Introduction

La Jolla, California, hosted the 235 attendees of the 23rd International Mammalian Genome Conference. The 47 presentations, including the Verne Chapman Memorial Lecture, 18 plenary speakers, and 3 student speakers selected from the satellite symposium, covered a wide range of topics divided into eight sessions. In addition, 120 posters were presented during three sessions.

High-throughput phenotyping was featured prominently this year, with updates on three large-scale resources. Presentations on mutagenesis, animal models of human disease, and highly diverse mouse populations highlighted different approaches to genetic analysis in model organisms. An abundance of mapping studies bridged these phenotyping and genetic analysis themes, demonstrating the increasing importance of genomics in mammalian genetics.

The student satellite symposium kicked off the meeting with a selection of 15 talks covering a wide range of topics, followed by the primary sessions. Topics for the primary sessions included Large-scale Resources; Infectious Disease, Host Resistance, and Epigenetics; Neuroscience, Behavior, and Sensory Perception; Metabolism and Physiology; Development; Neoplasia; Scientific Approaches to Animal Husbandry; and Population Genetics, Comparative Genomics, and Evolution. The Verne Chapman lecture was presented by Christopher Goodnow from The Australian National University and covered the genetic analysis of immunological memory and tolerance. The conference concluded with a presentation by Oliver Ryder of the San Diego Zoo’s Institute for Conservation Research on the Genome 10K project, followed by a trolley tour of the San Diego Zoo and a closing awards ceremony.

Several overarching themes were emphasized in many of the sessions. The benefits of high-throughput sequencing are becoming widely accessible, thanks to efforts such as the Sanger Mouse Genomes project. Collaboration is becoming increasingly important to meet the challenges posed by large-scale efforts like KOMP, EuCOMM, EUMODIC, and IMPC. Furthermore, several talks highlighted the importance of epigenetics in explaining phenotypic diversity, sex differences, and parent-of-origin effects.

Workshop and student presentations

A bioinformatics workshop on the Mouse Genome Assembly (Deanna Church, NIH/NLM/NCBI), Guide to Mouse Annotation (Carol Bult, The Jackson Laboratory), and Contributing Annotation to MGI (Janan Eppig, The Jackson Laboratory) jump-started this year’s conference. The workshop highlighted several useful resources,
including the Genome Resource Consortium (http://www.genomereference.org), for obtaining current information on the human and mouse genome assemblies.

The International Mammalian Genome Conference (IMGC) strongly encourages student participation and provides financial support to many students. There were 15 student presentations at the satellite meeting that were considered for awards and inclusion as platform presentations in the main conference. The talks were outstanding and covered diverse approaches to uncover genetic determinants of disease. ENU mutagenesis screening is a powerful tool that can generate valuable mouse models of human disease. This approach was used to identify genes responsible for genomic damage (Suzanne Hartford, Cornell University—genesis Award) and nonsyndromic hearing loss (Morag Lewis, Wellcome Trust Sanger Institute). Quantitative trait loci (QTL) mapping in F2 crosses facilitated identification of loci involved in inflammatory bowel disease (Andrew Hillhouse, University of Missouri—genesis Award), response to *Mycobacterium bovis* BCG (Tania Di Pietrantonio, McGill University), and susceptibility to mouse adenovirus type 1 (Tien-Huei Hsu, University of Michigan) and Coxsackievirus B3 infection (Sean Wiltshire, McGill University). Two students described novel transgenic mouse models that were methodically characterized to study the genetic underpinnings of hypertrophic cardiomyopathy (Wassim Basheer, University of South Carolina—Genomics Award) and the importance of connective tissue growth factor in maintenance and repair of the extracellular matrix (Heather Doherty, University of North Carolina). Kaoru Yamada (Okayama University) presented an approach to identify genes responsible for cataracts and dwarfism in the dwg/dwg mutant mouse model. Finally, three talks illustrated novel analytical approaches to identify genetic risk variants. John Calaway (University of North Carolina—genesis Award) used methylation-sensitive SNP analysis to identify CpGs subject to parent-of-origin methylation. Other methodologies include analysis of miscalled and uncalled SNPs to identify probe sequences with variable hybridization intensities that are candidate regions for resequencing (John Didion, University of North Carolina) and a comparative analysis of mouse and human QTL to investigate concordance rate that was low despite high sequence homology (Martin Goodson, University of Oxford—genesis Award).

Based on scientific merit, three students were chosen to present their work at the main conference. Lauren Walters (Vanderbilt University—genesis Award) described the use of haplotype analysis to identify genetic modifiers of *Sox10*, a gene involved in enteric ganglion development. Haplotype clusters that differ from the typical mouse phylogenetic tree were observed when two different methods of haplotype analyses were applied. The importance of modifier genes in modulating disease was further emphasized by the work of Amy Baran (Thomas Jefferson University—Genetics Society of America Award) and her characterization of a modifier locus of *Min1* (*Mom2*). Strategic breeding schemes between phenotypically divergent strains led to the identification of *Atp5a1* at the *Mom2* locus. A loss in heterozygosity is observed when the modifier gene *Atp5a1* is in cis with *Min2*. Finally, Krista Geister (University of Michigan—Genetics Society of America Award) characterized two complementary mouse models of human skeletal dysplasias, *pee wee* (*pwe*) and *chagun* (*cha*), yielding two critical regions involved in infertility and skeletal development. The mutation in *pee wee* maps to a region on chromosome 4 that contains 123 genes, including *Npr2*. Pharmacologic agents that inhibit signaling pathways downstream of NPR2 activation stimulated tibia growth. The *chagun* mutation maps to a 920-kb region on chromosome 9 containing three known genes that are being sequenced for causal variants. These findings underscore the use of mouse models as powerful tools for understanding disease mechanisms and developing effective treatment strategies.

The scientific contributions of students and post-docs were highlighted throughout the conference. Several young scientists were awarded prizes for their outstanding work (Table 1). New this year, the recipient of the Verne Chapman Young Scientist Award (Darren Logan) will also be a two-year member of the IMGS secretariat. This will provide an important career experience by allowing the award recipients to participate in leadership decisions while bringing a new perspective to the IMGS secretariat. The workshop along with the student presentations stimulated much scientific interest that persisted into the main conference.

### Large-scale resources

The first session included six plenary lectures covering a broad range of large-scale resources available to the community. David Adams of the Wellcome Trust Sanger Institute announced the availability of complete genome sequences from 13 classical and 4 wild-derived inbred mouse strains at an average of 20× coverage. He estimated that this effort has captured 95% of genetic variation among these strains, including 125 million SNPs and many structural variations. The data has been made available in the Ensembl genome browser as well as the Mouse Genomes Project website (http://www.sanger.ac.uk/resources/mouse/genomes/).

Next were updates on two projects [the Collaborative Cross (CC) and EuCOMM/KOMP] that have been ongoing for several years and were discussed previously at many IMGS meetings. David Threadgill (North Carolina State University) announced that the first 50 CC lines are...
scheduled to be completed and available for testing at the end of 2010, while Colin Fletcher of NIH/NHGRI reported that EuCOMM/KOMP is about halfway toward their goal of providing knockouts for 14,000 genes.

The remaining three presentations focused on large-scale phenotyping resources. Steve Brown (Medical Research Council) discussed EUMODIC, a global phenotyping effort to develop standard procedures, phenotyping platforms, and informatics tools to be shared across phenotyping centers. They have established two pipelines that encompass 20 platforms, 406 parameters, and 150 metadata parameters. Seven males and seven females from 500 mutant lines are being run through these pipelines, and two-thirds of these lines have been found to have a significant phenotype. The results of this project can be viewed in the EuroPhenome database (http://www.europhenome.org/). Mark Moore of the Wellcome Trust spoke on the process of planning the International Mouse Phenotyping Consortium. Finally, Janan Eppig (The Jackson Laboratory) presented the Mammalian Phenotype Ontology, a controlled vocabulary for phenotype annotation that will help improve bioinformatics tools.

### Infectious disease, host resistance, and epigenetics

This session began with a plenary presentation by the local host, Bruce Beutler (The Scripps Research Institute), on the role of Toll-like receptors (TLR) in host resistance and the identification of TLR signaling anomalies using an ENU mutagenesis approach. Over 50,000 G3 mice were screened for abnormal immune phenotypes, resulting in the identification of 31 mutations associated with aberrant TLR signaling. These mutations occur within 19 genes, suggesting that TLRs signal through four different adaptor proteins—MyD88, MAL, TICAM, and TICAM2—to activate downstream regulators of the cytokine cascade. These findings highlight the complex genetics underlying TLR involvement in host resistance and susceptibility, as well as in disease pathogenesis.
Diane Mathis (Harvard Medical School) gave a plenary talk discussing the mechanisms by which the autoimmune regulator (AIRE) causes APECED, an autosomal recessive polyglandular autoimmune disease. Over 60 Aire mutations have been identified, and knockout mice exhibit a similar multiple-organ phenotype. However, Dr. Mathis proposed that the genetic underpinnings are likely more complex, as phenotypic variability is observed among siblings and the AIRE phenotype is influenced by genetic background. AIRE is a unique transcription factor that is expressed in thymocytes and peripheral tissues where it uses its PHD domain to decipher the histone code and differentially regulates thousands of genes in different cell types. In summary, AIRE utilizes a complex mechanism to effect widespread transcriptional regulation influencing immunosusceptibility, and it is likely that modifier genes play an important role in the phenotypic variability.

A study of susceptibility to Rift Valley Fever using MBT/Pas and BALB/c was described by Jean-Jacques Panthier (Institut Pasteur). QTL were identified on chromosomes 2, 5, and 11 for survival time, and the absence of epistasis suggests that several mechanisms confer susceptibility. Katharina Brandl (The Scripps Research Institute) discussed an ENU mutagenesis screen that identified ten mutants with transmissible inflammatory bowel disease (IBD) phenotypes. The causative genes (Muc2, Mbtps1, Egfr) have now been identified for several IBD mutants. Bruce Hamilton (University of California San Diego) talked about the identification of Nsf1 as a semidominant modifier of the hypomorphic tremor model vibrator, proposing that modifiers are biased for genes with higher tolerance for functional variation and to networks with a high degree of plasticity and interaction. Fan Yang (University of Washington—Nature Award) contrasted differences between mice and humans with respect to clustering, temporal effects, and proposed mechanisms of genes that escape X-inactivation. Annie Park Moseman (Sackler School of Biomedical Sciences, Boston) presented results from a study of novel genetic mechanisms involved in CpG response in MOLF/Ei and C57BL/6J macrophages that indicate the importance of mannose receptor C type 1 (MRC1) in MOLF/Ei CpG hyporesponsiveness. Toyoyuki Takada (National Institute of Genetics, Japan) described the use of intersubspecific consomic strains to study age-associated physiological phenotypes between MSM/M and C57BL/6J mice, finding a 2-Mb critical region on chromosome 13 associated with late-onset fat deposition. Wei Yuan (University of Oxford) reported the identification of 110 physiological and behavioral QTL with significant parent-of-origin (POE) effects in heterogeneous stock (HS) mice and concluded that 30 eQTL genes warrant further investigation based on their overlap with POE QTL. Finally, David Aylor (University of North Carolina—Nature Genetics Award) presented results from genetic and metabolic phenotypic assessment of a panel of emergent Collaborative Cross (CC) recombinant lines that verify the high diversity, balanced allelic frequencies, and genomic contributions from each founder strain in the CC.

The Verne Chapman Memorial Lecture was presented by Christopher Goodnow (The Australian National University) and underscored the importance of examining heterozygotes that display intermediate phenotypes to further our understanding of recessive Mendelian syndromes. Many immunological studies are predicated upon recessive deleterious mutations that yield discrete syndromes that do not mirror the clinical patterns of common disorders. Dr. Goodnow reported that most recessive traits are semidominant at the level of the affected pathways and can interact with family-specific heterozygous variants epistatically or additively. This model may account for the missing heritability in various disease pathways since the interaction of genes with quantitative effects can be substantial within a large network of causal genes.

Neuroscience, behavior, and sensory perception

The third session opened with a plenary lecture by Catherine Dulac (Howard Hughes Medical Institute at Harvard University) entitled “Sex Battles in the Brain.” Dr. Dulac utilized a large-scale, RNA deep-sequencing method as a means to investigate the mouse brain “imprintome.” Differential maternal or paternal transcript levels (determined by SNPs in mRNA between reciprocal F1 hybrids of CAST/EiJ and C57BL/6NJ) identified over 1700 putative imprinted loci. Furthermore, by comparing the differences in parental expression levels between developing and adult brain tissue types, Dr. Dulac’s experiments reveal a complex and dynamic imprintome that is modulated both spatially and temporally with sex-specific and isoform-specific effects. Ardem Patapoutian (The Scripps Research Institute) gave the subsequent plenary lecture concerning thermal transient receptor potential ion channels (thermoTRPs) that are required for temperature sensation. By using a high-throughput forward genetic screen, Dr. Patapoutian and his group aim to unravel the fundamental activation process of thermoTRPs. The talk centered on two TRPs, TRPM8 and TRPA1, which are thermo- and mechano-sensors, respectively, but share a common cold-insensitivity phenotype when knocked out.

Karen P. Steel from the Wellcome Trust Sanger Institute offered a summary of a screen for new mouse deafness mutations. To date, over 425 mutants have been produced from KOMP/EUCOMM ES cells, displaying a wide range of defects. In addition to new mutations of known genes involved in deafness, Dr. Steel commented on three newly
identified genes—Lrig1, Meph1, and Spns2—that show moderate to severe deafness phenotypes. Using an ENU-induced screening methodology, Deborah Cabin (McLaughlin Research Institute) spoke about a genetic approach to determine the normal function of α-synuclein, a protein that is mutated in Parkinson’s disease patients. John Bermingham (McLaughlin Research Institute) presented his findings on LGH4 secreted protein and its role in peripheral nerve development. Wayne Frankel (The Jackson Laboratory) reported that inbred mice strains show a wide range of spike-wave discharges, a diagnostic for absence epilepsy, even among C3H mouse substrains. This study includes performing intra-C3H and interstrain crosses to map genetic modifiers orchestrating the phenotypic variation associated with absence epilepsy in hopes of one day providing insight into a complex human disease. Lastly, Darren Logan (The Scripps Research Institute) gave a spectacular presentation, for which he was awarded the Verne Chapman Young Scientist Award, on major urinary proteins that encompass a large gene family and influence intra/interspecies behavior.

Modeling disease I: metabolism and physiology

A lecture by Ron Evans (The Salk Institute) opened this session with an interesting discussion on the physiological coupling of metabolic and circadian rhythms. The central circadian clock associates light with morning and, together with feeding and activity, this activates nuclear receptors, AMP-activated protein kinase (AMPK), and the peripheral clocks that drive behavioral and physiological rhythms. AMPK activation shifts periodicity by altering the circadian rhythm, and such disruptions have previously been associated with obesity, metabolic disease, high blood pressure, and heart disease. Dr. Evans reports that AMPK stimulation increases activity and endurance in mice as a result of increased oxidative stress in the mitochondria. This highlights the idea that AMPK mimetics may replace actual exercise, although further studies are necessary to determine whether these findings translate to humans.

The session concluded with talks on mutant mouse models of cataract formation. Ryan Liegel (Medical College of Wisconsin) reported on the blind sterile 2 (bs2) mutant mouse, a model for human Rhizomelic chondrodysplasia punctata type 3 that is characterized by autosomal recessive congenital bilateral nuclear cataracts and male-specific infertility. Linkage analysis and fine mapping identified Agps, and subsequent sequencing indicated that the mutation occurs within the splice-donor site and results in the formation of two alternatively spliced transcripts. The lens opacity 13 (lop13) mutant mouse, which was discussed by Kate Merath (Medical College of Wisconsin), possesses a novel congenital autosomal recessive mutation that results in nuclear cataracts and localized skin fissures. A single-base-pair substitution was identified within the regulatory region of Srebp2, a cholesterol biosynthesis gene that contributes to the maintenance of lens integrity.

Modeling disease II: development

Carlos Perez from the University of Texas began the session with a presentation on the discovery of two hypomorphic alleles of the mouse Ass1 gene that models Citrullinemia type 1 (CTLN1), a disorder with a severe neurological phenotype. The bar and fold mutant alleles interact to produce a range of phenotypes, from severe (bar/bar) to mild (bar/foil), which enabled the identification of candidate genes in a 3-Mb region of chromosome 2. Cerebellar granule cell migration is disrupted in bar/bar mice and is proposed to be the cause of defective brain development. Jiri Forejt (Institute of Molecular Genetics, Prague) discussed the implication of Dobzhansky-Muller incompatibilities in M. musculus/M. domesticus hybrid sterility. He proposed that there are at least three genes that contribute to the hybrid sterility of (C57BL/6 × PWD/Ph)F1 mice. These crosses, along with chromosome substitution strains, were used to identify the Predm9 and Hstx2 genes, which interact to trigger the pachytene checkpoint, and an approximately 4-Mb region on M. musculus chromosome 5 that causes dysregulated expression of Bgalp1 on M. domesticus chromosome 3. Two ENU screens revealed novel genes involved in mammalian forebrain development and suppression of Mecp2. David Beier (Brigham and Women’s Hospital/Harvard Medical School) found seven mutations affecting central nervous system development, four of which have been identified by positional cloning. The most severe of these mutants is rudolph, which has both skeletal and brain defects. Defects in cholesterol biosynthesis and decreased cellular response to Shh are implicated in this phenotype, suggesting the necessity of embryonic cholesterol metabolism in CNS development. Monica Justice (Baylor College of Medicine) reported on a study to identify genetic suppressors of the mutation causing Rett Syndrome. Over 1400 male mice were screened, and four lines were found to carry suppressor genes. The most promising was mapped to chromosome 16, and 31 candidate genes have been identified. Amy Losise from Purdue University reported on a study to characterize noncoding RNAs within the Odz4 locus and to identify highly conserved ncRNAs that direct alternative splicing. Takanori Amano (National Institute of Genetics, Japan) discussed findings that suggest that a long-range enhancer, MFCS1, controls chromosomal dynamics at the Shh locus.
Development and neoplasia

The session began with a plenary lecture from Terry Magnuson (University of North Carolina) on how paternal X-inactivation occurs during early embryogenesis and the subsequent reactivation of the paternal X genes during midstage inner cell mass (ICM) development. Contrary to the current model, Dr. Magnuson presented experimental evidence that paternal X-reactivation occurs even in the presence of large noncoding RNA, Xist, and the repressive histone mark H3K27me3. Inder Verma (The Salk Institute) spoke about a siRNA/shRNA screen to unravel the molecular mechanisms behind the NF-κB inflammation pathway. More specifically, the presentation focused on Toll-like receptor 4 and its role in inflammation and macrophage-mediated insulin resistance, as observed when Tlr4 knockout mice fed a high-fat diet showed increased sensitivity to insulin in comparison with Tlr4 knockout mice fed a normal diet. Dr. Verma concluded with a discussion of future directions that will investigate the IKBKB regulatory kinase that modulates the stability of TRP53 to establish a link between inflammation and apoptosis.

Joe Nadeau (Case Western) presented a fascinating study that suggested that testicular germ cell tumors (TGCT) are caused by a transgenerational genetic interaction. During development, primordial germ cells interact with parental TGCT modifiers and can affect progeny cancer susceptibility. Dr. Nadeau reported that the Apobec1 modifier decreases TGCT susceptibility for paternal lineages but has no effect on paternal lineage as shown by survivability between reciprocal mouse crosses. A brief synopsis of recombination-induced mutation 4 (Rim4), a mouse model for partial trisomy 4q-ter syndrome in humans, was given by Masaru Tamura from the National Institute of Genetics in Japan. Bruce Herron (Wadsworth Center) described a global gene expression profiling method employed to elucidate the role of Sfn and Chuk, two genes that, when mutated, phenocopy one another during skin development. Teresa Gunn from Cornell University introduced the first identified extracellular matrix mutant, dark-like (dal), which is characterized by cardiac hypertrophy. This session ended with a summary of the Mouse Genetics Programme at the Sanger Institute by Ramiro Ramirez-Solis. A total of 4739 genes have been targeted in ES cells over the past several years. More than 300 mouse lines have been generated with over 220 in the phenotyping pipeline.

Population genetics, comparative genomics, and evolution

An interesting presentation on the origin and evolution of sex was given by Jennifer Graves (The Australian National University). Evolutionarily speaking, the battle of the sexes began less than 166 million years ago, as manifested by the emergence of the Y chromosome. Comparative sequence analysis of sex chromosomes in mammals and nonmammals strongly suggests that XY is a more recently derived system for determining sex. Gender in birds and reptiles is determined by sex chromosomes ZW. The XY of mammalian monotremes surprisingly maps to the ZW of birds rather than to the XY of other mammals. Similar to what is seen with birds and reptiles, the XY in monotremes are autosomal. This suggests that the same genome evolved to have various functions in different species. It is therefore likely that genes responsible for direct evolution are also responsible for sexual determination in mammals.

Scientific approaches to animal husbandry

Kent Lloyd (University of California Davis) opened this session with a plenary talk about archiving and distributing mutant mouse strains. Over 30,000 mutant mouse lines are available through The Mutant Mouse Regional Resource Centers (MMRRC), including some of the major collections of mouse mutants and embryonic stem cell lines. The KOMP repository is a collaborative effort between CHORI and UC Davis to maintain and distribute knockout mice. Dr. Lloyd also discussed the availability of resources to aid in mutant mouse studies, including Gene Cloud (http://www.genecloud.org), which uses existing data to identify interactions between genes of interest. The International Mouse Strain Resource (IMSR) allows users to determine where a mouse of interest can be found (http://www.gotmice.org), how to obtain it (http://www.getmice.org), and how to design it if it is unavailable (http://www.makemymouse.org). The National Academies’ “Guidelines for Scientific Publications Involving Animal Studies” and the Center for Genomic Pathology continue to be valuable resources for training and experimental procedures.

David Einhorn (The Jackson Laboratory) explained patent laws, which were intended to protect ownership of novel therapeutic agents, not to limit access to genetic mouse models, reagents, or similar resources that could otherwise be made available through repositories. Patents, commercialization, and licensing should not obstruct scientific progress, and efforts are underway to remedy this issue. The 2009 CASIMIR (Coordination and Sustainability of International Mouse Informatics Resources) Rome Agenda aims to drive global awareness and discussion on this matter, pushing for international regulation and access, as well as discouraging licensing and any other practices that limit data sharing and access to resources.
The Genome 10K Community of Scientists is poised to undertake the biggest scientific study of molecular evolution ever proposed: sequencing the whole genomes of 10,000 representative vertebrates, covering a wide range of evolutionarily divergent species. Oliver Ryder, from the San Diego Zoo’s Institute for Conservation Research, outlined the critical steps involved in undertaking such a bold yet feasible endeavor. The project is presently in phase 1, which entails collection of tissue and DNA samples from approximately 17,000 species, including mammals, birds, amphibians, and fishes. The wealth of information garnered from this feat will facilitate conservation efforts and lead to a much better understanding of the mechanisms underlying adaptation and animal biology.

A wonderful tour of the spectacular San Diego Zoo prior to the closing ceremony reminded us of both the great diversity and inter-relatedness among species present in our world. It was a perfect ending to a meeting filled with great scientific inquiries and discoveries.

Acknowledgments The authors thank Lisa Tarantino and Fernando Pardo-Manuel de Villena for their helpful and detailed feedback on this article. Many thanks to this year’s organizer, Dr. Bruce Beutler, and to the IMGS secretariat committee, Karen Steel (President), David Threadgill (President-Elect), Maja Bucan (Past President), Yoichi Gondo, Fuad Iraqi, Kent Hunter, David Beier, Ian Jackson, and Nancy Jenkins. We also thank Darla Miller and Ginger Shaw for their outstanding work organizing the conference. The meeting was supported in part by financial contributions from Applied Biosystems, aTyr Pharma, Biolegend, Springer, UCSD, The Ellison Medical Foundation, and Vical. Sponsors for this year’s presentation awards were Genetics Society of America, genesis, Genome Research, Genomics, Nature, Nature Genetics, Nature Reviews Genetics, and Mammalian Genome. Student scholarships were funded by 2R13HG002394 from the following Institutional Centers at NIH: NHGRI, NIMH, NIDCD, NIAID, NIEHS, and NINDS and from Mouse Genome.

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