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Meeting report of the 26th International Mammalian Genome Conference

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Introduction

A diverse group of geneticists, clinicians, and bioinformaticians converged on sunny St. Pete Beach, Florida, October 21–24, 2012, for the 26th International Mammalian Genome Conference (IMGC). Organized by Michelle Southard-Smith (Vanderbilt University) and Teresa Gunn (McLaughlin Research Institute) with help from the IMGS Secretariat, the conference attracted 148 participants from 14 countries. Investigators, postdoctoral fellows, and graduate students returned to the site of the popular 11th IMGC (1997) to share exciting advances in mammalian genetics and genomics research, findings that underscored the continued and future importance of mammalian genetic models to human genetics and disease research. Multiple presenters highlighted how powerful large-scale mapping and phenotyping resources, disease models, and strain resequencing projects are fundamentally altering our understanding of gene regulation and the genetic factors underlying complex disease. The plenary presentations especially provided insight on how these new technologies enable us to expand the scope of our research questions and the mammalian systems we use to answer them. At the same time, the Verne Chapman Lecture provided valuable historical perspective on the role of mammalian models over the last half-century, and predicted the future opportunities and challenges facing geneticists in the next 50 years. Abstracts from the meeting are available at www.imgs.org, and online databases and resources presented at the meeting are listed in Table 1.

The power of genetics

The power of High Throughput Sequencing (HTS) was on full display at this year's conference. Multiple groups successfully applied exome or whole-genome sequencing to identify spontaneous and ENU-induced mutations, while others utilized deep RNA sequencing in genetically diverse mice to add new insights to transcriptional control. In an intriguing plenary presentation, Greg Barsh (O-8, HudsonAlpha Institute for Biotechnology and Stanford University) illustrated how HTS technologies were opening up new opportunities to study classic genetic questions such as coat color patterning in nonmodel organisms like zebra and cheetahs. Along the same vein in a later plenary presentation, Vadim Gladyshev showed how HTS technologies enabled his group to identify a set of unique genome features and molecular adaptations that likely underlie the extremely long life span of the strange-looking but scientifically adorable naked mole rat. Indeed, it was evident throughout the conference that HTS is pervading all areas of mammalian genetics research, and as costs continue to fall, deep sequencing data will likely become the norm rather than exception. With this wealth of information comes complexity and potential analytical traps, and

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Table 1 Internet resources and databases presented at the 26th IMGC

Resource	Web address	Brief description (associated abstract numbers)
Mouse genome sequence, functional annotation data		
Genome reference consortium	http://genomereference.org	Mouse genome reference assembly (O-2, P-3)
Mouse genomes project	http://sanger.ac.uk/resources/mouse/genomes/	Full genome sequences for 17 inbred strains (O-1)
Mouse genome informatics (MGI)	http://informatics.jax.org	Curated mouse gene and phenotype database (P-19, P-36)
Fantom5 project	http://fantom.gsc.riken.jp/zenbu	Catalog of transcription start sites (TSS) for several model organisms (O-4)
CrePortal	http://creportal.org	Expression and activity data for Cre transgenes and knock-in alleles (O-15)
Mouse tumor biology (MTB) database	http://tumor.informatics.jax.org	Information on tumors, susceptibility, pathology in mice; includes patient derived xenograft (PDX) data; interactive QTL viewer (P-9, P-10)
Mutant mouse resources and data		
International mouse phenotyping consortium (IMPC)	http://mousephenotype.org	Systematic phenotype data available for hundreds of mutant mouse lines (O-31, P-5, P-6, P-19, P-46)
Sanger mouse genetics project	http://sanger.ac.uk/mouseportal/	Portal to Sanger resources, including vectors, targeted and gene-trap cell and mouse lines, phenotype data (O-29, P-55, P-56, SO-9)
Mouse mutant resource (MMR)	http://mousemutant.jax.org	Spontaneous mouse mutants available for study (O-5, O-6, O-7)
Knockout mouse project (KOMP and KOMP2)	http://komp.org/	Resources for generation and distribution of knockout mice, ESC lines, and vectors (P-40)
International mouse strain resource (IMSR)	http://findmice.org	Searchable online database of mouse strains, stocks, and mutant ES cell lines available worldwide (P-52)
European mouse mutant archive (EMMA)	http://emmanet.org	Mutant mouse repository and free mutant line archiving services (P-25, P-51)
International mouse knockout consortium (IMKC)	http://knockoutmouse.org	Development of knockout mice that cover protein-coding genes and microRNA (P-46)
Rare and orphan disease center	http://research.jax.org/rodc	Collaborative effort to make mouse models of disease commercially available (P-8)
Collaborative cross and diversity outbred mouse resources		
Collaborative cross (CC): UNC compgen tool suite	http://csbio.unc.edu/CCstatus/	Development status of CC strains; computational tools for analysis of CC and inbred strains (SO-8, SO-10, P-39, P-14, P-37)
Diversity outbred (DO) stock: data and analytical tools	http://do.jax.org	Repository for DO datasets and analytical tools (O-3, O-10, O-32, O-46)

attendees were cautioned against taking a "one reference aligns all" strategy when applying HTS methodologies to genetically heterogeneous mouse and human populations. As HTS technologies mature and human genome-wide association studies (GWAS) expand, it is clear that validation studies in nonhuman animal models, most likely the laboratory mouse, will be a critical component of gene discovery and drug validation pipelines. While new large-

scale resources and genomic technologies now make in-depth genetic studies possible for almost any species, the mouse arguably remains the most powerful mammalian model system.

Bioinformatics Workshop

Large-scale phenotype and genotype resources continue to increase in size and complexity, and it is clear that the successful integration of high-dimensional data will be essential to understanding disease susceptibility, mechanism, and prognosis. Therefore, the next generation of geneticists will need a new set of quantitative and computational competencies. An opportunity to gain these skills was provided by the optional Bioinformatics Workshop that once again preceded the main conference. Since 2003, instructors have trained attendees on how to navigate established and new genomic databases to find data pertinent to one's research. The conference organizers wish to extend their gratitude to Deanna Church, who steps down after 10 years serving as coinstructor with Carol Bult. Dr. Church has passed the torch to Laurens Wilming, who will work with Dr. Bult to ensure that next year's workshop in Salamanca will be as informative as the past 10.

Training geneticists for the post-genomic age

As in previous years, conference organizers placed a strong emphasis on the development and mentorship of trainees. Numerous travel scholarships were awarded, and graduate students and postdoctoral fellows were given many opportunities throughout the conference to share their research and interact with established investigators. The mentoring dinner gave students and postdoctoral fellows an opportunity to converse one-on-one with established researchers. The informal setting encouraged trainees to ask mentors about their research, career choices, and experiences that led them to become successful scientists.

Following the Bioinformatics Workshop, the Student Satellite Symposium provided an opportunity for trainees to share their research and receive valuable feedback from their peers and established investigators. Twenty graduate students and postdoctoral fellows gave outstanding talks on a wide variety of research topics ranging from infection causing dental bone loss to generating inbred pig lines. The student talks were scored by members of the IMGS Secretariat, and three students—Joy Gary, John Calaway, and Melissa Musser—were selected to present their work at the main conference.

Catherine Welsh (SO-10) described her work to generate tools and resources that provide users with haplotype reconstructions and inbreeding coefficients for mice from the Collaborative Cross (CC). Several other talks reported on studies incorporating CC mice, including Wenqi Pan's work on evaluating sperm quality across founder strains (SO-13) and Aysar Nashef's study on susceptibility to alveolar bone loss during infection (SO-19). Chen-Ping Fu (SO-8) discussed the development of an online genetic quality control resource for determining the strain composition of mutant mouse strains. Morag Lewis (SO-9) described her work using array competitive genomic hybridization (array CGH) and whole-exome sequencing to identify spontaneous mutations in the Sanger Institute's Mouse Genetics Project (MGP). Although the MGP focuses on creating knockout allele mice, some mice have pathological phenotypes that do not segregate with the knockout allele. These phenotypes are caused by spontaneous mutations that arose in the embryonic stem (ES) cell lines used for gene targeting, and the mutant mice represent novel disease models.

Other students and postdoctoral fellows have utilized the mouse as a human disease model. Christine Rubinshteyn (S-O3) presented work identifying the *Oprd1* (opioid-receptor, delta 1) as a gene influencing alcohol metabolism. $Apc^{min/+}$ mice serve as a model for colon cancer and Heather Mentrup (SO-2) examined how differential ITCH expression in these and other mouse models affects gut epithelium lineage proportions and proliferation. Min-Hyung Lee (SO-11) presented computational and molecular work identifying *CDCA7L* as a male-specific genetic modifier of astrocytoma tumorigenesis. The MTOR pathway has been implicated in several human diseases, including tuberous sclerosis and various cancers such as B-cell-derived multiple myeloma. Joy Gary (SO-6) described her research on the $Mtor^{m1.1Lgm/m1.1Lgm}$ KI mouse model of B-cell cancer. Several arrays and assays on various hematopoietic cell types revealed differential expression of mRNAs, microRNAs, and proteins. Analysis of these findings is further defining the role of MTOR in B-cell carcinogenesis. Diabetes is a growing healthcare concern, and research on mouse models is elucidating the mechanisms behind the disease. Work presented by Davide Cavanna (SO-7) on the *Dll1-b* KO mouse suggests that the notch signaling pathway plays a role in adult pancreas endocrine function, and Daniel Gradinger (SO-15) is utilizing the $Pax6^{leca2}$ mutant to elucidate PAX6's role in pancreatic development and maintenance. While the majority of talks focused on mouse models, Rong Zeng (SO-17) introduced the Banna Mini-pig Inbred Line (BMI). Over 30 inbred substrains with a variety of fascinating phenotypes have been generated and are ready to be studied as human disease models.

Several presentations in the Student Symposium focused on the mouse as a model for understanding development

and human developmental disorders. Joshua Blazek's work (SO-4) suggests that *Dyrk1a* overexpression could account for the appendicular skeleton phenotype of the Ts65Dn mouse model of Trisomy21 (Down syndrome), and he presented exciting data that epigallochatchin gallate (a green tea derivative) can partially rescue the phenotype. Melissa Musser (SO-5) described deficiencies in the enteric nervous system in the $Sox10^{Dom/+}$ model of Hirschsprung disease. These deficiencies could explain the intestinal motility defects and inflammation that many Hirschsprung patients suffer. Elaine Ritter's (SO-16) talk also focused on neural development, but it looked at the role of serotonin in neurons innervating the bladder. Little is known about neural development in the lower urinary tract, including temporal and spatial expression of genes important to neural crest migration, proliferation, and differentiation. Also pivotal to normal embryonic development is the ability of the mother to adapt to pregnancy. Jasmin Kristianto (SO-12) detailed her research on HcB8 mice and how an inability of the mothers' cardiovascular systems to adjust to pregnancy could account for reduced reproductive success. On a more molecular level, Elizabeth Adams (SO-1) characterized numerous mouse models to define the role of SEC24 proteins in transmembrane trafficking, and Petr Flachs (SO-18) analyzed the effect of altered copy number of the *Prdm9* gene on meiotic progress and fertility. Meng-Shin Shiao (SO-20) used mRNA-Seq to determine expression levels of genes involved in olfaction. Her data suggest that odor detection differs between sexes and that the main olfactory system could play a role in pheromone detection. John Calaway's work (SO-14) on X-chromosome inactivation demonstrates that certain haplotypes of the X-chromosome controlling element (*Xce*) locus skew the proportion of specific X-chromosomes that get inactivated.

Two scheduled sessions gave 75 poster presenters the opportunity to share and discuss their work with other meeting participants. These sessions also permitted attendees of the main sessions to hear and comment on work presented at the Student Symposium in an informal and interactive setting. To add a bit of fun to the last poster session, delegates were encouraged to dress for the occasion in Halloween costumes. Those brave enough to don their costumes (or a rubber mouse nose dating back to the 13th IMGC) were able to fortify their bravery with liquid courage in the form of extra drink coupons. Abstracts from poster presentations may be found at www.imgs.org. At the closing of the conference, attendees enjoyed a spectacular sunset and an informal beachside banquet. Over drinks and dessert, presentations were made to thank outgoing members of the Secretariat and the Nominations and Elections Committee for their service to the IMGS, and several students and postdoctoral fellows were awarded prizes for their outstanding oral and poster presentations (Table 2).

Large-scale resources: development and applications

The main conference began with updates on the Mouse Genomes Project and mouse genome reference assembly from Thomas Keane (Wellcome Trust Sanger Institute, O-1) and Deanna Church (National Center for Biotechnology Information, on behalf of the Genome Reference Consortium, O-2), respectively. Church reported on the release of an update to the mouse genome reference assembly, GRCm38 (http://genomereference.org). The latest assembly (GRCm38), compared to the previous one (NCBIm37), has added 83 Mb of sequence, closed 200 gaps, corrected several misassembled regions, and has significantly improved and expanded the Y Chromosome assembly (chromosome length increased from 15 Mb to 91+Mb). In a complementary project, The Mouse Genomes Project recently completed resequencing 17 common laboratory and wild-derived inbred strains to 40× coverage. In doing so, Keane and colleagues identified 56.7 million (M) unique SNPs, 8.8M unique indels, and 0.28M structural variants segregating among the sequenced strains (http://www.sanger.ac.uk/resources/mouse/genomes/). Later in the same session, Jin Szatkiewicz (University of North Carolina, O-6) presented genome-wide Copy Number Variation (CNV) predictions based on high-density genotyping array data in 162 strains of mice. The importance of an accurate mouse reference assembly and complete understanding of strain variation can hardly be overstated, especially as more groups apply HTS technologies (e.g., exome sequencing, RNA-Seq) to mutation discovery in nonreference strains or QTL mapping in genetically diverse reference panels like the CC and outbred populations like the Diversity Outcross (DO) heterogeneous stock.

Many presentations highlighted both the power and the potential pitfalls in large "Seq" datasets from genetically diverse populations. For example, Steven Munger (O-3) and Gary Churchill (O-10) from The Jackson Laboratory showed that liver RNA-Seq data combined with genetic mapping in DO mice could reveal new layers of information about gene regulation, including QTLs controlling isoform-specific expression (Munger) and RNA editing (Churchill). However, their enthusiasm was tempered by data showing that misalignment of SNP/indel-containing short reads could cause spurious eQTLs; highly homologous gene families and pseudogenes were most sensitive to misalignment from strain variation. That said, accurate estimates of gene expression are possible from RNA-Seq performed on highly conserved gene families, as evidenced by the heroic analysis of the 24,000 olfactory and vomeronasal receptor alleles in the 17 sequenced mouse strains from Darren Logan's group (Sanger Institute, O-12).

The DO heterogeneous stock and CC recombinant inbred strain panels continue to produce interesting results.

For example, three-quarters of incipient CC lines have failed to produce offspring at some point during the inbreeding process. David Aylor (University of North Carolina, O-11) analyzed the genetic and physiological defects underlying the reproductive incompatibilities that are causing extinction in 358 pre-CC lines. Dr. Aylor discovered that male, not female, infertility was the predominant defect responsible for reproductive failure, and based on high-density genotypes of the extinct lines, he and his colleagues mapped novel loci affecting fertility, testis weight, sperm count, and sperm quality (see also Wengi Pan SO-13/P-45). Dan Gatti (The Jackson Laboratory, O-46) presented perhaps the clearest illustration of an advantage of mapping with a genetic population derived from many diverse strains for gene discovery. As part of a project led by Jef French at NIEHS, Gatti mapped a private CAST allele on Chr 10 that protected DO mice from benzene-induced DNA damage, as measured by the proportion of micronucleated reticulocytes in bone marrow and blood. Moreover, by interrogating eQTL data in this

Table 2 IMGC award recipients

Awardee	Institute	Presentation title (abstract number)	Award/sponsor
Oral presentations			
Sarah Carpanini	MRC Human Genetics Unit, Edinburgh, UK	A novel *Rab18* mouse model of Warburg Micro Syndrome (O-26)	Verne M. Chapman Young Scientist Award, IMGC
David Aylor	University of North Carolina, USA	Genetic reproductive incompatibility in the mouse Collaborative Cross (O-11)	Nature
John Calaway	University of North Carolina, USA	High incidence of skewed X inactivation in laboratory mouse is a byproduct of domestication and speciation (SO-14/P-14)	Genetics Society of America
Joy Gary	CCR, NCI, NIH, and Michigan State University, USA	Characterization of an allelic variant of the mechanistic target of rapamycin (Mtor), a susceptibility allele for plasmacytoma formation in BALB/cAnPt mice (SO-6/P-22)	Nature Genetics
Poster presentations			
Davide Cavanna	Institute of Experimental Genetics, Neuherberg, Germany	Analysis of delta-like 1 (DLL1) in adult murine islets (SO-7/P-15)	Genetics Research
Petr Flachs	Institute of Molecular Genetics AS CR, Prague, Czech Republic	Incompatibilities of the *Prdm9* (*Hst1*) gene in mouse hybrid sterility (SO-18/P-20)	genesis
Daniel Gradinger	Institute of Experimental Genetics, Neuherberg, Germany	Molecular and histological comparison of pancreata from adult $Pax6^{leca2}$ mutant mice of different ages (SO-15/P-24)	Mammalian Genome
Min-Hyung Lee	NCI, Frederick, MD, USA	The potential male-specific oncogenic function of *CDCA7L* in astrocytoma (SO-11/P-34)	Nature Reviews Genetics
Morag Lewis	Wellcome Trust Sanger Institute, Cambridge, UK	Collateral damage: spontaneous mutations from a targeted knockout programme (SO-9/P-35)	genesis
Heather Mentrup	University of South Carolina, USA	Characterizing the role of the ubiquitin ligase Itch in C57BL/6J-$Apc^{min/+}$/J gut homeostasis and intestinal tumorigenesis (SO-2/P-38)	Genomics
Wenqi Pan	University of North Carolina, USA	Variation in sperm quality in Collaborative Cross founder strains and extinct lines (SO-13/P-45)	Genome Research
Christine Rubinshteyn	North Carolina State University, USA	Functional analysis of the opioid receptor, delta on alcohol metabolism (SO-3/P-54)	genesis
Meng-Shin Shiao	Academia Sinica, Taipei, Taiwan	Transcriptomes of mouse olfactory epithelium reveal sexual differences in odorant detection (SO-20/P-58)	genesis
Sari Suzuki	Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan	Multiple QTLs associated with age-related hearing loss in DBA/2J mice (P-60)	genesis
Kei Watanabe	University of Tsukuba, Tsukuba, Japan	A 5-bp insertion in insertion in *Mip* gene causes recessive congenital cataract in a Kyoto fancy rat stock, *kfrs44* (P-67)	genesis
Nomenclature excellence award			
Elaine Ritter	Vanderbilt University, USA	Serotonin signaling in neural crest-derived progenitors in the lower urinary tract (SO-16/P-53)	Nomenclature committee

region for genes with similar CAST-specific eQTLs, Gatti showed that protection from DNA damage was most likely conveyed by genetic variation in the sulfotransferase *Sult3a1* that caused it to be highly expressed only in CAST. In a later talk, Karen Svenson (The Jackson Laboratory, O-32) showed that not all traits mapped in the DO have yielded clear genetic answers, and she pointed out the need for new statistical models to fully exploit the structure of the DO. With a similar goal but different approach, Tim Wiltshire (University of North Carolina, O-30) showed that genetic modifiers of drug or toxicant response could be mapped in a petri dish rather than a mouse cage. Wiltshire presented GWAS results from a screen of mouse embryonic fibroblasts (MEFs) derived from 32 inbred strains that were exposed to 69 different drugs and environmental toxicants, and identified a 1.2-Mb locus on Chr X that was associated with variable cytotoxic responses to rotenone.

Large-scale genome functional characterization and mutant phenotyping projects were well represented at this year's meeting and promise to provide copious amounts of useful data to the research community for the foreseeable future. Alistair Forrest (Riken Yokohama Institute, O-4) summarized key findings from the FANTOM5 Project. Specifically, the group used Cap Analysis of Gene Expression (CAGE), developed at Riken, to identify more than 180,000 reliable Transcription Start Sites (TSSs) from a large panel of primary cells, cancer sublines, and whole tissues. This detailed atlas of gene expression will inform the characterization of tissue/cell-type-specific promoters, which will aid in the design of conditional Cre-driver lines. To that end, Stephen Murray (doing his best Janan Eppig impersonation, O-15) described the CrePortal (www.creportal.org), a freely accessible site that catalogs construct and expression patterns, including spatial and temporal expression specificity data, for a large and growing number of Cre-driver lines.

In addition, findings from a number of high-throughput mutant mouse phenotyping projects were summarized. Jacqueline White (Sanger Institute, O-29) presented the phenotyping pipeline employed by the Sanger Mouse Genetics Project, which has thus far generated over 600 mouse knockout lines and phenotyped each line at over 280 parameters. This large-scale phenotyping project has uncovered previously unknown roles for many genes, and White described examples of mutations that caused metabolic abnormalities (*Kptn*, *Dusp3*), skeletal changes (*Zc3hc1*), hematological alterations (*Crlf3*), and developmental defects (*Psat1*). All data are freely available on the Sanger Mouse Portal (http://www.sanger.ac.uk/mouseportal/). Martin Hrabé de Angelis (Technische Universität München, O-31) described the progress made at the German Mouse Clinic (GMC), which has so far phenotyped over 290 mutant mouse lines as part of the International Mouse Phenotyping Consortium (IMPC, www.mousephenotype.org). Indeed, systemic phenotyping has enabled the detection of unexpected phenotypes that reveal novel functions for genes already implicated in the development of human disease. As an example, de Angelis showed that *Nbea* (Neurobeachin), a known regulator of synaptic protein targeting that is associated with autism, also functions in mice as a regulator of body fat mass and feeding behavior.

Aging and human disease modeling

The Ellison Medical Foundation continued their strong support for the IMGC, sponsoring two excellent plenary presentations on aging by Vadim Gladyshev (Brigham and Women's Hospital, O-33) and Richard Miller (University of Michigan, O-34). Gladyshev has taken a comparative genomics approach to study aging by sequencing and analyzing the genomes of mammals whose life spans deviate significantly from expectations given their size. The naked mole rat is the Methuselah of the rodent world: despite being the size of a mouse, it can live for over 30 years. Gladyshev's group utilized HTS methods to analyze the naked mole rat genome and transcriptome and identified unique molecular features consistent with the mole rat's resistance to cancer, insensitivity to hypoxia, and surprising tolerance of extreme fluctuations in internal body temperature (poikilothermy). Miller presented new results from the NIA Intervention Testing Program, a multi-institutional collaboration that tests drugs for anti-aging effects in mice. Expanding upon earlier reports on the effects of dietary addition of rapamycin, Miller described research showing that rapamycin does indeed extend life span in mice, but the mode of action by which it confers its anti-aging effects is unclear. Miller stressed that rapamycin was not a silver bullet anti-aging cure, pointing out side effects that include cataracts and testicular degeneration. Although the anti-aging effects of rapamycin were greater in females, Miller highlighted two other agents, acarbose and 17-α-estradiol, that may have much stronger anti-aging effects in male mice. These data suggest an intriguing possibility that the genetic pathways and cellular processes that contribute most significantly to life span may differ between the sexes.

The genetic basis of age-related and adult-onset diseases was the topic of several presentations. Paul Potter (MRC Harwell, O-35) described a large-scale G3 recessive screen to investigate the interaction between genetic variation and the pleiotropic effects of aging. The goals of the screen are to identify new genes and pathways involved in age-related diseases as well as models for preclinical assessment of new therapies. Potter presented examples of mutations

related to cardiovascular disease, bone disease, and impaired renal and liver function. David Buchner (University of Michigan, O-36) described the complex genetic architecture of diet-induced obesity in a multiscale consomic and congenic mapping study. Surprisingly, dissection of obesity-associated chromosomes with congenics, subcongenics, and even down to sub-subcongenics, has revealed that potentially hundreds of QTLs with large effects regulate obesity and glucose homeostasis, a phenomenon Buchner and Joseph Nadeau refer to as "fractal genetics." The poster sessions provided further opportunities to learn about ongoing studies to identify and study genes that contribute to the regulation of body weight (Fuad Iraqi, P-3; Gregory Carter, P-14; Simon Horvat, P-26; and David West, P-70), type-2 diabetes risk (Michelle Goldsworthy, O-23 and Fuad Iraqi, P-27), stroke risk (Han Kyu Lee, P-33), hearing loss (Sari Suzuki, P-60), cataracts (Kei Watanabe, P-67), and lupus (Dana Tabor, P-62).

Many investigators presented their work utilizing mouse models to better understand cancer etiology. Several posters described studies to identify modifiers of colon cancer in the adenomatous polyposis coli (Apc^{min}) mouse (Linda Siracusa, P-59; Karla Otterpohl, P-44; Fuad Iraqi, P-29; Heather Mentrup, P-38). Karylene Reilly (National Cancer Institute, O-43) presented work on neurofibromatosis type 1, a familial cancer. Interestingly, patients with neurofibromatosis type 1 may go on to develop several different tumor types, including astrocytomas. Reilly and her colleagues have identified several genetic modifiers in a neurofibromatosis mouse model that are specific to tumor type and host sex, including a male-specific modifier for astrocytomas. They are using mouse and human data to better power their studies and determine the specific genes involved. Nigel Crawford (National Human Genome Research Institute, O-37) showed in a series of F1 crosses that tumor growth rates and metastasis in a mouse model of aggressive neuroendocrine prostate cancer [C57BL/6-Tg (TRAMP) 8247Ng/J] were modulated by genetic variation segregating among the CC founder strains. Crawford extended this F1 analysis to mapping intercrosses and presented preliminary data suggesting that regions on distal Chr 6 and proximal Chr 12 are associated with tumor growth in the TRAMP×NOD/ShiLtJ intercross. Kent Hunter (National Cancer Institute, O-38) presented his group's multipronged genetic and expression analysis of metastasis-susceptibility genes in human breast cancer patients. From multiple mapping crosses, they have identified a number of genes with expression signatures that predict metastatic outcome in estrogen receptor (ER)-positive breast cancer and that act in a tumor autonomous manner. Interestingly, SNP data from human breast cancer patients indicate that these genes may function more broadly but switch from a protective to a risk allele depending on tumor subtype.

The increasing feasibility of genome-wide and targeted HTS approaches has led to a boom in mutation discovery. Laura Reinholdt (The Jackson Laboratory, O-5), Kart Tomberg (University of Michigan, O-13), and Jabier Gallego (Brigham and Women's Hospital, O-14) described analytical pipelines for pruning whole-genome or exome sequences to identify and prioritize candidate variants. Morag Lewis (Sanger Institute, SO-9/P-35), Randall Westrick (University of Michigan, O-16), Stephen Murray (The Jackson Laboratory, O-18), Seungshin Ha (Brigham and Women's Hospital, O-19), Paul Potter (MRC Harwell, O-35), and Miriam Meisler (University of Michigan, O-39) described studies using these or similar pipelines to identify the causative variant in spontaneous/ENU-induced mouse mutants or human patients. David Bergstrom (The Jackson Laboratory, O-7) and Laura Reinholdt (O-5) described how these new HTS mapping approaches were being applied to The Jackson Laboratory's Mouse Mutant Resource (http://mousemutant.jax.org). Several poster presentations re-emphasized the utility of the mouse in human disease modeling, from developmental disorders (Kate Akerman, P-1; Dominic P. Norris, P-43) to autoimmune disease (Dana Tabor, P-62), to neural disorders (Y. Eugene Yu, P-74 and Gabor Szalai, P-61).

The power of ENU mutagenesis to generate new mouse models of human disease and identify genetic modifiers was emphasized in talks by Randall Westrick, Stephen Murray, Seungshin Ha, and Sally Cross. Humans carrying the Factor V Leiden mutation have an increased risk of developing venous thromboses, but the genetic modifiers that contribute to thrombosis risk are unknown. To identify modifiers, Westrick and colleagues (O-16) performed an ENU mutagenesis screen in mice with the Factor V Leiden mutation and a deficiency in tissue factor pathway inhibitor. Exome sequencing on surviving second-generation offspring revealed a suppressor mutation in *Actr2* and mechanistic studies are underway. Murray (O-18) reported on the role of LRP1 (low-density lipoprotein receptor-related protein 1) in development. Using several genetic methods, his group identified an ENU-induced *Lrp1* mutation in the *clfp4* mouse. These animals display several body wall, skeletal, and craniofacial defects. In conjunction with transgenic mouse models and a conditional *Lrp1* allele, *Lrp1* was shown to play a role in known craniofacial developmental pathways, as well as novel ones. Ha (O-19) provided an update on an ENU mutagenesis screen focused on identifying mutations that disrupt cerebral cortical patterning. Positional cloning in one line with abnormal cortical lamination revealed a novel mutation in *Reelin* (*Reln*). Whole-genome sequencing in another line with aberrant corticofugal axon development identified a mutation in

Lrp2. These mice hold promise as ideal neurodevelopmental disease models because many neurodevelopmental disorders (i.e., autism) are associated with disturbed cortical patterning and *Lrp2* has already been implicated in Donnai-Barrow Syndrome in humans. Cross (MRC Human Genetics Unit, O-41) presented her work on the iris-corneal strands (*Icst*) mouse, an ENU-induced mutant that recapitulates the kidney and glaucoma defects sometimes seen in humans with Nail-Patella Syndrome (NPS). Cross identified a missense mutation in *Lmx1b* that disrupts its ability to bind DNA targets and used *Lmx1b* knockout mice and BAC transgene rescue studies to show that the *lcst* mutation acts in a dominant-negative fashion. Her findings suggest that a similar mechanism may underlie some cases of NPS.

Another hot topic this year was infection. Humans differ drastically in their ability to contract and respond to infections. Several investigators are using the mouse to identify genes responsible for such differences. Xavier Montagutelli (Institut Pasteur, O-47) and his colleagues identified three QTLs (*Yprl1*, *Yprl2*, and *Yprl3*) in SEG/Pas mice that conferred resistance to *Y. pestis* infection. Further analysis of these regions in C57BL/6 mice revealed that combined effects from two different regions in both *Yprl2* and *Yprl3* were needed to confer resistance. Another type of infection caused by *Klebsiella* has emerged as a nosocomial nuisance and thus a large public health burden. Fuad Iraqi (Tel-Aviv University, O-42) presented a study aimed at identifying genes that lead to susceptibility to *Klebsiella pneumoniae* infections within the CC mouse resource. QTL mapping identified several genetic factors that play a role in host susceptibility. Interestingly, many of these factors had temporal effects, playing a role at very specific time points during the infection period. Gaetan Burgio (Macquarie University, O-48) discussed work covering an impressively large forward genetics screen that used ENU mutagenesis to generate mutations that confer resistance to murine malarial infection. Analysis of numerous resistant lines has led to the identification of several mutations and potential therapeutic targets. Focusing on a more molecular side of infection and the body's response to it, Beverly Mock (National Cancer Institute, O-45) reported on immunity defects in the *Mtor*-deficient mouse, which include failure to form normal germinal centers, higher mortality rates with *Streptococcus pneumonia* infections, and inability to form a high diversity of antibodies due to decreases in somatic hypermutations and class switch recombination. In vitro rapamycin treatment appears to act through AICDA (activation-induced cytidine deaminase) to rescue the class switch recombination phenotype.

Several presentations in the human disease modeling sessions focused on using spontaneous and transgenic mouse models to understand the molecular basis of disease. Miriam Meisler (University of Michigan, O-39) illustrated how mice with *Fig4* or *Scn8A* mutations have been used to evaluate the mechanism by which mutations in these genes in humans cause Charcot-Marie-Tooth disease and epilepsy, respectively. Teresa Gunn (McLaughlin Research Institute, O-40) is using gray tremor mice to understand the processes contributing to spongiform encephalopathy. Interestingly, the development of vacuoles in the brains of gray tremor mutants coincides with the onset of CNS myelination, which is also disrupted, suggesting that these processes may be linked. Sally Camper (University of Michigan, O-44) described studies in her laboratory to identify genes that modify susceptibility to congenital deafness caused by hypothyroidism in DW/J-*Pou1f1* mice. A QTL analysis located a strong locus on Chr 2, termed *Mdwh*. Through gene expression profiling specific to the cochlea, they narrowed the list of candidates to ten genes. Identification of *Mdwh* could lead to the development of therapeutics for affected children who do not respond to thyroid hormone supplementation. Lydia Matesic (University of South Carolina, O-17) presented a combination of biochemical and mouse studies to investigate the molecular basis of ventricular arrhythmias and sudden cardiac death. The WWP1 ubiquitin ligase was shown to bind and ubiquitinate gap junction protein alpha-1 (GJA1) (aka connexin 43, the main component of gap junctions between cardiomyocytes), targeting it for degradation. Global or cardiac-specific transgenic overexpression of WWP1 caused a significant reduction in GJA1 levels, and the mice developed ventricular hypertrophy and fatal conduction and repolarization defects. Increased WWP1, reduced GJA1, and increased colocalization of the two in intracellular vesicles were observed in heart samples from human arrhythmia patients, suggesting that this pathway may play an important role in human arrhythmogenic diseases.

Stem cells, development, and reproduction

Stephen Dalton (University of Georgia, O-20) kicked off the Stem Cells and Development sessions by demonstrating how pluripotent human stem cells could be used to generate epicardium cells. These induced epicardium cells provide a resource for drug studies and a means to study cardiovascular development, and have implications for future use in cell therapies. Many of the following stem cell and development talks spotlighted neurodevelopment. Work from Michelle Southard-Smith (Vanderbilt University, O-24) focused on enteric nervous system progenitors isolated via flow-sorting and cell differential expression of a *Phox2b* transgene. RNA-Seq analysis revealed

differential expression of multiple pathways in two distinct cell populations. This knowledge will aid in future studies to identify distinct subpopulations of enteric nervous system progenitors as well as provide needed information to direct enteric lineage cell segregation for cell therapies. William Pavan (National Human Genome Research Institute, O-25) discussed genetic modifiers that increase phenotypic severity of neurocristopathies in *Sox10* haplosufficient mice, including a mutation in *Actl6a* that appears to affect the quantity of melanoblasts and expression levels of many *Sox10* targets. Warburg Micro Syndrome also presents with neurodevelopmental anomalies, as well as ocular abnormalities. Sarah Carpanini (MRC Human Genetics Unit, O-26) presented her work characterizing a *Rab18* mutant mouse. Detailed analysis identified ocular and peripheral nervous system phenotypes that closely recapitulate those associated with Warburg Micro Syndrome in humans, indicating that these mice may help unravel the molecular etiology of this disease. Carpanini was awarded the Verne Chapman Young Scientist Award and 2 years on the IMGC Secretariat for her exceptional research and outstanding presentation (Table 2).

Several talks focused on reproduction. In humans, genetic factors contributing to deficits in reproduction, such as infertility, are still relatively obscure. Because of shorter gestation periods and the ability to control environment and genetic background, mouse models promise to expedite the discovery of factors contributing to reproductive processes. Takuya Murata (RIKEN BRC, O-23) introduced an infertility mouse model in which a *Ctnnb1* (catenin (cadherin associated protein), beta 1) mutation confers infertility in both male and female mice. Infertility in male mice is due in part to a seminal vesicle duplication event, while females have vaginal atresia. Chiao-Ling Lo (University of West Lafayette, O-27) revealed a role for *Nle1* (notchless homolog 1) during peri-implantation. Mutations in *Nle1* can be lethal during this time period and, interestingly, this lethality appears to be mediated by NLE's effect on WNT and cell cycle pathways, not notch signaling. After implantation, full gestation periods are critical to avoid health risks associated with prematurity, such as cognitive dysfunction and respiratory distress. Leah Rae Donahue (The Jackson Laboratory, O-28) and colleagues identified two mouse strains (C57BL/6J and A/J) that differ dramatically in gestation time. Chromosome substitution strains from these two lines were used to identify regions that influence gestation time. Data from these mouse studies, human studies, and innovative computational methods are aiding in locating genetic risk factors. Another study, presented by John Schimenti (Cornell University, O-21), revealed genes important to meiosis checkpoints. Aneuploidy and chromosome aberrations are the leading cause of spontaneous abortions. Checkpoints during meiosis I and II identify such abnormalities and serve to halt further development, but deficits in these checkpoints can lead to birth defects. Using genetic studies, Schimenti and colleagues demonstrated that *Chek2* (checkpoint kinase 2) plays an essential role in surveying DNA integrity and further studies are underway to unravel CHEK2 interactions. If oocytes pass all meiosis checkpoints and are successfully fertilized, zygotes successfully implant in the uterus and then rely on specific maternal–fetal interactions for normal development. Jiri Forejt (Institute of Molecular Genetics AS CR, O-9) highlighted the regulatory role of *Prdm9* in hybrid sterility and meiotic recombination, as did several poster presentations (Petr Flachs, SO-18/P-20; Zdenek Trachtulec, P-64; Pavlina Ivanova, P-30; and Petko Petkov, P-47).

Joseph Nadeau (Pacific Northwest Research Institute, O-22) reported on his group's progress in understanding the complex (and unconventional) inheritance of susceptibility to testicular germ cell tumors (TGCT) in 129 mice. Nadeau's group previously showed that genetic variants of *Dnd1* (dead end homolog 1) induce heritable epigenetic changes that affect the TGCT phenotype of subsequent generations. Since *Dnd1* shares sequence homology with *A1cf*, the RNA-binding subunit of the Apobec1 RNA-editing complex, they used a targeted null allele to investigate whether *Apobec1* also acts as a modifier of TGCT susceptibility. They observed increased TGCT susceptibility in $Apobec1^{+/-}$ sons that inherited the null allele from their father but reduced susceptibility when they inherited it from their mother. The maternal protective effect (but not the increased susceptibility associated with the paternal allele) persisted for at least two generations and was fully reversed after transmission for two consecutive generations through the alternative parental germ lineage. These data suggest that reduced dosage of maternal *Apobec1* induces a heritable epigenetic change that persists over multiple generations. Tests for interactions between *Apobec1* and *Dnd1* produced different results depending on parental genotypes: the effect of inheriting a maternal *Apobec1* null allele was neutralized in males inheriting a paternal $Dnd1^{Ter}$ allele, while maternal $Dnd1^{Ter/+}$ heterozygosity and paternal $Apobec1^{+/-}$ heterozygosity resulted in strong segregation distortion, with substantial loss of both double-heterozygous and single-heterozygous mutant mice. The latter result was particularly surprising given that these genotypic classes are fully viable when produced by other crosses, and it indicates that *Dnd1* and *Apobec1* play a role in gametogenesis and/or fertilization as well as in susceptibility to TGCT.

Verne Chapman Memorial Lecture: Eva Eicher

The conference organizers were honored to have Eva Eicher (The Jackson Laboratory) give the Verne Chapman

Lecture this year. Dr. Eicher's talk, entitled "Why did C57BL/6J win the race and how did it facilitate gonad development research?", began with a tribute to Dr. Chapman, who she warmly remembered as "a very tall person, and he was gentle as they come." Verne was an excellent mouse geneticist, recounted Eicher, but equally important, he was a generous scientist and freely shared his mice, technical knowledge, and time with anyone who asked. Incorporating her sharp wit and unique historical perspective throughout, and with a special focus on the trainees in the audience, Dr. Eicher described the people, decisions, and fortuitous discoveries that helped her find her way from a disillusioned graduate student in Rochester working under the famed geneticist Ernst Caspari to a distinguished staff scientist at The Jackson Laboratory. She noted the freedom and encouragement that Dr. Caspari gave her throughout her time in his lab. She also pointed out that one paper, Mary Lyon's seminal Nature paper on random X-inactivation, rejuvenated her interest in genetics and "saved my career." Eicher joined The Jackson Laboratory in 1973, at a time when new technologies, specifically chromosome banding and in situ hybridization, were enabling the golden age of linkage mapping. The pace of discovery was exciting—early on, Margaret Green would keep track of all the linkage results throughout the year on $3'' \times 5''$ cards and update the linkage map once per year on a single sheet of paper. Later, the maps became so big that they could wallpaper their walls with it, and by 1985, the linkage map contained so many genes that it was no longer legible and thereafter no longer printed.

It was during this period that C57BL/6J (B6) emerged as the reference strain, and just as a graduate student may stumble into a hot project that ultimately propels them to a successful career, B6 benefited from being in the right lab at the right time. Specifically, Elizabeth "Tibby" Russell's lab was studying the W (*Kit*) and Steel (*Kitl*) mutations, which cause not only germ cell loss but also pigmentation defects, and the white spotting phenotype was most easily observed on a nonagouti (i.e., black) background. To make genotyping easier, Tibby backcrossed her mutations onto the B6 background; similarly, spontaneous W and Steel mutations were discovered in the mouse production facility and sent to Russell. Soon, all investigators at the laboratory were following Russell's lead and backcrossing all of their mutations to the B6 background. The adoption of B6 as the reference strain proved particularly fortuitous to Eicher's future research in the area of gonadal sex determination, as the B6 genetic background turned out to be uniquely sensitive to sex reversal. Eicher exploited this sensitivity to map new autosomal regulators of sex determination and reveal sex reversal phenotypes in existing mutations that had previously gone unnoticed due to a resistant strain background. She described the sexism pervading the field of sex determination early on, and showed how she was able to disprove the prevailing theory that testis determination was the active genetic pathway, while the ovary was the default, passive pathway. Dr. Eicher finished her presentation by highlighting the continuous cycle of scientific inquiry that connects all scientists past, present, and future. "My use of the mouse as a genetic tool to address biological questions was built on the work of those who came before me. These scientists left behind unanswered questions that I tried to address. As I approached finding an answer to a question, more questions arose. Waiting in the wings are those who will address my unanswered questions, and leave behind new questions to be addressed in the future."

Looking forward

At the annual business meeting of the International Mammalian Genome Society (IMGS), multiple members voiced concern that the pace of discovery in human disease research could be severely compromised by recent efforts in the United States and abroad to stop commercial carriers from transporting laboratory animals. Society members reaffirmed their opposition to any attempts to block responsible animal research.

The IMGS Secretariat also solicited volunteers to organize future conferences. John Schimenti outlined a proposal from the Genetics Society of America (GSA) to have the IMGS join the Unified Multi-Organism Conference being planned for 2016, the GSA's centennial year. Already on the books is the 27th IMGC, which will be held September 15–19, 2013, in beautiful Salamanca, Spain. Organized by Elena de la Casa Esperón (PCYTA and University of Castilla-La Mancha), Fernando Pardo Manuel de Villena (University of North Carolina), Lluis Montoliu (Centro Nacional de Biotecnología and CIBERER), and Jesús Pérez Losada (University of Salamanca), the next conference is sure to provide a paella of exciting scientific advances in an idyllic setting. The IMGS continually strives to provide a welcoming atmosphere for trainees to share their research and interact with leaders in their respective fields, and to that end, the Society will award a number of travel scholarships to the next meeting. We encourage graduate students and postdoctoral fellows to submit abstracts and join us in Spain.

Acknowledgments The IMGS acknowledges Teresa Gunn and Michelle Southard-Smith for stepping up on short notice to serve as the local organizers for this year's conference. Currency fluctuations forced the conference to be moved from Tasmania to Florida, and Drs. Gunn and Southard-Smith worked diligently with Darla Miller, David Threadgill, and In Conference Ltd. (Margaret Sherry, Gayle Hodge, and Lotte Kerr) to make this year's meeting a success. The

IMGS also thanks the Secretariat, comprising David Threadgill (President), David Beier (Vice-President), Karen Steel (Past President), Simon Foote, Xavier Montagutelli, Jessica Van Schaick, Piero Carninci, Teresa Gunn, Steven Munger, Klaus Schugart, and Linda Siracusa, as well as the Nomination and Election Committee, comprising Morag Lewis, Amy Lossie, Tim Wiltshire, Sally Cross, Bruce Herron, and William Pavan, for their service to the Society. The meeting was supported in part by generous financial contributions from The Ellison Medical Foundation, abcam, Australian Animal Care Systems Pty Ltd (AACS), Macquarie University, Mutant Mouse Regional Resource Centers (MMRRC), GeneSeek (Neogen), and The Jackson Laboratory. Sponsors for this year's presentation awards included The Genetics Society of America, Nature Publishing Group, Cambridge Journals, Genomics, genesis, and Springer. Funding for student scholarships was made possible by 2R13HG002394 from NHGRI and NICHD at NIH, and from Mouse News Letter, Ltd.