designed to generate comprehensive phenotypic data on knockout mice generated in KOMP (called KOMP^2); and the expansion of the Encyclopedia of DNA Elements (ENCODE) project to include the mouse genome using funds from the American Recovery and Reinvestment Act (ARRA). The KOMP and KOMP^2 projects join with European and Canadian efforts to make up the International Knockout Mouse Consortium. Collins then went on to discuss work from his own laboratory that is focused on three projects where mouse models are being employed to understand the genetics of human disease and develop medical interventions. In one project, a knockout mouse for *Igfbp2* had been created using a conditional-ready construct from the EUCOMM (European Conditional Mouse Mutagenesis Program) to explore the function of this gene, which had been previously identified by his lab and collaborators in a genome-

[1] There were 375 participants from approximately 19 countries. The meeting was partially sponsored by the IMGS, the GSA, NHGRI and NICHD of the NIH, The Ellison Medical Foundation, and Mouse News Letter, Ltd. The meeting program and abstracts are available online at http://www.imgs.org and http://www.mousegenetics2011.org/.

wide association study (GWAS) of type II diabetes. He also described work in his lab for identifying possible asthma susceptibility genes that has made use of the pre-Collaborative Cross Mouse strains. In his last example, Collins detailed work toward understanding the rare accelerated-aging disease Hutchinson-Gilford progeria, which has been linked to a heterozygous mutation in the *LMNA* gene. This mutation leads to a shortened protein by introducing a splice donor site. In this effort a transgenic mouse for the mutant *Lmna* gene was used to test potential drug treatments for children with this disease. Collins happily reported that farnesyl transferase inhibitors, which had been shown to be effective in his mouse model, had been brought into the clinic, and a phase II clinical trial was now into its second year with 40 children enrolled. The work presented in this keynote exemplified the usefulness of the mouse as a model of human disease not only for increasing our understanding but also for translating molecular discoveries into useful therapeutics.

William Dove of the University of Wisconsin gave the Verne Chapman Lecture. As the concluding talk of the conference, Dove provided a unique perspective on the advances made in molecular biology, enabled by model organism genetics, and detailed some of the remarkable opportunities for future work to answer previously intractable questions of biomedical research.

Beginning with a quote by the famed naturalist John Muir, "When we try to pick out anything by itself, we find it hitched to everything else in the Universe," Dove described how the recent emergence of systems biology approaches is reflective of the long-standing principle of holism in biology. Dove enumerated seven themes for moving biomedical research forward with mouse models: reductionism to holism, dissecting the genetic system, phenotyping and rephenotyping, genome-wide mutational analysis, somatic mutations meet epigenetics, and diversity drives genetics. Reflecting on work in his own lab, Dove described how one of the most widely used mouse models of cancer, the Apc^{Min} mouse, was identified by careful observation of offspring from the mutagenesis screen as having pale feet, which was later found to be a result of blood loss from cancerous intestines. Dove also detailed on-going work in his lab, including a rat mutagenesis screen that identified a *Pirc* mutation that leads to tumors of the colon, in contrast with the small-intestine tumors seen in the Apc^{Min} mouse. Work focusing on epigenetic changes in carcinogenesis was also discussed. Advocating for the sharing of discoveries openly with the greater scientific community, Dove pointed to the 1,100 + publications from researchers around the world using the Apc^{Min} model, which has been openly distributed via The Jackson Laboratory for many years.

Unraveling disease: genetics of physiology and development

Many of the talks and posters at the meeting demonstrated how mouse models were being used to give insight into congenital human diseases such as the neurodegenerative diseases Charcot-Marie-Tooth, Parkinson's, and ALS; congenital disorders such as Rett syndrome, autism, Down syndrome, hereditary hemorrhagic telangiectasia, and ophthalmo-acromelic syndrome; and normal and aberrant immune system function, including the autoimmune disorder lupus.

Two plenary talks from human geneticists Han Brunner and David Valle provided context for how new genome and exome sequencing platforms are dramatically reshaping the identification of candidate gene polymorphisms in rare hereditary developmental and intellectual disorders. Both speakers underscored that while genomic technologies may be rapidly accelerating the identification of gene polymorphisms of these diseases, the furthering of the biological understanding for these candidate genes will be accomplished almost exclusively with mouse models.

The application of a systems biology approach to understanding the complex signaling cascades of the immune system was presented during a plenary talk by Aviv Regev. The experimental paradigm of "observe → model → perturb" was demonstrated in work aimed at understanding the gene regulatory circuitry of toll-like receptors (TLR) in primary mouse dendritic cells. Regev explained that her findings show many transcriptional regulators downstream of an individual TLR, and the activation of these regulators can vary dramatically and yield quite different transcriptional changes based upon the type of immune stimulation. In a particular example, two cell cycle genes (*Plk2* and *Plk4*) had been co-opted in the nondividing dendritic cells to modulate the overall antiviral transcriptional response.

The plenary talk by Miriam Meisler focused on the mechanism of neurodegeneration in the *pale tremor* mutant mouse, which was found to have a mutation in the *Fig4* gene. *Fig4* is involved in the PI3K pathway, and its mutation leads to spongiform degeneration in the central and peripheral nervous systems of mutant mice. The phenotype of the *Fig4* mutant mouse was similar to that of patients with Charcot-Marie-Tooth (CMT) syndrome, and sequencing of this gene in patient samples found several *Fig4* mutations. In the severely neurodegenerative CMT4F disease variant, all 16 patients sequenced had *FIG4* mutations, with 14 having mutations leading to the same I41T substitution. Neurodegenerative diseases were the focus of a number of posters as well, including α-synuclein function in Parkinson's disease (123C Cabin and 125B

Casey), loss of *Tsg101*, as a model for neurodegenerative pathology due to endo/lysosomal sorting dysfunction (216C Walker), *SOD1* knock-in mice as a model of ALS (122B Bunton-Stasyshyn), and an overview of mouse models of neurodegenerative disease (196A Sasner).

In addition to the excellent plenary talks, several short talks presented how mapping of modifiers in mice was providing new insights into rare human diseases. Strain differences in the penetrance of vascular leakage in *Tgfb1* knockout mice were exploited to identify modifier genes that could be related to the severity of hereditary hemorrhagic telangiectasia (HHT) in humans. Studies are underway using a large patient cohort to determine if SNPs in *TGFBM2*, a candidate for the vascular leakage modifier, are associated with human HHT (Akhurst). Loss of SMOC-1 was shown to lead to ophthalmo-acromelic syndrome in both mice and humans. This finding provides evidence that BMP antagonism leads to the eye and limb phenotype seen in both the human disease and the mouse model (Rainger). An ENU mutagenesis screen to uncover the molecular mechanisms of cystic kidney disease was presented. This screen has led to the discovery that downregulation of Hedgehog signaling prevents renal cystogenesis (Beier). Work on the lupus-prone (NZB × NZW)F1 model of autoimmune disease was presented, implicating estrogen receptor α (ERα) in the pathogenesis of lupus (Gould).

There were a number of platform talks and poster presentations detailing efforts to gain new insights into human neurodevelopmental diseases, including Down syndrome, Rett syndrome, and autism spectrum disorders (ASD). Two talks and a poster focused on modifier genes of the *Mecp2* mutation phenotype. *Mecp2* mutations have been shown to cause the X-linked neurological disorder Rett syndrome. An ENU mutagenesis-based approach identified suppressor genes linked to cholesterol biosynthesis and epigenetic regulation (Buchovecky and Justice; 121A Brown). Efforts to unravel the molecular basis of the heterogeneous ASD involved large exomic, miRNA, ncRNA, and candidate gene sequencing studies of 18 affected patients. The data produced from this study found tremendous genetic heterogeneity among individuals, even when compared to affected siblings. To help unravel this complexity, efforts were expanded to the mouse and rat, which identified a series of rare SNPs in mouse-human-rat conserved sequences, as well as to phenotypic studies of mouse knockouts for a large number of candidate ASD genes (Bucan). Studies of mouse genotypes sharing autistic phenotypes (115A Blake) and new modules for the autism database (AutDB) (160A Kumar) were also showcased.

Several presentations highlighted the use of the Ts65Dn transgenic mouse model to understand the molecular contributions of trisomy 21 to the Down syndrome phenotype. Cerebellar dysmorphology seen in this model demonstrated that a single exposure to small-molecule sonic hedgehog agonists at the time of birth could restore the cerebellar morphology to wild type. Furthermore, this treatment improved the performance of these mice in behavioral tests designed to assess cognitive tasks related to hippocampal function (Reeves). Work was also presented using this mouse model to uncover the molecular basis of craniofacial phenotypes seen in the mouse and patients with Down syndrome. Differences in proliferation and migration of neural crest cells were found linked to *Dyrk1a* expression (Deitz). A number of posters were also presented using mouse models of Down syndrome to investigate molecular changes and phenotypes related to trisomy 21, ranging from skeletal development to cancer risk (116B Blazek, 142A Franca, 145A Marechal, 180C Olson, 191B Reinholdt, 192C Roper, 211A Tischbein, and 223A Yang).

Reversing the immortal: genetics of cancer

This year's conference featured many excellent speakers and posters on the complex genetics underlying cancer initiation, promotion, susceptibility, diet, and treatment. Furthermore, many of these studies were able to link their findings to human cancer, exemplifying the usefulness of utilizing mouse genetics to dissect the genetic complexities contributing to human disease. The genetics of cancer initiation was highlighted in a study involving *Prdm14*, a pluripotency gene involved in the self-renewal of ES cells. Overexpression of *Prdm14* in mouse bone marrow caused the expansion of lymphoid progenitor cells in irradiated mice prior to leukemia onset. These progenitors, found through gene expression analysis, abnormally express many known oncogenes as well as microRNA suppressors. The ability of *Prdm14* to induce expansion of lymphoid progenitors highlighted its importance in the initiation of leukemia (Simko).

Identification of modifier loci responsible for susceptibility to skin tumor promotion was examined in the mouse two-stage chemical skin carcinogenesis model. The *Gsta4* gene in the *Psl1* locus was found to be associated with skin tumor susceptibility in mice, and susceptibility to skin cancer in humans was found to be associated with polymorphisms in *GSTA4*. Different skin tumor-promoting agents were found to cause a variation in tumor response in recombinant inbred strains of mice. Linkage mapping identified a susceptibility locus containing several promising candidate promotion susceptibility genes that may alter the response to different skin tumor-promoting agents. This study highlights the genetics underlying the variable responses of individuals to carcinogen exposure (Angel).

Susceptibility to breast cancer was examined in the *Mcm4*^{Chaos3} mouse model. Mutation of *Mcm4*, a gene important in controlling DNA replication, caused mammary tumors, histiocytic sarcomas, and lymphomas depending on the strain background of the mouse. A combination of mouse genetic crosses and exome resequencing was used to pinpoint *talin1* as a potential modifier gene causing these differences in tumor phenotypes. Additionally, mammary tumors were further examined and several interesting regions were identified as being commonly amplified or deleted, including a region containing the tumor suppressor *Nf1*. Furthermore, in vivo studies with different mutations in *MCM* genes revealed varying phenotypes involving growth and cancer, highlighting the importance of controlling DNA replication (Schimenti).

Another cancer susceptibility study examined the strain-specific effects on developing lymphohematopoietic disease induced by ionizing radiation. As ionizing radiation induces DNA strand-break repair, in vitro analysis of hematopoietic stem cells from different strains were examined and found to have differences in DNA repair genes. Furthermore, in vivo studies using genetically diverse F1 strains of mice given doses of ionizing radiation found differences in penetrance, latency, and aggressiveness of lymphomas and leukemia based on strain background. These studies further support the complex nature of polygenic traits underlying cancer susceptibility (French).

The effects of diet in cancer susceptibility were highlighted in a study of intestinal neoplasia using mice susceptible and resistant to diet-induced obesity. Although strain background plays a role in the susceptibility of mice to obesity, an increase in the number of intestinal polyps and an induction in the inflammatory response were found in strains fed high-fat diets regardless of obesity status. However, mice fed a high-fat diet with specific fatty acids from olive oil did not show the same effects. This study shows the importance of studying specific components in the diet and their relationship to cancer formation and the inflammatory response (Doerner).

Use of mouse models to bridge studies of modifier loci to cancer treatment is critical for effectively targeting cancer in the human population. In a study examining potential therapeutics for multiple myeloma (MM), a mouse model of plasmacytoma was used to predict the pathways important for targeted treatment of MM. A combination of the mTOR inhibitor rapamycin and the histone deacetylase (HDAC) inhibitor MS-275 was chosen for use and found to effectively synergize and decrease the growth of human myeloma cell lines in vitro and in vivo. Additionally, a decrease in the activation of the AKT/MAPK pathways and increased apoptosis and cell cycle arrest were found with combination treatment. The use of gene expression profiling found cooperative expression changes in many genes as a result of this combination therapy. Pathway analysis identified roles for these genes in the cell cycle, DNA damage response, and immune surveillance pathways. Human microarray data sets from MM patients exhibited differential expression of many of these additive genes. These data highlight the importance of targeting multiple pathways in cancer therapeutics and shed light on the mechanisms behind the synergy of HDAC and mTOR inhibitors (Simmons).

A variety of interesting posters were presented on the genetics of cancer susceptibility and development. The molecular mechanism by which the regulation of metastasis occurs by SIPA1 was studied in the context of breast cancer. This study demonstrated that the interacting partners, the subcellular location, and the GTPase-activating function of SIPA1 all play roles in the mechanism by which SIPA1 regulates metastasis (69B Geiger). Another study examined whether the strain background had an impact on susceptibility to hepatocarcinogenesis. *Statb* was knocked out in several different mouse strains and was found to cause differences in susceptibility to liver cancer as well as tumor multiplicity and size differences dependent on the genetic background of the mouse (72B Oberley). The genetic contribution of strain background to tumor morphology was studied in the context of colorectal cancer (111C Bautz). Depending on the strain, tumor morphology was found to range from flat lesion tumors to polyploid lesion tumors. Gene analysis of flat and polyploid lesion tumors identified that host-specific genomic differences contribute to tumor morphology. Furthermore, mouse genetic crosses identified two potential loci causing these phenotypic differences (111C Bautz). The contribution of *MYC* to cancer initiation was studied in a novel mouse model of pancreatic ductal adenocarcinoma. *MYC* expression was spatially and temporally controlled in the pancreatic ductal epithelium and the mice were found to develop cancer in less than 6 months. This study showed the association of *MYC* with early cancer progression and additionally found that the growth of *MYC*-induced pancreatic cancer cells depends on continuous expression of the gene (164B Lin).

Understanding vulnerability: the genetics of pathogen susceptibility

Investigators in this session focused on using intercrosses and whole-genome sequencing (Benson), ENU mutagenesis (Yuki, Eva), and gene expression profiling (222C Wilk, Schughart) and recombinant inbred (Schughart), Collaborative Cross (Durrant), and recombinant congenic (Beatty, Schughart) strains to map and characterize susceptibility

genes linked to a variety of pathogens, including numerous gut microbiota, *Salmonella*, *Mycobacterium*, *Influenza*, and *Aspergillus*. The use of systems-level analyses to uncover sets of genes that determine pathogenesis was emphasized in the influenza model where gene expression profiles were monitored in the lungs of recombinant inbred mice over time (Schughart). Studies of *Salmonella* susceptibility in recombinant congenic strains (RCS) illustrated the usefulness of combining traditional intercrosses between two distinct RCS with gene expression profiling to identify candidate loci for the QTLs mapped (Beatty). ENU mutagenesis (Yuki, Eva) and Collaborative Cross (Durrant) studies are emphasized in the Tools subsection below.

The plenary talk by Andrew Benson highlighted the complexities involved in identifying host genes that affect gut flora development. Benson used 16s rRNA fingerprinting and pyrosequencing to quantify the top 100 genera of gut microbiota in 645 G4 intercross mice derived from mating C57BL/6J mice with an ICR-derived outbred line, HR. They identified 13 significant QTLs and 5 additional suggestive QTLs dispersed over eight chromosomes. They have also analyzed data from 187 pre-Collaborative Cross strains (F8/9) and found that there were overlapping QTLs affecting gut microbiota between the different linkage studies. While the host strain was the most important driver affecting the distribution of gut microbiota, they did observe both cohort and litter effects accounting for 26 and 5% of the variation, respectively.

Tools for answering the most complex questions

Bioinformatics workshop

The Mouse Genetics 2011 meeting kicked off with a full day dedicated to students and young researchers, offering a bioinformatics workshop and a student symposium. During the bioinformatics workshop, Carol Bult (The Jackson Laboratory) and Deanna Church (National Center for Biotechnology Information) introduced some 40 participants to bioinformatics issues concerning genome assemblies, gene alignments, and the analysis of high-throughput sequencing data. All analyses were carried out using freely available software like Galaxy (http://main.g2.bx.psu.edu/) or NCBI Genome Workbench (http://www.ncbi.nlm.nih.gov/projects/gbench/). As an example of how to use bioinformatics, we conducted a simple workflow for processing RNA sequencing data. After a brief check for low-quality sequence reads, mapping to a reference genome was performed with TopHat (http://www.tophat.cbcb.umd.edu/), which also accounts for splicing. Next, the data were associated with genome annotations using Cufflinks (http://cufflinks.cbcb.umd.edu/), estimating the abundance of transcripts and allowing for statistical analysis or visualization of differential expression.

Genetic resources and their applications

High-throughput sequencing

The vast sequence variation among different mouse strains, both laboratory and wild-derived, enables the mapping of various physiological and disease-related traits to allelic variation. However, accurate mapping requires good reference genomes. To this end, Adams reported on the high-throughput sequencing of 17 different mouse genomes. Their analyses revealed up to an order-of-magnitude more sequence variation than previously known, as well as functional consequences of allele-specific variation on transcript abundance. Many presenters detailed the use of next-generation exome sequencing, which focuses only on the coding portion of the genome. Reinholdt presented a sequence capture probe pool of over 200,000 exonic regions, covering more than 50 Mb. This collection will be of great use to identify spontaneous or induced mouse mutations. However, it remains challenging to detect differentially expressed isoforms unless they are expressed at relatively high levels and with large differences (Bottomly).

The collaborative cross

Complementary to next-generation sequencing analysis, SNP arrays can be a powerful genotyping tool, especially when higher throughput is needed more than the depth of genomic coverage provided by sequencing. Gary Churchill gave an overview of ongoing efforts to generate high-density SNP arrays for genotyping mouse strains. Using their custom-made Mouse Diversity Array with over 600,000 SNPs and over 900,000 invariant genomic probes, Churchill and colleagues have characterized numerous mouse strains for phylogenetic origin. The Mouse Phylogeny Viewer and other analytical tools are available at http://cgd.jax.org/. The Mouse Universal Genotyping Array (MUGA), with 7,851 SNPs, is a simpler and less expensive platform designed for genotyping the Collaborative Cross (CC) mouse genetic reference panel and related strains (see below). A new genotyping array is being developed that will contain roughly 100,000 SNPs. The goal is to make the 100 k array available by the end of 2012, and input from the community is wanted on the selection of SNPs to be included.

Fernando Pardo-Manuel de Villena discussed newer findings with the CC. This genetic reference panel consists of recombinant inbred lines derived from eight different founder strains and was designed for high-resolution mapping of QTLs (http://compgen.unc.edu/wp/?page_id=99 and CC genome browser: http://csbio.unc.edu/ccv/). Nine recombinant inbred strains are now complete, with 30–40 more anticipated to be completed in 2011, and up to 100 completed

lines by the end of 2012. It appears that overall, all eight founder strains contribute equally to the recombinant inbred lines; however, some distortions exist within individual lines. Also, there is a higher than expected extinction rate in the CC inbred strains, peaking between five and nine generations of inbreeding and possibly caused by male infertility (Aylor and poster 90C Odet).

Several researchers reported data derived from the partially inbred pre-CC strains: Durrant and colleagues used 66 partially inbred CC lines (inbreeding for 6–12 generations) and assessed survival after *Aspergillus fumigates* infection. This analysis revealed a number of statistically significant and suggestive QTLs associated with resistance against *Aspergillus* infection. The same group also presented a poster on susceptibility to *Klebsiella pneumoniae* (149B Iraqi) and periodontal infection (176B Nashef). Several more posters underscored the power of the pre-CC panel, looking for susceptibility to respiratory viruses (141C Ferris), house dust mite allergens (84C Kelada), blood alcohol clearance rate (95B Powell), or baseline hematological parameters (92B Peck). Complementary to the CC, the Diversity Outcross (DO) panel is a heterogeneous stock population derived from the CC founders and maintained by The Jackson Laboratory. Two posters reported preliminary data derived from DO mice tested for pain sensitivity (97A Recla) and different metabolic traits (103A Svenson). A talk by Valdar illustrated how one can modify QTL analyses to find regulators affecting the variability of a trait (vQTL) rather than the mean value of the trait, as in conventional QTL studies.

Table 1 Student and postdoctoral awards (abstract no.) presented at the 25th IMGC Banquet

Verne Chapman Young Scientist Award	Systems genetic analysis reveals a complex and dynamic transcription network governing sex determination	Steven Munger (38), Duke University Medical Center
GSA Postdoctoral Award	Genetic effects at pleiotropic loci are context-dependent with consequences for the maintenance of genetic variation in populations	Heather Lawson (34), Washington University, St. Louis
GSA Graduate Student Award	Mapping and identification of suppressors of MECP2 symptoms in the mouse	Christie Buchovecky (5), Baylor College of Medicine
	Effect of genetic and environmental variation on differential DNA methylation in mouse	John Calaway (50), UNC at Chapel Hill
	Specific fatty acids exert differential effects on inflammation and intestinal neoplasia	Stephanie Doerner (3), Case Western Reserve University
GSA Undergraduate Poster Presentation Award	Quantitative trait analysis of baseline hematological parameters using developing lines of the Collaborative Cross	Bailey Peck (92B), NHGRI, NIH
Poster Presentation Awards	An integrated Bayesian hierarchical model for multivariate eQTL mapping (iBMQ)	Marie Pier Scott-Boyer (271B), Institute de Recherches Clinique de Montreal University
	A locus mapping to mouse chromosome 8 determines infarct volume in a mouse model of ischemic stroke	Christopher Bennett (112A), Duke University
	Fine-mapping QTL and inferring causal pathways that underlie sixty murine phenotypes	Jon Krohn (4), University of Oxford
	Modes of action of miR96 in developing inner ear hair cells	Morag Lewis (162C), Wellcome Trust Sanger Institute
	Understanding the genetics of vesicoureteric reflux using inbred mouse models	Christine Watt (219C), McGill University
	The role of meiotic sex chromosome inactivation in sterility of interspecific hybrids	Tanmoy Bhattacharyya (7), Institute of Molecular Genetics, Prague
	Haploinsufficient role for Pax2/Emx2 in vesicoureteral reflux and other CAKUT-like malformations	Sami Boualia (117C), McGill Goodman Cancer Research Centre
	Sequencing of the mouse pseudoautosomal region	Takaoki Kashahara (235B), RIKEN Brain Science Institute
	A genetic locus mapping to Chromosome 4 unrelated to collateral circulation determines cerebral infarction in a mouse model of ischemic stroke	Sehoon Keum (157A), Duke University
	Use of pre-Collaborative Cross mice to characterize the genomics of allergen response	Samir Kelada (84C), NHGRI
	Genetic and functional analysis of infertility in high growth FVB/NJ female mice	Rashida Lathan (85A), UC Davis

ENU mutagenesis

Yoichi Gondo from RIKEN gave an overview of the latest developments in their ENU-mutagenized strain library. RIKEN has generated and distributes 10,000 G1 strains from ENU-treated C57BL/6 males crossed to wild-type C3H/HeJ or DBA/2 J females (http://www.brc.riken.go.jp/lab/mutants/genedriven.htm). Roughly 10% of coding mutations in this collection are expected to be equivalent to a knockout of the respective gene due to the introduction of a nonsense mutation. Analysis of almost 50 Mb of exome sequences revealed there to be 50–70 ENU-induced mutations per G1 genome. In the classic analysis, backcrossing and generation of congenic strains would isolate the various mutations for phenotypic analysis. However, next-generation sequencing may now enable the study of genetic interactions of different ENU-induced mutations and QTL mapping. A number of speakers and poster presentations showed data derived from ENU-mutagenized mice: Burgio identified lines with increased resistance against malaria infection and Yuki found lines with a higher susceptibility to *Salmonella typhimurium* infection and hemolytic anemia as a result of mutations in *Ank1*. Lee characterized an ENU-induced mutation in the obesity gene, *Negr1*.

High-throughput phenotyping

Steve Brown represented the International Mouse Phenotyping Consortium (IMPC) that is coordinating efforts to both knock out all protein-coding genes and characterize the subsequent phenotypes. The European Mouse Disease Clinic (EUMODIC) is phenotyping hundreds of parameters in 500 lines of mice, utilizing standardized workflows. Two thirds of the more than 300 mutant lines analyzed so far show a phenotype; many are pleiotropic (http://www.europhenome.org/). However, it is not always straightforward to reveal whether an observed phenotype is a direct consequence of the mutated gene or a secondary effect, a concept shown by Gerdin (143B), who assessed metabolic phenotypes. The lessons learned from EUMODIC will be implemented into the larger IMPC project. Phase I of the IMPC phenotyping project will be launched soon, establishing a phenotype pipeline and workflow for 4,000 strains. Comments on the draft phenotype pipeline are requested (http://www.mousephenotype.org/workgroups_phenotyping.html); funding for phase I is completed, and institutes have been appointed. Phase II, which will comprise 15,000 strains, is expected to start in 2016. de Angelis presented the ongoing phenotyping screens at the German Mouse Clinic (www.mouseclinic.de). Following from their systematic standardized basic phenotype screen, they have now moved to assess environmental influences, including diet, stress, infection, and exercise. In the future, the effect of drugs and compounds will be implemented and a pilot study is ongoing. Work from the Japanese Mouse Clinic (http://www.brc.riken.jp/lab/jmc/mouse_clinic/en/index.html) was presented by Wakana (255A). Engelhard introduced KOMPCluster as an alternative data analysis and presentation system for phenotyping projects, and Eppig presented the Mouse Genome Informatics (MGI) database (http://www.informatics.jax.org/), a vast resource on mouse phenotypes.

At the conclusion of the meeting, several awards for presentations of outstanding science were given to postdoctoral fellows and graduate students (Table 1).

Future meetings

The IMGS looks forward to your participation at future meetings:

26th IMGC (2012): St. Petersburg, Florida, USA
27th IMGC (2013): Salamanca, Spain

The CTC looks forward to your participation at future meetings:

11th CTC (2012): Paris, France
12th CTC (2013): Madison, Wisconsin, USA

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