Mamm Genome (2011) 22:148–155
DOI 10.1007/s00335-011-9314-x

MEETING REPORT

# The 24th International Mammalian Genome Conference meeting report

**Marsha Wallace · Christopher N. Vlangos · Elena de la Casa-Esperon**

Received: 21 December 2010 / Accepted: 21 January 2011 / Published online: 5 February 2011


## Introduction

The 24th International Mammalian Genome Conference was held on the shores of the Mediterranean Sea on the Island of Crete, Greece. This is an annual meeting organized by the International Mammalian Genome Society (IMGS) (http://imgs.org/; http://www.facebook.com/mammalian.genome). The organizational committee was composed of Joe Nadeau, Rudi Balling, David Galas, George Kollias, and John Lambris, and was advised by the IMGS Secretariat. This year, the conference was attended by over 170 participants representing nearly 20 different countries. The 43 oral presentations were divided among eight sessions, and 89 authors also presented posters during two formal poster sessions. Abstracts are available at http://imgs.org/. Three bioinformatics workshops on using the mouse genome and phenome databases were also offered.

Following the workshops, the meeting started with an exciting student symposium where 15 students and postdocs were invited to present their work on a wide variety of topics. Four presentations were selected from the student symposium for presentation at the main conference. The main conference was broken up into eight sessions, including Infection and Immunity; Modeling Disease: Development, Metabolism and Physiology; Large Scale and Genome-Wide Resources; two sessions on Neuroscience, Behavior, and Sensory Systems; and two sessions focusing on Epigenetics, Neoplasia and Aging. In addition, a special session on Human Diseases and Mouse Models focusing on lupus and cancer was presented. The annual Verne Chapman lecture was given by Steve D. M. Brown from the MRC Mammalian Genetics Unit, Harwell, UK, describing his work on mouse models of human middle-ear disease and therapy.

## Workshops, student presentations, and posters

Three bioinformatics workshops were organized by Carol Bult (The Jackson Laboratory), Deanna Church (NCBI), and Valerie Schneider (NCBI): *Getting the most from the mouse reference genome assembly* (instructed by Dr. Schneider), *Mouse Phenome Database at phenome.jax.org* (Terry Maddatu, The Jackson Laboratory), and *A tour of mammalian genome annotation* (Lauren Wilming and Mark Thomas, Wellcome Trust Sanger Institute).

The student symposium comprised 15 excellent presentations whose topics ranged from disease models to olfactory receptor evolution in marsupials. Four students were selected to present their talks during the main symposium (Table 1). Jessica Schaick (NCI and The George Washington University) won the Verne M. Chapman Young Scientist Award (Table 1) for her work identifying the imprinted growth factor receptor-bound protein 10 (Grb10) as a tumor susceptibility modifier of spontaneous malignant peripheral nerve sheath tumors (MPNSTs) in an

M. Wallace
Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY 14850, USA
e-mail: mdw38@cornell.edu

C. N. Vlangos
Departments of Pediatrics and Human Genetics, University of Michigan, Ann Arbor, MI 48109, USA
e-mail: cvlangos@med.umich.edu

E. de la Casa-Esperon (✉)
Albacete Science and Technology Park, Regional Center for Biomedical Research (C.R.I.B.), University of Castilla-La Mancha, Albacete 02006, Spain
e-mail: elena.casaesperon@uclm.es

**Table 1** International Mammalian Genome Conference award recipients

| Name | Award | Institute |
|---|---|---|
| Presentation awards (cash prize) | | |
| Jessica Van Schaick | Verne M. Chapman Young Scientist Award and 2 years on Secretariat | The George Washington University, USA |
| Paraskevi Goggolidou | Genetics Society of America | MRC Mammalian Genetics Unit, Harwell, UK |
| Christopher Vlangos | Genetics Society of America | University of Michigan, USA |
| Poster awards (journal subscriptions) | | |
| Gregory Boivin | *Mammalian Genome* and IMGS membership | McGill University, Canada |
| John Didion | *Genome Research* | University of North Carolina, USA |
| Alexandra Niti | *Genetics Research* | BSRC Alexander Fleming, Greece |
| Marsha Wallace | *Genomics* | Cornell University, USA |
| Poster awards (various books) | | |
| Diana Connolly | Book donated by Genesis | Albert Einstein College of Med. Of Yeshiva University, USA |
| Sabyasachi Das | Book donated by Genesis | Emory University, USA |
| Takuya Murata | Book donated by Genesis | RIKEN BRC, Japan |
| Nomenclature excellence award | | |
| Charlotte Lindfors | Small gift from Nomenclature Committee | Karolinska Institute, Stockholm, Sweden |

*Nf1* and *Trp53* mouse model. John Calaway (University of North Carolina) reported the first genome-wide survey of the mouse differential methylome via digestion of inter-subspecific $F_1$ hybrid DNA samples with methylation-sensitive or -insensitive endonucleases and subsequent hybridization to high-density mouse diversity array chips. This allowed him to identify new strain-specific or parent-of-origin-specific methylated sites. Fotios Iokeimidis (BSRC Alexander Fleming, Greece) reported the identification of a novel member of the DNAJC family that localizes to mitochondria and causes neuromuscular disease in mice. The human homologous protein (DNAJC) has approximately 96% identity and can rescue the mouse phenotype. Rebecca Smith (Kings College London) examined the effects of paternal age on behavioral and molecular changes of progeny in C57BL/6J mice. She found that older C57BL/6J fathers had pups with significantly reduced social/exploratory behavior and significantly higher methylation levels, suggesting that de novo mutations in the father's sperm might be involved in the behavioral changes.

Approximately 100 posters were presented in two sessions covering a range of basic research, diseases, genomic studies, facility services, and large-scale databases. Four researchers were granted poster awards with journal subscriptions (Table 1): Gregory Boivin (McGill University) found three new QTLs for influenza susceptibility and uncovered a novel influenza susceptibility mechanism related to lipid biology; John Didion (University of North Carolina) described new methods for analyzing allele-specific methylation across the mouse genome; Alexandra Niti (BSRC Alexander Fleming, Greece) found that overexpressing human RANKL (a bone-remodeling regulator) in transgenic mice results in osteoporosis; and Marsha Wallace (Cornell University) found recurring amplifications and deletions in mammary tumors of Mini chromosome maintenance 4 (*Mcm4*) mutant mice. While pregnancy and ovariectomy studies of the mutants show a protective effect against breast cancer (as seen in humans), these mice become susceptible to developing other cancer types instead. Additional awards are presented in Table 1.

## Infection and immunity

The first session began with Katia Karalis (Biomedical Research Foundation of the Academy of Athens and Harvard Medical School), who spoke on inflammatory and infectious stimuli, which are challenges to the immune system and cause activation of stress response. One hypothalamic mediator of stress response is Corticotropin Releasing Hormone (CRH). Dr. Karalis found dual effects of CRH on the immune/inflammatory response: suppressive by central CRH and stimulatory by peripheral CRH. Understanding the complex regulation of genes involved in stress response provides new therapeutic targets for inflammatory conditions.

Beverly Mock (National Cancer Institute, NIH) described how constitutive reductions in mTOR levels compromise immune function. mTOR is a serine/threonine protein kinase known to contribute to tumor susceptibility. *Mtor*

knockout mice die during embryogenesis, so her lab generated a hypomorphic mouse with reduced expression of *Mtor*. The mutants demonstrate several immune deficiencies, including a block of B-cell development, impaired B- and T-cell receptor signaling, and decreased production of NP-specific antibodies, and have impaired IgG1 switching in resting B cells. This novel model demonstrates that mTOR is required for the maturation and differentiation of multiple immune cell lineages.

Dr. Tomoji Mashimo (Kyoto University) reported his success in creating severe combined immunodeficiency (SCID) rats using the exciting new zinc finger nuclease (ZFN) technology. Despite the many benefits of the use of rat as a model, the inability to utilize germline-competent embryonic stem (ES) cells has been a major drawback. However, ZFNs have recently been designed to generate DNA double-strand breaks at specific sites in order to make targeted gene mutations. Dr. Mashimo microinjected mRNAs encoding custom-designed ZFNs targeting the rat interleukin-2 receptor $\gamma$ gene into fertilized oocytes of pseudopregnant females. This yielded 25% gene-modified offspring and faithful transmission of SCID phenotypes to the next generation. The study emphasizes the value of the emerging ZFN technology for creating new animal models of human disease.

The session concluded with a presentation by Thomas Brodnicki (St Vincent's Institute of Medical Research, Australia) on the type-1 diabetes (T1D) susceptibility locus *Idd11*. Non-obese diabetic (NOD) mice provide insight into human T1D since their lymphocytes specifically destroy insulin-producing B cells. Sequence analysis showed NOD mice and 25 other inbred strains had high levels of haplotype diversity around the *Idd11* locus due to a recombination hotspot. The *Latet* gene is within this locus and exhibits deficient splicing and decreased expression in relevant immunological tissues of NOD mice. These results imply that diabetes, as well as other complex human diseases, may be affected by the genome's approximately 33,000 hotspots.

## Modeling disease: development, metabolism, and physiology

This session included a presentation by Kathryn Hentges (University of Manchester) on the importance of the non-muscle myosin IIB gene *Myh10* in the formation of the coronary vasculature. Resulting from a mutagenesis screen, this mutant displays embryonic hydrocephalus and heart defects, including lack of formation of the cardiac vessels and the morphological defect double-outlet right ventricle. Because *Myh10* localizes to the epicardium, the presumable loss of function of *Myh10* may cause a decrease in the interaction between the epicardium and myocardium, resulting in coronary vascular failure.

Michael Parsons (MRC Mammalian Genetics Unit, Harwell, UK) described a novel role for the transcription factor *Zfhx3* in lung development through the study of an ENU mutant called short circuit (*sci*). The *Zfhx3* gene had a previously known function in neuronal development but no known role in lung development. The *sci* mutation of *Zfhx3* is embryonic lethal in homozygosity, while heterozygous animals display decreased locomotor activity and weight. Upon further examination it was found that both heterozygous and homozygous embryos have reduced airway volumes at embryonic day 18.5, and morphological changes were also seen as early as E15.5. Studies in heterozygous *sci* mutants showed decreased lung flow and resistance. Interestingly, an increase in proliferation is seen in the lungs of E16.5 and 18.5 embryos. These studies implicate *Zfhx3* as an important gene for proper lung development.

Christopher Vlangos (University of Michigan) was awarded a prize from the Genetics Society of America (Table 1) for his presentation describing work in identification of the mutation causing the Danforth's short tail (*Sd*) phenotype, which spontaneously arose in a research mouse stock in the early 1900 s. While heterozygous animals have shortened tails, homozygous animals are more severely affected, having no tail, kidney agenesis, severe spinal anomalies, and no urogenital openings, and they die within 24 h of birth. The mutation had long been maintained but was still unidentified. Next-generation sequencing and novel bioinformatic analysis of the data were used to identify the insertion of a retrotransposon as the cause of the mutant phenotype.

Also awarded a prize from the Genetics Society of America (Table 1), Paraskevi Goggolidou (MRC Mammalian Genetics Unit, Harwell, UK) presented her findings on the DNA damage response locus *Atmin*, which encodes a zinc finger factor required for normal ciliogenesis. Mutant mice die around E13.5 and demonstrate phenotypes indicative of ciliopathy, such as exencephaly, pulmonary hypoplasia, and L-R patterning defects. Cilial structure is important in Sonic hedgehog signaling, for which the *Atmin* mice are also deficient due to GLI3 processing defects. Data support that ATMIN controls ciliogenesis through modulation of dynein light chain expression.

The session also included a presentation by Randal Westrick (University of Michigan) who spoke on his work to identify modifier genes affecting expression of a risk factor polymorphism (factor V Leiden) causing venous thrombosis in mouse. Sabrina Spiezio (Case Western Reserve University) presented intriguing data showing diet-induced changes in alternative exon splicing and mRNA expression in mouse inbred and consomic strains

with different obesity susceptibility. Ruth Arkell (Australian National University, Canberra) described how abnormal SUMOylation disrupts nuclear localization of the Zic5 transcription factor in two hypomorphic mutant mouse lines.

This session concluded with a presentation by David Threadgill (North Carolina State University) on the Collaborative Cross (CC) and analysis of complex traits on the mouse lines emerging from the cross. Studies of 200 of the 600 emerging recombinant inbred lines from the CC have shown that there is no global selection from any of the eight founder strains, and all strains have contributed equally across the genome. Dr. Threadgill presented several mapping studies that have successfully been performed with the pre-CC lines, which are currently 85% inbred on average. In one of these studies, *Kit1* was identified as a candidate gene for the white head spotting Mendelian trait seen in the WSB/EiJ inbred line. In addition, analysis in the CC allowed identification of a number of new body weight QTLs coming mainly from NZO (New Zealand Obese) and C57BL/6. Among these, haplotype analysis of the Bwqtl14 peak narrowed down the candidate region to a single gene (*Asph*). Global gene expression in liver was also analyzed in pre-CC lines. Of the 23,000 genes present on the Affymetrix expression array, 11,000 are differentially expressed in the pre-CC. Furthermore, 5,700 genes have an eQTL, with over 800 genes displaying more than one eQTL. Very few *trans* eQTLs were identified and most QTLs were predicted to have a *cis*-effect. The data presented indicate that analysis of only 200 lines is sufficiently powerful to detect QTLs and shows the power of the emerging CC lines. The first inbred line from the CC is expected to be available within a few months, and 50 lines will be completed in 2011.

## Human disease and mouse models

The session was opened with a lecture by Edward Wakeland (University of Texas Southwestern Medical Center) about lupus. Studies of lupus-prone mouse models have revealed that environmental or stochastic events are essential to trigger the initiation of the disease. Affected animals show dysregulation of the innate immune system and a breach of tolerance in the adaptive immune system. While in mice a minimum of two susceptibility loci are required for the development of the severe disease, studies in humans have identified more than 30 loci. However, these account for only 10% of the genetic component. Association studies are in progress to identify susceptibility genes. The second and final talk was given by Reuven Agami (The Netherlands Cancer Institute) about the regulation of microRNAs in cancer. MicroRNAs often contribute to tumorigenesis by repressing tumor suppressor genes through association with their RNA 3′ untranslated regions (UTRs). In a study of the p27 tumor suppressor, they identified two microRNAs (miR-221 and miR-222) which downregulate p27 in many cancer cell types. Interestingly, they also found that the accessibility of these microRNAs to the 3′-UTR of p27 transcripts is modulated by RNA-binding proteins such as DND1 (dead-end) and Pumilio. Therefore, the effect of microRNAs does not depend only on their cellular levels, because their interaction with RNA binding proteins can regulate their function during cell cycle and in cancer.

This year, Steve Brown (MRC Mammalian Genetics Unit, Harwell, UK) gave the Verne Chapman Lecture. He began his compelling talk, "Realizing the potential of mouse disease models—from pathway to therapy," by emphasizing the importance of mouse models to elucidate the mechanisms behind human disease. The International Mouse Knockout Consortium (IKMC) and others are revolutionizing the availability of mouse models to study diseases and broadening the platform to develop new therapeutic approaches. Dr. Brown's primary research is on otitis media (OM), an inflammatory disease of the middle ear that affects millions of children around the world. When OM becomes chronic, it can lead to a thickened lining, hyperplasia, and polyps in the middle-ear lining. These changes result in hearing loss, learning difficulty, and language delays. OM is estimated to be responsible for approximately 20,000 deaths annually. Some forms of OM are known to have a strong genetic component, but nothing was known about the underlying human genes. In an ENU mutagenesis screen for new mouse models of human genetic deafness, Dr. Brown identified *Jeff* and *Junbo* mutants. *Jeff* carries a mutation in the *Fbxo11* gene, and *Junbo* carries a mutation in the *Evi1* transcription factor. Both mutants have deregulation of TGF-$\beta$ signaling, which impairs the response to hypoxic conditions. Hypoxia response is also mediated by HIF, which interacts with the TGF-$\beta$ pathway. As a result of these studies, new target pathways for therapeutic intervention have been identified. In fact, some of the potential treatments had been previously used in cancer, although their topical administration to children still poses problems. For instance, SMAD3 and HIF synergistically upregulate *Vegf*, and VEGF targets are seen to be upregulated in the *Jeff* and *Junbo* mutants. Thus, VEGF inhibitors are potential treatments, and Dr. Brown found that they do significantly rescue hearing loss in mice.

## Large scale and genome-wide resources

This session included ten presentations that covered a range of genomic resources, including genome annotation,

mouse repositories, SNP mapping, and several phenotyping services and databases. Mark Thomas (HAVANA Group, Wellcome Trust Sanger Institute) discussed the annotation of long noncoding RNA (ncRNA) transcripts. While only about 2% of the genome encodes for proteins, up to 90% may be transcribed. Promoter regions of ncRNAs can be more conserved than protein-coding transcripts, suggesting a functional role. Proposed ncRNA annotation is based on functional grouping with the template: gene name_ relational suffix_ locus number. The annotative repositories can be found at http://vega.sanger.ac.uk. Dr. Petr Danecek (Wellcome Trust Sanger Institute) gave an update on The Mouse Genomes Project, whose goal is to create a comprehensive catalog of all SNPs in 17 inbred mouse strains. They find that their SNP calling closely matches the Perlegen data set. The SNP database is available at http://www.sanger.ac.uk/mousegenomes. Current work focuses on cataloging transposon insertions across the strains. David Beier (Brigham & Women's Hospital, Harvard Medical School) used *PiggyBac*-mediated transient transgenic RNAi expression for rapid characterization of gene function during embryonic development. The method yields phenotypic results in just a few weeks, making it a useful alternative to gene targeting in embryonic stem cells. The method is also adaptable for multigene knockdown, expression of affinity-tagged proteins, and analysis of presumptive transcriptional regulatory sequences.

Stephen Murray (The Jackson Laboratory) reported on the characterization of 26 Cre strains, part of the JAX mouse repository of 200 + Cre driver strains. With the IKMC generating knockout mice for almost every gene, many being conditional, there is a need for Cre driver strain mice that are well characterized. Of note, their results indicate that the majority of the Cre driver strains exhibit unexpected recombinase activity, leading to loss of Cre-tissue specificity, and that genetic background can also affect Cre activity. The data shared at MGI's website (http://creportal.org) can help researchers determine the best strain for their experiments. On a related note, Aris Economides (Regeneron Pharmaceuticals) presented the new COIN (conditional by inversion) technology, which uses an inverted gene trap-like cassette that is activated when exposed to Cre recombinase. Upon activation, the COIN cassette is flipped into the sense strand, thereby disrupting transcription of downstream exons, while simultaneously providing a reporter (such as GFP) for tracking the mutation. This new method of conditionality is useful for targeting genes that cannot be knocked out (because of resulting lethality) or when tissue specificity is desired.

There were several presentations on mouse phenotyping. Ramiro Ramírez Solís (Wellcome Trust Sanger Institute) provided information on the Mouse Genetics Program, which has generated more than 400 mutant mouse strains using ES cell resources from EUCOMM and KOMP. They perform large-scale genotyping and phenotyping of the strains and make the information available at http://www.sanger.ac.uk.mouseportal. Martin Hrabe de Angelis presented the German Mouse Clinic Consortium's work with 100 mouse lines for next-level systemic phenotyping. They focus on envirotypes—environmental conditions that are important for humans (exercise, nutrition, stress, air, immunity/inflammation). Their goal is to decipher these effects on disease etiology and progression (the mechanisms of genome-environment interactions). Dr. Renee LeBoeuf (University of Washington) described the Mouse Metabolic Phenotyping Consortium (http://www.mmpc.org), an NIH-funded consortium focusing specifically on diabetes and metabolic diseases.

William Skarnes (Wellcome Trust Sanger Institute) presented the website http://www.knockoutmouse.org as a portal to large-scale mouse knockout resources. Many different knockout alleles of 21,000 genes have been generated, and the database provides a summary of availability. It also may be the most integrative, pooling data from many other repositories (such as the BioMart data-mining tool and the EMMA repository), and provides links to Europhenome. Dr. Anna Anagnostopoulos (The Jackson Laboratory) reported on the MGI compilation of a mouse genome database aimed at incorporating data on phenotypes and disease models from the literature, ENU screens, IKMC, and KOMP/EUCOMM, collaborating institutions, and others. The International Mouse Strain Resource (IMSR) summary can be found at http://www.findmice.org and uses mammalian phenotype ontology to present a standardized characterization of the mice for researchers to explore strains of interest.

## Epigenetics, neoplasia, and aging

This session began with two lectures about the mechanisms that regulate the expression of genes within imprinted domains, which are transcribed only from the paternally or maternally inherited copy. Jo Peters (MRC Mammalian Genetics Unit, Harwell, UK) discussed her studies of the *Gnas* domain, a complex imprinted domain that contains paternally, maternally, and biallelically expressed transcripts that share several downstream exons. She reported how noncoding RNAs (such as *Nespas*), differentially methylated regions, and other epigenetic marks contribute to the regulation of the *Gnas* cluster. Nora Engels (Temple University) analyzed the role of enhancers in the regulation of gene expression in two other imprinted regions, the *H19/Igf2* and *Kcnq1* domains. By chromatin conformation capture studies, she showed how the interaction of these

enhancers with promoters is modulated by insulators and antisense transcripts. In the case of *Kcnq1*, these interactions change as gene expression switches from monoallelic to biallelic during development.

Two lectures focused on aging. Toyoyuki Takada (National Institute of Genetics, Japan) presented the identification of several QTLs associated with age-related changes of energy metabolism. A panel of mouse intersubspecific consomic (chromosome substitution) strains was used, containing each of the MSM/Ms chromosomes in a C57BL/6 background (http://molossinus.lab.nig.ac.jp). Rong Yuan (The Jackson Laboratory) reported on a life-span study of 31 mouse inbred strains. Among the multiple parameters analyzed, they observed an inverse correlation between circulating IGF1 levels at 6 months and median life span, while positive correlation was detected between life span and age at sexual maturation (vaginal patency). The identification of several loci that control these phenotypes (plasma IGF1 levels and age at vaginal patency) will open new avenues in the understanding of the genetics of aging.

The session also included talks about new avenues in genomic and genetic diversity studies for the analysis of complex traits in humans and mice. David Galas (Institute for Systems Biology) discussed the advantages of combining whole-genome sequencing with family studies. In a pilot study of two parents with two children affected by rare genetic diseases ("The Family of Four"), this approach allowed a substantial noise reduction (due to the identification of sequencing errors), the discovery of thousands of polymorphisms, and the fine mapping of the diseases' candidate genes. In addition, it provided an accurate description of the intergenerational mutation rate and a detailed recombination map of a human family. Although family genome analysis has enormous potential, the identification of the genetic components of complex diseases will require the development of computational tools for testing diverse genetic models.

Fernando Pardo Manuel de Villena (University of North Carolina) presented a high-resolution map of the phylogenetic origin of the genome of inbred strains. This comprehensive study was based on the genotyping of hundreds of wild caught mice, which allowed identification of diagnostic polymorphisms for each one of the three *Mus musculus* subspecies. This approach revealed that classical inbred strains are derived from a small pool of mice, predominantly of *M. m. domesticus* origin, with the remainder derived mostly from *M. m. molossinus*. Most importantly, the data showed that intersubspecific introgression is also common in wild-derived strains, even in those that have been used as references for the mouse subspecies. These data have very important implications for mouse genetic studies and genomic imputation and are available at http://cgd.jax.org.

Although these studies highlight the ample genetic diversity present within *Mus musculus*, not all mouse crosses produce fertile offspring, as noted by Jiri Forejt (Institute of Molecular Genetics, Academy of Sciences of the Czech Republic). Male sterility is observed in the $F_1$ offspring of PWD/Ph females (*M. m. domesticus*) and C57BL/6 males (mostly *M. m. musculus*). By using chromosome substitution strains, Dr. Forejt's group has identified at least three hybrid sterility loci in chromosomes 17 (specifically the *Prdm9* gene, which codes for a histone methyltransferase), 19, and X (*Hstx2*). His results suggest that this sterility is the result of meiotic male sex chromosome inactivation defects.

Cancer susceptibility was also discussed in this session. Jason Heaney (Case Western Reserve University) presented genetic studies of inbred strains susceptible to testicular germ-cell tumors (those of the 129 family and 129 consomics). They found that the cells that originate these tumors, the primordial germ cells, show delayed silencing of pluripotent gene expression, premature expression of undifferentiated A-spermatogonia markers, and initiation, but not completion, of meiosis in susceptible strains. Moreover, Angabin Matin (MD Anderson Cancer Center) indicated that the incidence of testicular germ-cell tumors increases dramatically in 129 mice if the *dead-end* (*Dnd1*) gene is inactivated. DND1 is essential for germ-cell viability and binds to the 3′-UTRs of several mRNAs, displacing microRNA interaction with mRNAs. This function can be affected by interactions with other proteins, such as APOBEC3, which are postulated to regulate the role of DND1 in preserving germ-cell integrity.

Finally, a talk about the genetic basis of the susceptibility to metastasis by Kent Hunter (National Cancer Institute, NIH) closed this excellent session. His laboratory has identified several genes that contribute to breast cancer metastasis susceptibility. Such is the case of *Sipa1*, which is involved in predisposition to metastasis in both human and mouse. Interestingly, despite the diversity and complexity of the steps that result in metastasis, many of the identified genes code for proteins that interact and also converge in common transcriptional control pathways.

## Neuroscience, behavior, and sensory systems

Tim Wiltshire (University of North Carolina) opened the session with a talk about the genetic basis of depression behavior in mice. The study was performed in a panel of genetically diverse inbred strains and included analyses of baseline depression behavior, response to a treatment with an antidepressant (fluoxetine), global gene expression, and levels of selected biochemical molecules in diverse brain regions. By haplotype association mapping, several QTLs

were obtained for these phenotypes, in which expression, behavior, and/or biochemical data converge. Of particular interest, cell adhesion molecule 1 (*Cadm1*) was identified as a candidate gene for depression susceptibility or differential antidepressant response. Deborah Cabin (McLaughlin Research Institute) presented a study of α-synuclein, a neuronal protein linked to Parkinson's disease. In order to unravel its physiological function, an ENU sensitization screen of α-synuclein-null mice was performed. A sensitized mutation was found in *Atp7a*, a Golgi transporter that is also mutated in Menkes disease, another disease causing neurological damage. Studies of both genes suggest a neuroprotective function of α-synuclein. Also from the McLaughlin Research Institute, George Carlson described his work in the identification of 333 differentially expressed genes that play a role in pathogenesis during prion infection.

An interesting study by Nikoletta Charizopoulou (National Institutes of Health) was presented on the genetics of hearing loss in humans and mice. The age-related hearing loss (*Ahl5*) and juvenile audiogenic mongenic seizure 1 (*jams1*) loci contain genes responsible for age-related hearing loss in Black Swiss mice. DNA sequencing identified a G → A transition that changes a glycine to an arginine in a conserved PDZ domain in the *Gipc3* gene at both loci. The Gipc3 protein was shown to localize within the inner-ear sensory hair cells and spiral ganglia, and mutants showed reduced protein levels within the cochlea. The identified *Gipc3* mutation disrupts the structure of the stereocilia and reduces survival of the spiral neurons. Auditory brainstem response studies in mutant animals suggested a correlation between the level of auditory neuronal excitability and the susceptibility to the audiogenic seizures. Further, a *GIPC3* mutation was identified as the cause of autosomal recessive hearing loss (DFNB95) in humans through study of a family segregating with the phenotype.

Takahashi Kuramoto (Kyoto University) described how the mutation of the *Mrs2* gene causes a demyelination (*dmy*) phenotype in rats. Specifically, *dmy* mutants have a defect in myelin maintenance. Myelination is completed postnatally, but the neurons of the central nervous system (CNS) (not the PNS) subsequently demyelinate in mutant animals. Positional cloning identified the *dmy* mutation in the *Mrs2* gene, which was rescued with a wild-type *Mrs2* transgene. The *Mrs2* gene is an important factor for magnesium homeostasis in the mitochondria. Mutant rats displayed functionally defective mitochondria. These interesting findings suggest that initial production of myelin is genetically distinct from its maintenance and that maintenance of myelin is dependent on magnesium homeostasis.

Sally Cross (MRC Human Genetics Unit, Edinburgh, UK) presented an interesting ENU mouse mutant called iris-corneal strands (*Icst*), which is a dominant eye mutation. The phenotype includes bulging eyes with displaced and misshapen pupils, anterior segment scarring, and neovascularization. Homozygosity of *Icst* is embryonic lethal and animals show limb and skull abnormalities, while the cerebellum is absent. A missense mutation of the *Lmx1b* gene within the homeodomain of the transcription factor was identified in *Icst* mice. The human *LMX1B* ortholog is the cause of Nail-Patella syndrome (NPS). The *Lmx1b* gene has been knocked out and, while homozygous KO animals display a phenotype consistent with *Icst* mutants, heterozygous KO animals display no phenotype, suggesting that the *Icst* mutation is acting as a dominant negative. Transgenic studies indicate that excess of the mutant protein is preventing normal limb development, even in the presence of an increased amount of wild-type Lmx1b protein. Therefore, the levels and ratio of mutant Lmx1b protein to wild-type protein are crucial for proper development. These data give insight to the human cases of NPS, where haploinsufficiency of *LMX1B* is thought to cause the disease, although dominant negative mutations have yet to be reported.

Gail Herman (The Ohio State University) spoke on the role of the NADH steroid dehydrogenase-like gene (*Nsdhl*) required for proper cholesterol metabolism. Mutations of the X-linked *Nsdhl* gene are lethal in affected males in two mutant mouse lines ("bare patches" and "striated"). Disorders of cholesterol biosynthesis in humans can show CNS abnormalities. Recently, two families with segregating X-linked mental retardation have been found to carry hypomorphic mutations of the *NSDHL* gene. Dr. Herman created a floxed allele of the *Nsdhl* gene to study the gene function in CNS development. Ongoing studies are helping to elucidate the role of cholesterol biosynthesis during neuronal development by crossing the floxed allele to numerous mouse lines expressing Cre during neuronal development.

The organizers arranged a wonderful conference that highlighted the breadth of cutting edge research occurring in our field; it was a great success. In addition to the scientific presentations, the IMGS Secretariat met and there was a Mentor breakfast where students and postdocs could meet with more senior researchers to talk about career plans. The conference attendees were also treated to a tour of the Minoan Palace of Knossos where the legends of the Minotaur and Icarus and his wax wings were said to have been born. The meeting ended with an outdoor closing awards ceremony, featuring Greek dancing and a Mediterranean banquet complete with ouzo under the swaying palms and olive trees of Greece.

**Acknowledgments** Many thanks to the organizational committee (Joe Nadeau, Rudi Balling, David Galas, George Kollias, and John Lambris) and to the IMGS Secretariat, composed of Karen Steel (President), David Threadgill (Vice-President), Maja Bucan (Past-President), David Beier, Ian Jackson, Nancy Jenkins, Darren Logan, Simon Foote, Xavier Montagutelli, Kent Hunter, and Teresa Gunn. We also thank Aegean Conferences for administrative support for the meeting and Darla Miller and Ginger Shaw for their outstanding work organizing the conference. The meeting was supported in part by financial contributions from The Ellison Medical Foundation and BGI Shenzhen. Sponsors for this year's presentation awards were Cambridge Journals, Genomics, Genesis, Genetics Research, Genetics Society of America, Genome Research, and Springer-Verlag. Student scholarships were funded by 2R13HG002394 from the following Institutional Centers at NIH: NHGRI, NIMH, NICHD, NIAID, NIEHS, NCRR, and NINDS and the Mouse News Letter, LTD.