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Meeting report: 31st International Mammalian Genome Conference, Mammalian Genetics and Genomics: From Molecular Mechanisms to Translational Applications

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Abstract
High on the Heidelberg hills, inside the Advanced Training Centre of the European Molecular Biology Laboratory (EMBL) campus with its unique double-helix staircase, scientists gathered for the EMBL conference "*Mammalian Genetics and Genomics: From Molecular Mechanisms to Translational Applications*," organized in cooperation with the International Mammalian Genome Society (IMGS) and the Mouse Molecular Genetics (MMG) group. The conference attracted 205 participants from 30 countries, representing 6 of the 7 continents—all except Antarctica. It was a richly diverse group of geneticists, clinicians, and bioinformaticians, with presentations by established and junior investigators, including many trainees. From the 24th–27th of October 2017, they shared exciting advances in mammalian genetics and genomics research, from the introduction of cutting-edge technologies to descriptions of translational studies involving highly relevant models of human disease.

Introduction

Mammalian Genetics and Genomics: From Molecular Mechanisms to Translational Applications was the 31st International Mammalian Genome Conference (IMGC), which followed on the successes of the IMGC2016, which was part of Mouse Genetics 2016 at The Allied Genetics Conference in Orlando, Florida, USA (Bloom et al. 2017), and IMGC2015, held in Yokohama, Japan (Gonzales et al. 2016). The 2017 conference started with workshops on GeneWeaver 2.0, Next Generation Sequencing, and the Alliance of Genome Resources (AGR). These workshops were followed by the much-anticipated Trainee Symposium, which gives students and post-doctoral researchers the opportunity to give a talk on their research in a mentoring and scientifically stimulating environment and vie for a podium presentation spot in the main meeting. The conference was divided into 10 sessions, 3 plenary lectures, and 2 poster sessions (93 posters) covering a wide range of topics that reflected the diverse and expanding interests of the community. Abstracts from the meeting are available at http://www.imgs.org (History tab).

Trainee Symposium

The mentorship and development of young scientists is a prominent feature of every IMGC. In this year, 59 students (including 1 undergraduate and 11 master's students) and 23 post-doctoral researchers attended the conference, many of whom received travel scholarships from the IMGS or EMBL. Continuing long-standing IMGC traditions, trainees

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also participated in a mentor lunch at which they discussed their science and career paths with established scientists, and vied for a number of presentation awards. The Trainee Symposium incorporated 16 oral presentations, five of which were given the Lorraine Flaherty Outstanding Oral Presentation Award (Table 1), which comes with a certificate and a podium presentation slot in the main meeting. The wide range of topics presented during the Trainee Symposium exemplified the versatility and usefulness of mammalian models for basic and translational research.

Table 1 Mammalian Genetics and Genomics: From Molecular Mechanisms to Translational Applications Trainee Awards

Awardee	Institute	Title	Award—Sponsor
Lauren Tracey	Hospital for Sick Children, CA	The pluripotency regulator *Prdm14* hijacks hematopoietic partners to initiate leukemia in mice	OOP—Lorraine Flaherty Memorial Award—IMGS Verne Chapman Young Scientist Award—IMGS
Anthony Doran	Wellcome Trust Sanger Institute, UK	Multiple mouse reference genomes define subspecies-specific haplotypes and novel coding sequences	OOP—GSA
Rebekah Tillotson	University of Edinburgh, UK	Radically truncated MECP2 rescues Rett syndrome-like neurological defects	OOP—DMM
Jingtao Lilue	Wellcome Trust Sanger Institute, UK	Allelic diversity of immunity loci in wild-derived and classical inbred mouse strains	OOP—Lorraine Flaherty Memorial Award—IMGS
Jorge Rodriguez-Gil	National Institutes of Health, USA	Neonatal lethality and genetic modifiers in a new mouse model of Niemann-Pick disease, type C	OOP—Lorraine Flaherty Memorial Award—IMGS
John Shorter	University of North Carolina-Chapel Hill, USA	Male infertility is responsible for nearly half of the extinction observed in mouse collaborative cross	OOP—Lorraine Flaherty Memorial Award—IMGS
Gennadiy Tenin	University of Manchester, UK	From GWAS to gene function: analysis of the gypician 6 and its involvement in cardiac septation and tetralogy of fallot	OOP—Lorraine Flaherty Memorial Award—IMGS
Kärt Tomberg	Wellcome Trust Sanger Institute, UK	Unbiased in vivo CRISPR screen to identify novel T-cell immune checkpoints for cancer immunotherapy	ORP—AACR
Catherine Bélanger	Université du Québec à Montréal, CA	Characterization of mouse models of CHARGE syndrome suggests a key role for co-transcriptional alternative splicing in male sex determination	ORP—EMBL
Erica Macke	University of Wisconsin-Madison, USA	Mutation in chondroitin sulfate synthase 1 causes retinal abnormalities, neurodegeneration, and early aging phenotypes in mice	ORP—EMBL
Luke Laudermilk	University of North Carolina-Chapel Hill, USA	Identification of a causal variant and mechanism for a lung eQTL related to neutrophil chemotaxis	ORP—Springer-Verlag
Alexander Johnston	Oakland University, USA	Platelet PAI-1, SERPINE1, is regulated by a major chromosome 5 eQTL in inbred mice	ORP—Springer-Verlag
Samuel Widmayer	North Carolina State University, USA	Genetic architecture of hybrid male sterility in the mouse	ORP—*Genome Research*
Yichen Dai	University of Oxford, UK	Comparative and functional analysis of *Psammomys obesus* pancreatic duodenal homeobox 1 (*Pdx1)*	ORP—*Genetics Research*
Selene Howe	Texas A&M University, USA	Genetic background-dependent cardiotoxicity from long-term pharmacological inhibition of EGFR	ORP—*Genesis*
Vita Fedele	Institute of Cancer Research, UK	Parity-related changes in gene expression at the 11p15.5 breast cancer risk locus	ORP—*Genesis*
Nirav Chhabra	Helmholtz Zentrum München, DE	Protein disulfide isomerase-associated 6 gene is important for pancreatic ß-cell homeostasis	ORP—*Genesis*
Biswajit Padhy	National Institute of Science, IN	Pseudoexfoliation and Alzheimer's associated *CLU* risk variant, rs2279590 lies within an enhancer element and regulates *CLU, EPHX2, and PTK2B* gene expression	Nomenclature Excellence (Poster) Award—ICSGNM

OOP outstanding oral presentation, *ORP* outstanding research poster, *IMGS* International Mammalian Genome Society, *ICSGNM* International Committee on Standardized Genetic Nomenclature for Mice, *AACR* American Association for Cancer Research, *DMM* Disease Models and Mechanisms, *EMBL* European Molecular Biology Laboratory

Presentations by Amy Royall (University of Oxford, UK), Ilaria Lavagi (Ludwig-Maximilians-Universität, Germany), and Nirav Chhabra (Helmholtz Zentrum München, Germany) focused on development. Royall discussed the role of mouse Eutherian Totipotent Cell Homeobox (ETCHbox) genes in preimplantation development, showing that they regulate development of the embryo itself as well as its interaction with the endometrium. Lavagi used single-cell RNA-sequencing (RNA-seq) to demonstrate high heterogeneity in early differentiation processes in in vitro fertilized cow embryos. Chhabra presented his work on the protein disulfide isomerase associated 6 *(Pdia6)* gene, characterizing its role in the pancreas and its possible contribution to the progression of diabetes.

John Shorter (University of North Carolina (UNC)-Chapel Hill, USA) and Samuel Widmayer (North Carolina State University, USA) addressed the genetics of male fertility. Shorter found that male infertility was responsible for the extinction of almost half of the Collaborative Cross (CC) lines and used quantitative trait locus (QTL) mapping to show that this phenotype was driven by alleles from two of the inbred founder strains, PWK/PhJ and CAST/EiJ. This implicates subspecies incompatibilities as a key driver of infertility in CC lines and provides insight into mechanisms underlying mammalian infertility. Widmayer, in turn, studied hybrid male sterility (HMS), a reproductive barrier restricting gene flow between two subspecies of mice, *Mus musculus musculus* and *M. m. domesticus*. He described how hybrids with identical HMS-linked loci have a wide variation in fertility and reproductive traits, and identified candidate QTL for these traits.

The importance of genetic background was highlighted in talks by Jorge Rodriguez-Gil (National Human Genome Research Institute (NHGRI), USA) and Selene Howe (Texas A&M University, USA). Rodriguez-Gil presented a new mouse model of Niemann-Pick Disease, Type C (NPC), and demonstrated a significant effect of strain background on lifespan. He plans to map genetic modifiers that influence NPC severity, which he hopes will improve our understanding of the highly variable phenotype (age of onset and severity) observed in NPC patients and facilitate the development of better therapies. Howe assessed cardiotoxic effects of long-term anti-epidermal growth factor receptor (EGFR) therapy, commonly used to treat cancer, in four genetically distinct mouse strains. Her data suggest that genetic background influences drug response by determining which compensatory mechanism is adopted in response to chronic EGFR inhibition.

Marisa Brake (Oakland University, USA) and Gennadiy Tenin (University of Manchester, UK) presented work on the cardiovascular diseases venous thromboembolism and tetralogy of fallot (TOF), respectively. Brake is using whole exome sequencing to identify thrombo-suppressive variants generated through ENU-mutagenesis. Tenin is focused on discovery of novel genes involved in congenital cardiac defects and shared his work demonstrating that loss of *Gpc6* leads to cardiac septation abnormalities, a significant contributor to TOF.

Jingtao Lilue (Wellcome Trust Sanger Institute, UK) examined whole-genome sequence data in an effort to explain strain-specific allelic diversity in immunity-related loci. His work could have significant implications for our understanding of the genetic basis for variability in pathogen susceptibility and resistance. FX Reymond Sutandy (Institute of Molecular Biology, Johannes Gutenberg University of Mainz, Germany) described the development and use of an in vitro individual-nucleotide resolution UV crosslinking and immunoprecipitation (iCLIP) system paired with mathematical modeling to assess the function of several RNA binding proteins (RBPs). His studies thus far have uncovered novel RBPs that regulate splicing factor U2AF2, and therefore modulate RNA splicing events.

Talks by Hsiang-Hsuan Fan (National Taiwan University College of Medicine, Taiwan), Annapurna Pranatharthi Haran (National Center for Biological Sciences, India), and Lauren Tracey (Hospital for Sick Children, Canada) focused on cancer. Fan's work centered on developing an inducible CRISPR/Cas9 system to generate targeted somatic mutations in transformation-related protein 53 *(Trp53)*, providing a platform for in situ cancer gene screens. Pranatharthi Haran addressed the role of Rho-associated coiled-coil containing protein kinase 2 (ROCK2) in patients that develop resistance to radiotherapy following initial treatment for cervical cancer. Her results indicate that ROCK2 interacts with DNA repair machinery and thus confers resistance to radiation. Tracey discussed her work focusing on the role of PR domain containing 14 (PRDM14) in the onset of T-cell acute lymphoblastic leukemia (ALL). Her data suggest that PRDM14 interacts with specific domains of other proteins within pre-leukemic cells and hijacks them to initiate ALL. This work could have a profound impact on our mechanistic understanding of leukemia initiation. Tracey was awarded the Verne Chapman Young Scientist Award for her outstanding presentation.

Other trainees at the conference joined Symposium presenters in sharing their research with all meeting participants during the two poster sessions. Awards were presented for outstanding oral and poster presentations by trainees in the Symposium and main meeting (Table 1).

Comparative genomics, computational methods, and evolution

The IMGC is an important venue for sharing information about large-scale mammalian genetics resources, as well as a place to initiate discussion of matters affecting our scientific

community. The main meeting of the 31st IMGC kicked off with a discussion about reproducibility in mouse research. In his presentation entitled "Proposal to increase the rigor and reproducibility of mouse research through genetic quality control," Fernando Pardo-Manuel de Villena (UNC-Chapel Hill, USA) proposed that sex, inbred status, genetic origin, and presence of genetic constructs be verified prior to the publication of studies involving mice, and that a public repository be established for genotypes of the most common stocks, strains, and cell lines. His talk prompted much thoughtful discussion, and the importance of genetic quality control and scientific rigor was touched on throughout the meeting. Slides from this presentation are permanently archived under the links tab on the IMGS website (http://www.imgs.org).

The topic of genetic and phenotypic diversity in laboratory and wild-derived mouse strains was revisited by a number of speakers in this session. Anthony Doran (Wellcome Trust Sanger Institute) presented interesting findings from detailed de novo whole-genome annotation following the Mouse Genome Project, which generated genomic sequence data for 12 classical laboratory and 4 wild-derived inbred mouse strains. Combining evidence from the mouse reference GENCODE annotation and strain-specific RNA-seq and PacBio cDNA, Doran showed they could improve the annotation of the reference genome at many loci, and identified novel strain-specific gene structures and alleles. He also found highly polymorphic loci enriched for genes that function in defense and immunity. Jing Zhang (Institut Pasteur, France) studied host gene involvement in susceptibility to *Salmonella typhimurium* in CC mice, identifying five QTLs for spleen and liver bacterial load with distinct patterns of contrast between founders, originating mainly from wild-derived founders. He refined the QTL intervals to obtain a promising list of candidate genes and showed that the CC042/GeniUnc strain is highly susceptible to *Salmonella* infection.

Evolution of the mammalian X and Y chromosomes was the starting point for Alyssa Kruger (University of Michigan, USA), who discussed the spermatogenic functions of the *Mus* lineage-specific Sycp3 like X-linked *(Slx)* and Slx-like 1 *(Slxl1)* gene family regions on the X Chromosome (Chr). These genes are exclusively expressed in post-meiotic spermatogenic cells. Kruger generated single and double deletion mutants for these large gene families and is assessing their effect on spermatogenesis. Frank Chan (Max Planck Tübingen, Germany) addressed the common issue of hybrid sterility when utilizing different mammalian species for genetic dissection of trait variation. Using the small molecule inhibitor ML216 to induce random mitotic crossovers, Chan was able to generate "in vitro crosses" in hybrid mouse embryonic stem cells (ESC). This is an exciting new approach to increasing mapping capabilities and address fundamental questions in evolutionary biology. Adam Hargreaves (University of Oxford) described his unexpected foray into "dark DNA" when whole-genome sequencing of the sand rat suggested that the pancreatic and duodenal homeobox 1 (*Pdx1*) gene, essential for insulin production, was missing from the genome. Further investigation revealed that the "missing" region had in fact undergone massive sequence change and divergence, which likely contributes to a high nutritionally induced diabetes susceptibility in the sand rat. His findings demonstrate that delving into "dark" DNA may be critical for the discovery of novel disease susceptibility loci.

David Beier (Seattle Children's Research Institute, University of Washington, USA) presented his group's approach to predicting which genes will have developmental effects in humans by characterizing the strength of heterozygote selection (s_het) in genes throughout the exome. Notably, they found that s_het was highly correlated with the likelihood of recessive lethality. Richard Mott (University College London, UK) concluded this exciting session with a look into how different QTLs influence complex traits, specifically alleles with non-additive effects such as dominance and over-dominance. Using various models, Mott's group phenotyped over 100 complex traits and identified significant non-additive effects, including a small number of QTLs exhibiting strong heterosis. This talk also highlighted analysis of expression data to identify non-additive gene expression QTLs (eQTLs) overlapping with previously found complex trait QTLs, representing promising candidates for complex traits.

Cancer and Immunology

The Cancer and Immunology session covered a broad array of topics including genetic and environmental initiating factors, therapeutic efficacy, and model development. David Masopust (University of Minnesota, USA) began the session with a talk highlighting the importance of the microbiota in shaping mouse immune development. He demonstrated that feral mice with more complex microbiota have $CD8^+$ T-cell subsets more representative of human populations than laboratory mice. Masopust's data raise fascinating questions regarding the advantages and disadvantages of using highly selected specific-pathogen free laboratory mice to study phenotypes influenced by the immune system. Beverly Mock (National Cancer Institute, USA) and Carolina Mantilla Rojas (Texas A&M University) discussed potential therapeutic pathways for cancer treatment. Mock showed the utility of an HDAC/MTOR inhibitor drug combination in targeting signaling pathways involved in plasmacytomas, while Mantila Rojas demonstrated increased penetrance of adenomatosis polyposis coli (*Apc*)-dependent colorectal cancer (CRC) in *Egfr* mutant mice, indicating an important role

for EGFR-independent pathways that need to be understood in order to develop more effective CRC treatments.

Ari Elson (Weizmann Institute of Science, Israel) addressed a phenomenon in which a single protein may have a promoting or suppressing effect in tumor development in a model of B cell chronic lymphocytic leukemia. His work demonstrates that loss of protein tyrosine phosphatase, receptor type, O (PTPRO) decreased disease severity via reduced B cell receptor, and Src family kinase signaling, but loss of a single *Ptpro* allele induced the opposite phenotype. Viive Howell (University of Sydney, Australia) presented new findings from her group's forward genetics screen that indicate a functional contribution of haemogenic endothelial cells to leukemogenesis, highlighting the need for therapeutics that target this cell population. Christopher Vakoc (Cold Spring Harbor Laboratory, USA) discussed the use of the CRISPR/Cas9 system to target transcriptional activation of bromodomain containing 4 (BRD4), an established therapeutic target in acute myeloid leukemia. This approach demonstrates how new technologies can be exploited to achieve domain-specific disruption of transcription of target proteins in cancer.

Epigenetics and gene regulation

Talks in this session emphasized the message that non-coding sites can have significant functional roles in diverse processes, such as cell fate determination, embryonic viability, and phenotypic outcome. Mitinori Saitou (Kyoto University, Japan) described his laboratory's unique in vitro system to study sexual differentiation in germ cells which led to the discovery that DNA methylation and sexual differentiation are separate events. He demonstrated that, during expansion, primordial germ cell-like cells lose their methylome signature and become sexually uncommitted. This has allowed his group to study factors that lead cells to a germ cell fate. Myriam Hemberger (Babraham Institute, UK) made the case that a defective placenta is an often-underappreciated factor in embryonic lethality. She demonstrated that trophoblast stem cell pluripotency is maintained by the epigenetic modification activities of tet methylcytosine dioxygenase 1 and 2 (TET1/2), which promote cell cycle progression and prevent the endoreplication cycle associated with differentiating trophoblast stem cells.

Christopher Baker (The Jackson Laboratory, USA) presented data on the identification of *cis* and *trans* regulatory sites that influence meiotic recombination hotspots by regulating histone-3-lysine-4-trimethyl (H3K4me3) levels. Looking at these sites in multiple cell types, his group found that chromatin regulatory systems are cell-type-specific, demonstrating the complex nature of gene regulation. Zdenek Trachtulec (Institute of Molecular Genetics of the ASCR, Czech Republic) described his work on the H3K4me3 transferase PR domain containing 9 (PRDM9), which influences the determination of hotspots during meiotic recombination in mice, dogs, and apes. While *Prdm9*-deficient mice and dogs are infertile, a human female lacking PRDM9 function produced offspring. Trachtulec's group found that *Prdm9*-deficient rats are fertile, making them a better model for studying human germ cell development and identifying genetic modifiers of PRDM9. Siddharth Sethi (MRC Harwell Institute, UK) shared his work on the identification of regulatory elements, including super-enhancers and tissue-specific promoters. Combining these regulatory elements with gene expression and protein interaction profiles, he reported a significant improvement in predicting phenotypic outcomes.

Development and stem cells

Topics in session ranged from the genetic regulation of neurodevelopment to ciliary signaling. James Briscoe (Francis Crick Institute, UK) and Kian Koh (Katholieke Universiteit Leuven, Belgium) emphasized different factors required for central nervous system development. Briscoe discussed the importance of spatial gradients created by the spread of morphogens from a localized source in establishing cell identity during development, using the generation of distinct neuronal subtypes in a precise spatial order in the ventral neural tube and its regulation by a sonic hedgehog-dependent gene regulatory network as an example. His group's work demonstrates the value of combining mathematical modeling with experimental observations to provide new insight into embryonic pattern formation. Koh discussed the TET family's role in controlling cell differentiation via DNA demethylation during various stages of embryonic development and, ultimately, neural tube closure. His findings establish an epigenetic basis for neural tube defects resulting from *Tet1* loss-of-function.

Michelle Southard-Smith (Vanderbilt University, USA) described bladder dysfunction associated with spina bifida (SB), a common neural tube defect. By crossing the *Pax3* model of SB with a transgenic reporter line, her group found that neural crest progenitors exhibit abnormal migration and patterning throughout the lower urinary tract. Magdalena Götz (Helmholtz Zentrum München, Germany) focused on the roles of novel proteins in cerebral development and neuronal reprogramming, as well as the ability to integrate transplanted neurons into a preexisting network. The final speaker of the session, Laura Reinholdt (The Jackson Laboratory), discussed a novel role for the kinetochore-associated 1 protein (KNTC1) in ciliary signaling during development. KNTC1 was previously shown to be an important component of the mitotic machinery. Reinholdt noted distinct

similarities between *Kntc1* mutants and mice with disrupted ciliary signaling, and which led her group to demonstrate that KNTC1 localizes to primary cilia in various cell types.

International Resources and INFRAFRONTIER

Progress in mouse genetics depends heavily upon the global community's ability to access databases that provide a wealth of information for investigators. Informing the community about these research resources is an important part of every IMGC. Table 2 provides a listing of database websites and other key resources that were discussed by speakers in this and other sessions during the meeting, as well as additional sites that will be useful to members of the mammalian genetics community.

The 2017 International Resources session was sponsored by INFRAFRONTIER (https://www.infrafrontier.eu/), the European Research Infrastructure for the generation, phenotyping, archiving, and distribution of model mammalian genomes. Terry Meehan (EMBL-European Bioinformatics Institute, UK) updated the community on the efforts of the International Mouse Phenotyping Consortium (IMPC) to phenotype knockout mice for each protein coding gene. To date, over 5000 knockout mouse lines have been generated and phenotyped for over 250 parameters. Sabine Fessele (INFRAFRONTIER GmbH, Germany) demonstrated INFRAFRONTIER's services, which include the distribution and archiving of IMPC and other mutant mouse lines. Jacqueline Finger (The Jackson Laboratory) discussed the extensive resources provided through The Gene Expression Database (GXD). GXD curates a variety of datasets from published literature, integrating expression assays with other genetic, functional, phenotypic, and disease-oriented data to provide comprehensive information about endogenous gene expression during mouse development. Together, these resources provide global access to a vast array of genetic tools.

The sustainability of genome information resources has become a cause for concern since the National Institutes of Health (USA) announced upcoming significant budgetary reductions for model organism databases (MODs). To reduce costs required to operate and maintain individual MODs, the AGR was introduced as an initiative to establish a common framework for data from several different model organisms. It is a consortium of six MODs, including the Mouse Genome Database (MGD), Rat Genome Database (RGD), and the Gene Ontology (GO) Consortium. Carol Bult (The Jackson Laboratory) updated the community on the AGR's progress towards launching the collaborative database, and described future plans to try to offset the effect of reduced financial resources.

Human Disease Models

Two Human Disease Models sessions provided exciting insight into the development and analysis of animal models for a variety of human diseases. The first session started with a 3D insight into the mammalian genome, presented by Stefan Mundlos (Max Planck Institute for Molecular Genetics, Germany). He explained how mammalian genomes are organized in distinctly folded chromatin modules, called topologically associated domains (TADs), separated from each other by boundary regions that restrict possible contacts between enhancers and their target genes. His group has explored how genomic structural variation interferes with TAD structure and may contribute to human disease, focusing on limb malformations. He gave elegant examples that included the use of CRISPR/Cas9 genome editing to generate chromosomal rearrangements involving TAD boundaries to investigate their phenotypic effects.

Throughout the conference, there was a strong focus on genetic network-level regulation of complex traits and the utility of genetically diverse animal models to dissect disease spectra. These two themes were especially evident in the Human Disease Models sessions. Cecilia Lo (University of Pittsburgh, USA) emphasized the genetic combinatorial nature of complex diseases and how they can be modeled using ENU mutagenesis to generate animals with multiple, interacting mutations. Her group has identified 100 genes involved in congenital heart disease, consistent with a large network underlying these complex disorders. Rolf Stottmann (Cincinnati Children's Hospital Medical Center, USA) described progress in dissecting the tetratricopeptide repeat domain 21B (*TTC21B)* genetic network involved in ciliopathies. His group identified four genes from human cohorts that interact with *TTC21B* and modify ciliopathy severity and they are currently working to identify modifier genes of microcephaly caused by TTC21B-deficiency.

Lluis Montoliu (National Centre for Biotechnology, National Research Council, Spain) recounted his work using mouse models to dissect non-syndromic albinism. His group is employing CRISPR/Cas9 gene editing to generate mice carrying patient-specific mutations in order to investigate the molecular mechanisms underlying specific phenotypes and identify therapeutic approaches to treat visual abnormalities found in this human rare disease. Felix-Antoine Simard (University of Quebec, Canada) spoke about his work on chromodomain helicase DNA binding protein 7 (*CHD7*) mutation-negative CHARGE syndrome, focusing on the family with sequence similarity 172, member A *(Fam172a)* gene. His work has revealed a pathogenic mechanism that involves

Table 2 Mouse databases and online resources

Resource	Acronym	URL address
Collaborative Cross status page and tools	CC	http://www.csbio.unc.edu/CCstatus/index.py
CrePortal Resource for Conditional Mutagenesis in the Mouse		http://www.creportal.org
The CRISPR page at CNB		http://wwwuser.cnb.csic.es/~montoliu/CRISPR/
Diversity Outbred stock and datasets	DO	http://www.do.jax.org
Functional Annotation of the Mammalian Genome	FANTOM5	http://www.fantom.gsc.riken.jp/5/
Gene eXpression Database	GXD	http://www.informatics.jax.org/expression.shtml
Human-Mouse: Disease Connection	HMDC	http://www.diseasemodel.org
International Mouse Phenotyping Consortium	IMPC	http://www.mousephenotype.org
INFRAFRONTIER Mouse Disease Models		http://www.infrafrontier.eu
MouseBook (MRC Harwell phenotype and genomic data)		http://www.mousebook.org
Mouse Encyclopedia of DNA Elements	ENCODE	http://www.mouseencode.org/
Mouse Genome Informatics	MGI	http://www.informatics.jax.org
Mouse Phenome Database	MPD	http://www.phenome.jax.org
Mouse Tumor Biology Database	MTB	http://www.tumor.informatics.jax.org
NHGRI-EBI Catalog of PublishedGWAS		http://www.ebi.ac.uk/gwas
Rat Genome Database	RGD	http://www.rgd.mcw.edu/
Sanger Mouse Genomes Project	MGP	http://www.sanger.ac.uk/resources/mouse/genomes/
Sanger Mouse Resources Portal		http://www.sanger.ac.uk/mouseportal/
Analysis tools		
Combined Analysis of Pleiotropy and Epistasis Package	CAPE	http://www.cran.r-project.org/web/packages/cape
DOQTL: a package for genetic mapping in the Diversity Outbred stock	DOQTL	http://www.bioconductor.org/packages/release/bioc/html/DOQTL.html
EM estimation of allele-specific expression	EMASE	http://www.github.com/jax-cgd/emase
GeneWeaver System		http://www.geneweaver.org
MouseMine: integrated mouse data		http://www.mousemine.org/mousemine/begin.do
Multi-String Burrows Wheeler Transform Utility Suite	MSBWT	http://www.pypi.python.org/pypi/msbwt
Multispecies genome browsers		
Alliance of Genome Resources	AGR	http://www.alliancegenome.org
Ensembl Genome Browser	ENSEMBL	http://www.ensembl.org
National Center for Biotechnology Information	NCBI	http://www.ncbi.nlm.nih.gov/
UCSC Genome Bioinformatics		http://www.genome.ucsc.edu/
Nomenclature guidelines		
Human Gene Nomenclature Committee	HGNC	http://www.genenames.org/
Mouse Nomenclature Home Page		http://www.informatics.jax.org/mgihome/nomen/
Rat Nomenclature Guidelines		http://www.rgd.mcw.edu/nomen/nomen.shtml
Repositories		
Canadian Mouse Mutant Repository	CMMR	http://www.cmmr.ca
Database for Exchangeable Gene Trap Clones	EGTC	http://www.egtc.jp/action/access/index
European Mouse Mutant Archive	EMMA	http://www.emmanet.org, https://www.infrafrontier.eu
European Mouse Mutant Cell Repository	EuMMCR	http://www.eummcr.org
International Mouse Strain Resource	IMSR	http://www.findmice.org
JAX Mice Database	JAX	http://www.jaxmice.jax.org/query
Knockout Mouse Project Repository	KOMP	http://www.komp.org
NCI at Frederick Mouse Repository		http://www.ncifrederick.cancer.gov/Lasp/MouseRepository/
The Mouse Mutant Resource	MMR	http://www.mousemutant.jax.org

the global dysregulation of alternative splicing, which can be corrected by acute rapamycin treatment. Bill Pavan (NHGRI) described how his group identified the genetic mutation responsible for reduced viability and dilution of yellow pigment in the coat hairs in the classic coat color mutant, grizzled. The mutation disrupts the *Mfsd12* gene, which encodes a lysosomal protein also implicated in human skin color. A role for this relatively uncharacterized gene in mammalian pigmentation was confirmed using CRISPR/Cas9 DNA editing to generate *Mfsd12*-null mice.

Danny Arends (Humboldt-Universität zu Berlin, *Germany)* presented his work on the Berlin Fat Inbred Mouse line, a model for juvenile obesity. He has identified candidate genes in the *Jobes1* region that contribute to the obesity and visual impairment phenotypes. Ozgun Gokce *(*Klinikum der Universität München, Germany) spoke about his efforts to classify striatal cells, "beyond the D1/D2 dichotomy" using single-cell RNA-sEq. He hopes to understand how these unique cellular identities are altered in disease.

Walee Chamulitrat (University Heidelberg Hospital, Germany) shared her progress in understanding how phospholipase A2, group VI (PLA2G6), which is associated with Parkinsonism in humans, is involved in disease. She reported that *Pla2g6* knockout mice not only displayed Parkinsonism phenotypes but also had liver fibrosis and bowel disease. Sabine Cordes (University of Toronto, Canada) presented her group's findings that the vertebrate- and neural-specific protein SRRM4 (nSR100) regulates splicing of brain-specific microexons, which are evolutionarily conserved exons 2–27 nucleotides in length that modulate the function of interaction domains of proteins involved in neurogenesis. Cordes and her collaborators demonstrated that the brains of patients with autism spectrum disorder (ASD) frequently show misregulation of microexons and reduced levels of SRRM4. In keeping with this finding, Cordes shared a movie depicting altered social behaviors in SRRM4-deficient mice. Koichiro Abe (Tokai University School of Medicine, Japan) presented his work identifying a role for activity of the Src family tyrosine kinase FGR proto-oncogene in auto inflammatory bone disease. His research findings, supported by both mouse studies and exome sequencing of human *FGR*, suggest that this protein is a promising target for therapy for inflammatory disorders. The session concluded with Yann Herault's (Université de Strasbourg, France) talk on mouse models of Down syndrome. His laboratory has found that using diverse mouse genetic backgrounds increased the spectra of clinical symptoms modeled, an improvement that will benefit future investigations into the molecular mechanisms behind this and other complex disorders.

Translational & systems genetics

In this session, researchers presented new and encouraging avenues for treatment of inherited human diseases. Topics included identification of candidate genes by QTL mapping, functional studies of causative genes, and gene therapy. Fuad Iraqi (Tel-Aviv University, Israel) described his group's progress in identifying candidate genes involved in periodontitis. QTL mapping in CC mice revealed eight candidate genes whose orthologous regions in the human genome were also associated with periodontitis. His talk demonstrated the power of using CC mice to identify human susceptibility genes. The utility of genetically diverse models such as the CC in uncovering previously unobserved disease spectra was a common theme throughout the conference.

Shalini Roy Choudhury (Jawaharlal Nehru Centre for Advanced Scientific Research, India) identified the zinc finger, GRF-type containing 1 (*ZGRF1)* gene as a causative locus for hot water-induced epilepsy in humans. She shared her progress in characterizing the biological role of *ZGRF1* in cell culture, revealing a role in DNA repair and mitotic division. Rebekah Tillotson (University of Edinburgh, UK) presented her research on the methyl CpG binding protein 2 *(MECP2)* gene, which is mutated in Rett syndrome patients. She generated knock-in mice in which endogenous *Mecp2* was replaced with a shortened sequence encoding only the methyl-CpG binding and NCoR/SMRT interaction domains, in order to test their therapeutic potential. In comparison to *Mecp2*-null mice, knock-in mice displayed mild neurological and motor defects. Tillotson's work provides evidence supporting the use of a much shorter *MECP2* sequence in future gene therapy approaches. Fatima Bosch (Universitat Autònoma de Barcelona, Spain) described a gene therapy approach for treatment of lysosome storage deficiency diseases such as Mucopolysaccharidosis Type II (MPS II). Genes associated with the glycosaminoglycan degradation pathway were delivered to intracerebrospinal fluid via an adenoassociated viral vector. In a mouse model of MPS II, this approach resolved symptoms and normalized gene expression. This work was replicated in dogs and has been approved for human clinical trials.

Steven Munger (The Jackson Laboratory) addressed the important concept that transcriptional changes do not necessarily equate to direct changes in the proteome. He emphasized the importance of choosing appropriate methods to test hypotheses, as factors that influence the proteome, such as age and diet, are often post-translational in nature. To illustrate this, Munger presented his findings that local QTLs tend to be conserved across tissues and involved in transcriptional regulation, whereas distant QTLs tend to be tissue-specific and influential at the post-transcriptional level.

Technological advances

The IMGC provides a platform to inform the community of new developments that influence the generation and analysis of mouse models. The first two talks demonstrated the large-scale capabilities of current single cell and genome editing technologies. Ido Amit (Weizmann Institute of Science, Israel) described the utility of large-scale, single-cell RNA-seq, particularly for categorizing tissues into cell types and facilitating analysis of the transcriptional states of the various cell types within their tissue environment. Amit shared his group's progress in using this approach to dissect pathways involved in myeloma progression, a disease characterized by its extremely high plasma cell heterogeneity. Marie-Christine Birling (Université de Strasbourg) presented an innovative genome editing method developed in her laboratory called CRISMERE (CRISPR mediated rearrangement), which can be used to generate duplications, deletions, inversions, and translocations. Her laboratory has successfully used CRISMERE to make structural edits as large as 24.4 Mb, including the creation of a Down syndrome rat model with a duplicated mini Chr 17. This gene editing method is faster to implement than the traditional Cre-lox system. Birling also discussed the advantages of droplet digital PCR and PCR junction sequencing in validating genetic modifications.

The final three talks illustrated significant advances in imaging capabilities as speakers demonstrated how we can exploit new technology to address hypotheses in previously unmatched ways. Both Robert Prevedel (EMBL Heidelberg, Germany) and Rui Benedito (National Center for Cardiovascular Research, Spain) have established new imaging techniques with substantially advanced spatial and temporal resolution. Prevedel demonstrated the application of his new technology through visualization of calcium-mediated changes in deep cortical tissue in the in vivo mammalian brain. Benedito has generated novel transgenic mice and ESC lines with a capacity for inducible, fluorescent and functional genetic mosaic analysis, allowing for high-resolution investigation of gene function. Teresa Gunn (McLaughlin Research Institute, USA) concluded the session by describing a transgenic mouse that expresses a novel, Cre-inducible, highly sensitive fluorescent sensor that can be used to quantify and image diacylglycerol signaling in vivo, in real time. These new methods and resources demonstrate how new technologies continue to enhance our ability to investigate genetic processes at higher resolution.

Verne Chapman Memorial Lecture

In 1997, the IMGS established a lectureship to celebrate the life, work and ethos of society co-founder Dr. Verne M. Chapman. Speakers selected for this honor are scientific leaders in their field, community builders, and mentors, generous in sharing time, ideas and tools. The IMGS was honored to have Maja Bucan from the Perelman School of Medicine at the University of Pennsylvania (USA) as the 2017 Verne Chapman Memorial Lecturer, presenting "The Role of Essential Genes in Human Disease." Bucan described her life's "dance between mouse and human genetics," working at the interphase between human and mouse genetics to gain valuable insight into complicated psychiatric diseases. She explained how large-scale genetic studies have promoted an understanding of the genetic landscape for complex neurodevelopmental disorders such as ASD. This work has helped researchers understand how the disease burden arises from a background of common genetic variants, explaining disease heritability as well as rare de novo variants that have strong biological effects. Bucan's recent work has focused on identifying a set of "Human Essential Genes" as likely candidates for the common variant background. These genes are necessary for normal development and enriched for human disease genes. They are also intolerant to mutations and likely to be haploinsufficient, therefore under strong selection pressure. Using a cohort of 1781 ASD patients and their parents, Bucan's team determined the allele frequency of both de novo and inherited damaging variants in these essential genes. Clusters of these genes are co-expressed in the developing human brain and contribute to ASD risk. As Bucan's group works to expand our knowledge about these genes, they hope to also identify candidate genes for other complex human diseases.

Rosa Beddington Memorial Lecture

The Rosa Beddington Memorial Lecture is hosted each year by the Mouse Molecular Genetics group to remember Rosa Beddington, a distinguished scientist, extraordinary mammalian experimental embryologist, and talented artist who made seminal contributions to the field of developmental genetics. The 2017 honoree was developmental biologist Alexandra L. Joyner (Sloan Kettering Institute, USA). Joyner's talk, which was interspersed with some of Rosa Beddington's wonderful mouse sketches, focused on the regeneration of neurons in the cerebellum. The cerebellum undergoes significant changes in size, patterning, cell composition and connections at early postnatal stages, making it particularly vulnerable to injury soon after birth and in premature babies. A key challenge in the field of regenerative medicine is the ability to identify and manipulate progenitor populations in vivo. Joyner's group found that the neonatal mouse cerebellum can recover from ablation of most proliferating granule precursor cells. Surprisingly, this did not involve expansion of the surviving cells but rather an adaptive reprogramming response by Nestin-expression

progenitors that normally produce interneurons and astrocytes during cerebellar development. Joyner's group also found that Purkinje cells could be rapidly replenished in the neonatal period through an age-dependent adaptive response involving a FoxP2-expressing progenitor population. These exciting results challenge the accepted belief that postmitotic neurons are not capable of regeneration, and suggests that there is a window of time during which some progenitors can switch cell fate, acting as backup populations to buffer against early postnatal stress. Joyner's work provides a mechanistic understanding of neonatal regeneration that may translate to new approaches to activate regeneration in the adult brain.

Darla Miller Distinguished Service Lecture

The Darla Miller Distinguished Service award acknowledges Darla Miller's commitment and invaluable involvement in the IMGS and honors an individual who has provided outstanding service and contributions to the IMGS and/or the wider mouse genetics community. The 2017 recipient was Thomas L. Saunders, who spoke of his involvement in mouse genetics through "30 years of transgenesis." Saunders helped establish the Transgenic Animal Model Core facility at the University of Michigan (UM, USA) with Sally Camper with two goals: to generate transgenic mice, and to disseminate knowledge by providing training in transgenic procedures. Saunders' lecture was a journey through the history of transgenesis, highlighting the exciting challenges and great achievements in this rapidly evolving field. He showed a slide of UM transgenic mouse production over time (Fig. 1) that demonstrates how transgenesis is constantly changing and driven by technological advances; a productivity peak in the early 1990s coincided with the isolation of mouse ESC and their use for targeted mutagenesis, while a slump in 2014 may have been due to investigators holding off on new projects while assessing the ability of CRISPR/Cas9 technology to effectively generate mouse models and replace ESC-based methods. Our understanding of the genetic basis of health and disease have advanced, to a great extent, through mouse transgenesis and the efforts of scientists such as Thom Saunders.

Looking to the future

With ever more sophisticated methods to manipulate and sequence the mouse genome and transcriptome, and advances in imaging techniques that improve our ability to assess gene function and cell-level phenotypes, the mouse remains an ideal system for answering basic biological and genetic questions, modeling mammalian disease, and performing translational studies. Along with increased accessibility to technology and generation and sharing of sophisticated mouse models comes the need for scientific rigor and reproducibility. This year, the IMGC provided a platform for discussions on the need for basic guidelines for mouse genetic studies, brought forward by Fernando Pardo-Manuel de Villena in his "*Proposal to increase the rigor and*

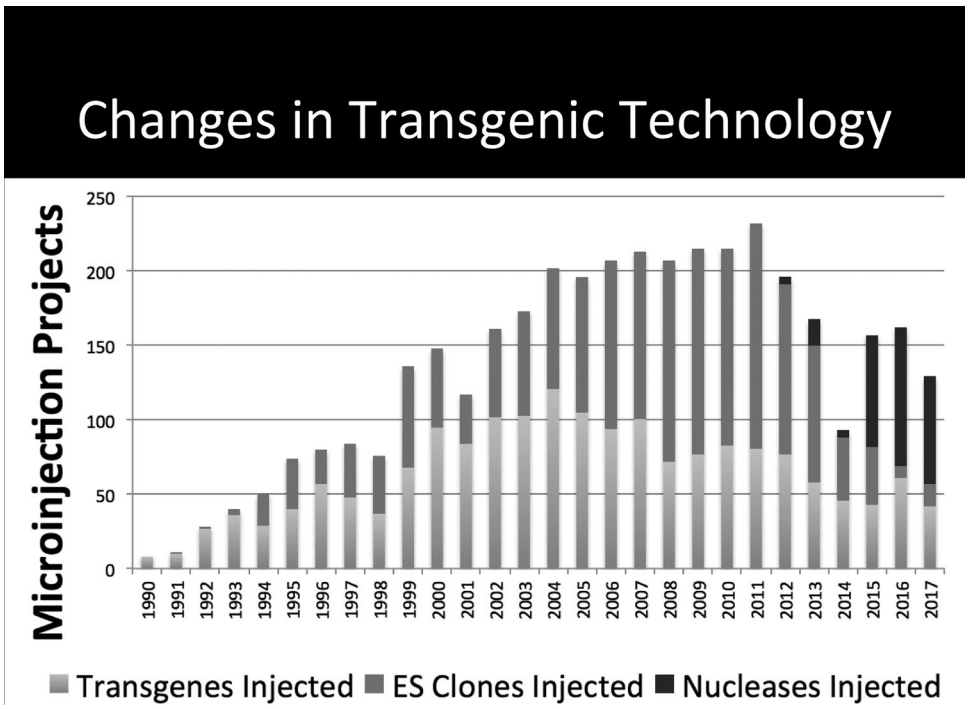

Fig. 1 A timeline of microinjection projects performed at the University of Michigan Transgenic Animal Model Core Facility. The graph shows how technological advances such as homologous recombination in mouse ESC (late 1980s) and CRISPR/Cas9-mediated genome editing (2013) have influenced production involving different transgenic procedures. This figure was kindly provided by Thomas Saunders

reproducibility of mouse research through genetic quality control." This topic, which will continue to be discussed within the community, highlights the importance of common minimum standards for performing and reporting studies involving laboratory mice.

Continuing its efforts to mentor young scientists and promote equality for women investigators, the IMGS has established the Mary Lyon Award for outstanding early-stage independent women scientists (pre-tenure Assistant Professor or equivalent) in the mouse genetic community. Awardees will be invited to present their research at an IMGC and their costs to attend will be covered by the IMGS. The inaugural Mary Lyon Award will be presented at IMGC2018. The IMGS encourages all community members to send their nominations (including self-nominations) to imgsgeneral@gmail.com; nominations will be accepted year-round. More information is available on the IMGS website (http://www.imgs.org).

The IMGS invites you to join IMGC2018, which will be held in beautiful Puerto Rico, November 11–14, 2018, at the beachfront Wyndham Grand Rio Mar Beach Resort & Spa (http://imgs.org/?run=conference.imgc2018). The Verne Chapman Lecture will be presented by Terry Magnuson, Vice Chancellor for Research at UNC-Chapel Hill. Careful consideration was given to the choice of venue given the devastating effects of hurricane Maria, but the resort suffered minimal damage and is ready to welcome our community. Puerto Rico offers an idyllic setting for the conference, and we expect there to be opportunities to engage and interact with local scientists. The organizers anticipate an interactive and stimulating conference that will bring together trainees and established scientists from around the world. Trainee travel scholarships will be available; applications from under-represented minorities are particularly encouraged. Application information will be posted on the IMGS website.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

Bloom JC, Tran TN, Yamulla RJ (2017) Mouse genetics 2016: meeting report. Mamm Genome 28(3–4):81–89

Gonzales NM, Howell VM, Smith CM (2016). 29th International Mammalian Genome Conference meeting report. Mamm Genome 27(5–6):169–178