33rd International Mammalian Genome Conference

Strasbourg - France
September 25th - 28th 2019

igbmc institut de génétique et de biologie moléculaire et cellulaire
phenomin CS EXCELLENCE IN MOUSE PHENOGENOMICS
INTERNATIONAL MAMMALIAN GENOME SOCIETY
CERBM gie centre européen de recherche en biologie et en médecine
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Université de Strasbourg
INVESTIR L'AVENIR

Welcome to the 33rd International Mammalian Genome Conference

IGBMC - Illkirch-Strasbourg, FRANCE
September 25-28, 2019

A warm welcome to the 33rd annual conference of the International Mammalian Genome Society and to the Institute of Genetics, Molecular and Cellular Biology, Strasbourg, France. We hope you will enjoy the meeting with an exciting and stimulating program based on state-of-the art research on mammalian genetics and genomics.

The meeting will start with several Bioinformatics satellite workshops. The Trainee Symposium will feature presentations by students and post-docs who will compete for awards and presentation slots in the main meeting. A mentoring lunch will give those looking for career advice the opportunity to interact with established scientists.

Sessions of the main conference will address:
Technical Advances and Resources
Comparative genomics, computational methods and evolution
Development, Epigenetics and Stem cells
Human disease models: Cancer and environmental factors, Neurobehavior, Infection and immunology, Metabolism and Blood

Capital of Alsace, Strasbourg is one of Europe's most attractive European cities. After the two World Wars, the city has become the symbol of Franco-German reconciliation, and by extension, of European friendship. Seat of the Council of Europe since 1949, it also plays host to the European Court of Human Rights and the European Parliament. The Old Town district is a gem waiting to be discovered, with its monumental cathedral featuring carvings as delicate as any piece of lacework and the enchanting Petite France district. Thanks to the richness and sheer density of its heritage sites, the entire town centre has been listed as UNESCO World Heritage. Strasbourg is definitely well worth a visit, to discover its history, its cuisine and its unique atmosphere.

Strasbourg, a city of many cultures, gastronomy and firmly rooted traditions, is also the number one place for foreign students. Strasbourg's sense of hospitality has contributed to enhancing its tourist appeal, notably with its famous Christmas market. Finally, Strasbourg is a pioneer city in terms of respect for the environment, a very pleasant place to live in and a good start to visit the wonderful Alsace.

Welcome to Strasbourg !

TABLE OF CONTENT

GENERAL INFORMATION

Certificate of Attendance

Certificates will be emailed to delegates after the conference upon request only at emailimgs@igbmc.fr

Insurance

The Conference Organizers cannot accept any liability for personal injuries or for loss or damage to property belonging to delegates, either during, or as a result of the meeting. Please check the validity of your own personal insurance before traveling.

Meeting Etiquette

Delegates are advised that they are not allowed to take photographs of any posters or presentations without the author's presenter's consent. Delegate should also obtain consent from an author before citing any of their work that was presented at the conference.

Cell phones or other devices that have notification sounds should be switched off or placed on silent during sessions. Please also respect speakers and other delegates and refrain from talking during presentations. Thank you for your cooperation.

Internet Access

Internet access at IGBMC (meeting site) will be freely accessible, connection details will be provided at your arrival the conference.

Catering

The lunch boxes (ticketed) after the workshops and the opening reception and cocktail will be in served in the marquee near our main auditorium, directions will be signposted on site. Breakfast is to be arranged at your hotel. Lunches and breaks will be in the marquee. The final Awards Dinner (ticketed) will be at the Storig Brewery. Transportation by bus to this stunning location will be provided. If you requested a special diet at the time of registration, this has been be taken into account. Since most meals will be served buffet style, except for vegetarian diet, you must present yourself and your special diet to the caterer team directly at lunch time.

Exhibition and Poster Times

The Exhibition area will be open during all conference hours but please follow these guidelines:

- Odd Posters Numbers:
  Hanging: starting at 08:00 AM on Thursday, September 26th and removal by 6 PM on the same day
  Presenters should be by their posters on THURSDAY, September 26 from 3:20 until 5:15 PM
- Even Poster numbers:
  Hanging: starting at 08:00 AM on Friday, September 27th and removal by 6:30 PM on the same day
  Presenters should be by their posters on FRIDAY, September 27 from 4:30 until 6:30 PM

Registration Desk

All delegates will receive their name badge and meeting documents upon arrival at the IMGC2019 registration desk in the Main Lobby at the main entrance of IGBMC. The registration desk will be open during all normal conference hours starting at 8AM on Wednesday, September 25.

Speaker Presentation Check-in

Presenters should bring their presentation on a USB drive to the conference. All presentations will be loaded onto a main presentation computer in the session room. Presenters will not be using their own laptops for presentations. Please check your presentations in at least one session prior to your presentation time.

Mentoring Lunch

Those students and post docs interested in participating in the Mentoring Lunch on THURSDAY, September 26, should look for the designated tables in the Dining Room when entering for that meal.

Enjoy the 33rd IMGC!!

AWARDS

The Secretariat and members of The International Mammalian Genome Society are proud of the students, postdoctoral fellows and junior faculty who present oral and poster presentations at the annual meeting. The outstanding contributions of these young scientists are recognized through several awards.

The first of these awards is the Verne Chapman Young Scientist Award, which is given to the most outstanding oral presentation from a postdoctoral fellow or student. This is a monetary award of $500 and a two-year position on the IMGS secretariat that reflects Dr. Chapman's dedication to mentoring junior scientists.

A selection of publishing companies have sponsored this year's presentation prizes, which are a one year subscription to their journal or a donation of books. A cash award is given by The Genetics Society of America.

These awards are given to the most outstanding poster or oral presentations by graduate students and postdoctoral fellows, and are chosen by members of the IMGS Secretariat and other judges during the course of the meeting.

This year the sponsors are

Genetics Research from:

CAMBRIDGE JOURNALS
journals.cambridge.org

GSA

Springer

GENOME RESEARCH

STUDENT SCHOLARSHIPS

Funding for student scholarships was made possible by from **NHGRI and NIEHS** under grant R13HG002394 and from the **University Of Strasbourg** under the framework of the **Idex Unistra** and benefits from a funding from the State managed by the French National Research Agency as part of the investments for the future program.

IMGS COMMITTEES

IMGS Secretariat

Martin Hrabe de Angelis, Past President (2020)
Linda Siracusa, President (2022)
Fernando Pardo-Manuel de Villena, Vice-President (2024)
Kuniya Abe (2019)
Lauren Tracey (VM Chapman Award Winner)
Ruth Arkell (2020)
Laura Reinholdt (2020)
Junyue Cao (VM Chapman Award Winner)
Elizabeth Bryda(2021)
Yann Herault (2021)
Michelle Southard-Smith (2021)

IMGS Nomination and Election Committee

Marty Ferris (2019)
Viive Howell (2019)
Beth Dumont (2020)
Atsushi Yoshiki (2020)

33rd IMGC Scientific Organizers

Yann Herault
Xavier Montagutelli,
Joelle Pensavalle
Myriam Rebetez

IMGS COO

Darla Miller

International Committee on Standardized Genetic Nomenclature for Mice

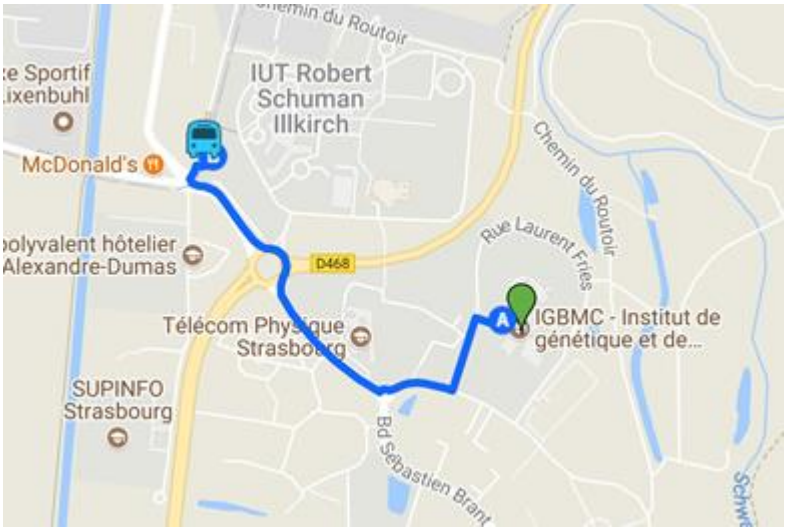
Ruth Arkell	Judith Blake	Elspeth Bruford
Elizabeth Bryda	Sandra Buhl	Teresa Gunn
Ann-Marie Mallon	Doug Marchuk	Monica McAndrews
Lluis Montoliu	Steve Murray	Valerie Schneider
Cynthia Smith (Chair)	Lydia Teboul	David Threadgill
Jacqui White	Laurens Wilming	

MEETING VENUE: ACCESS INFORMATION

MEETING VENUE: IGBMC, 1 rue Laurent Fries, Parc d'Innovation, 67404 Illkirch
Phone (reception Desk): + 33 (0)3 88 65 32 00
Link to the interactive map for further details:

BY TRAMWAY

Direct connection Meeting venue – City Center: Take Line A, direction "Illkirch-Graffenstaden", "Campus d'Illkirch" exit.



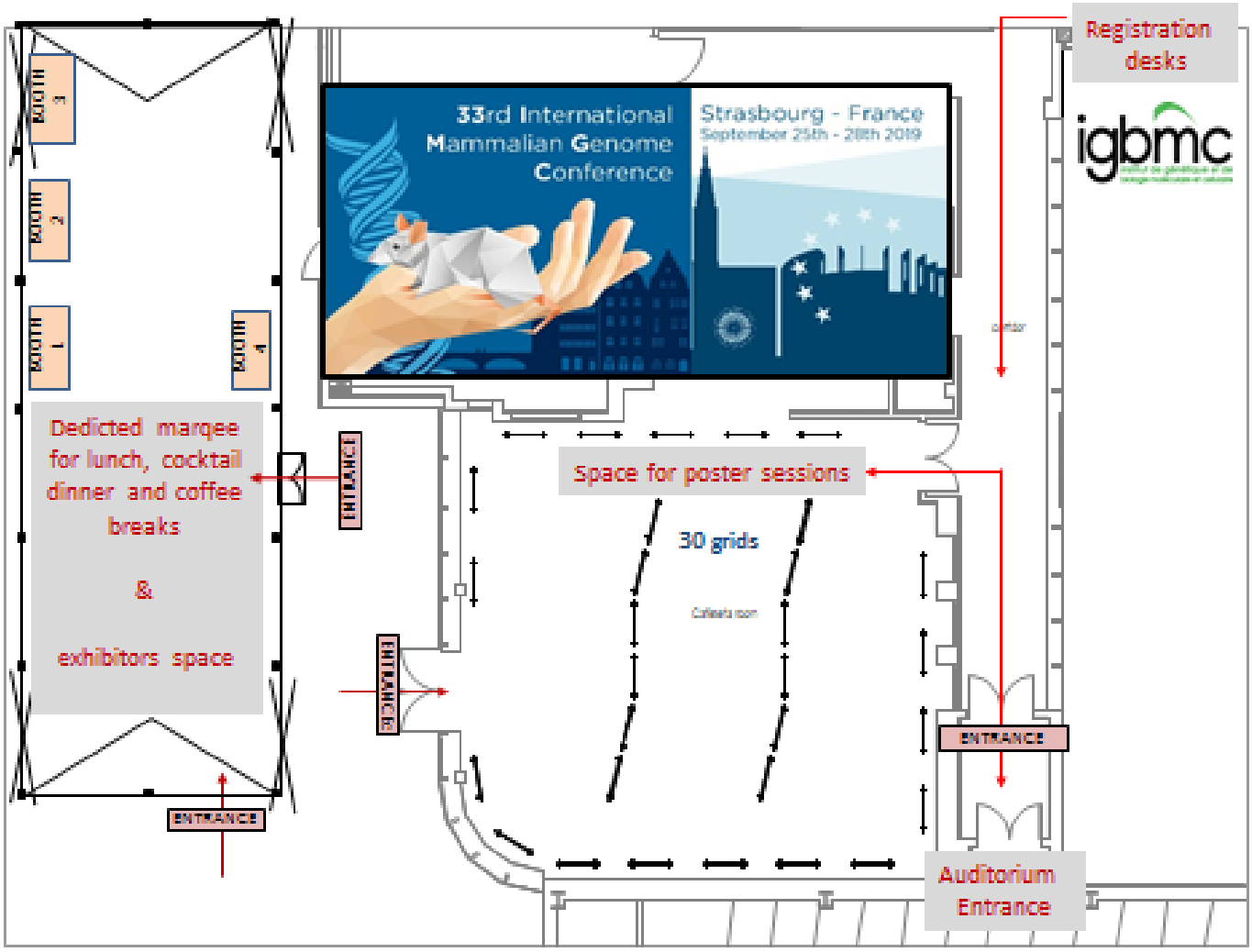
By foot from the "Campus d'Ilkirch" tram/bus station:
Walk towards "Parc d'Innovation" indicated on the street panels. At the second roundabout, the second exit leads to IGBMC (10 min).

Strasbourg Public Transportation Company: CTS www.cts-strasbourg.fr
Strasbourg Major Taxi company: Taxi 13 www.taxi13.fr +33(0)3 88.36.13.13

BUS SHUTTLES ARE ORGANIZED

Basically each morning from Down town Strasbourg to IGBMC meeting venue, except on Wednesday 25th
At the end of each day from IGBMC meeting venue to Down town Strasbourg.
For the gala dinner: From IGBMC in Illkirch and down town Strasbourg to Gala dinner and back at the end of the gala.

IGBMC CONGRESS AREA



EXHIBITORS/ SPONSORS

The International Mammalian Genome Society would like to thank the following exhibitors and sponsors for their support:

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www.transtechsociety.org

International Society for Transgenic Technologies

The International Society for Transgenic Technologies (ISTT) seeks to foster communication and technology sharing, to enhance scientific research, to advance the field of animal transgenesis, particularly as it applies to useful experimental models in biology, medicine and biotechnology, and to represent the interests of an international body of professionals (scientists, technicians, and graduate students) working in the field of transgenic technologies.

Become a member! Be part of our community!

Member benefits include:

- Reduced registration fees to the Transgenic Technology (TT) meetings
- Priority and/or reduced-fee registration for ISTT-sponsored courses, workshops, seminars and meetings
- Free on-line access to *Transgenic Research*
- 33% discount on selected Springer books related to the field of animal genetics or animal transgenesis
- Exclusive access to unique on-line content (pictures, videos, methods, talks, posters) on the ISTT website
- Subscription to the ISTT_list and archives, the discussion email list for ISTT members
- Eligibility for ISTT registration/travel awards to attend ISTT co-sponsored events
- Opportunity to contribute to ISTT committees

Further information on membership can be found at:

www.transtechsociety.org

PROGRAM AT A GLANCE

Tuesday 24- Sept.

2:00 PM	Secretariat Meeting		IIGBMC Room iCS 3013
6:00 PM	END		

Wednesday 25- Sept.

9:00 AM	Workshops		
12 :00 PM	Lunch Boxe (if ordered)		
1:00 PM	Trainee Symposium	Session 1	Auditorium
3:00 PM	Break		
3:30 PM	Trainee Symposium	Session 2	
6:30 PM	Cocktail reception/dinner		
8:30 PM	Chapman Lecture	Rudi Balling	
9 :45 PM	Bus Leaves to Down town		

Thursday 26-Sept.

8:45 AM	Welcome		
9:00 AM	Session I	Development, Epigenetics and Stem cells 1	
10:30 AM	Break		
11:00 AM	Session II	Development, Epigenetics and Stem cells 2	
12:15 PM	Mentor Lunch Editorial Board Lunch		
1 :45 PM	Session III	Human disease models : Neurobehavior	
3:15 PM	Posters (odd) Break		
5:15 PM	Panel Discussion	INFRAFRONTIER	Sustainability of Mouse Informatics Resources Panel Discussion
6:30 PM	Buses leave		
	Optional Tours	Dinner on Own	

Friday 27-Sept.

8:45 AM	Announcements		
9:00 AM	Session IV	Human disease models : Infection and immunology	
10:35 AM	Break		
11:00 AM	Session V	Human disease models : Metabolism and Blood	
12:30 PM	Lunch Nomenclature lunch		
2:00 PM	Session VI	Technical Advances and Resources	
3:30 PM	IMGS Business Meeting		
4:30 PM	Poster Session (Even)/Break		
6:30 PM	Buses leave		
	Optional Tours	Dinner on Own	

Saturday 28-Sept.

8:45 AM	Announcements		
9:00 AM	Session VII	Technical Advances and Resources 2	
10:30 AM	Break		
	Session VIII	Human disease models : Cancer and environmental factors	
12:15 PM	Lunch & Secretariat lunch		
2:15 PM	Session IX	Comparative Genomics, Computational Methods & Evolution	
3:35 PM	Summary remarks		
3:45 PM	END		
4:00 PM	Buses leave		
7:00 PM		Gala Dinner	

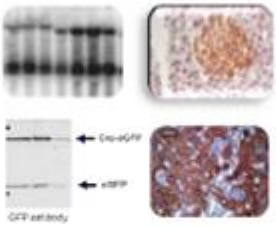
Custom Model Generation and Phenotyping

Generation

- Targeted strategy in accordance with your needs
- > 200 Transgenic and > 1300 Targeted mutagenesis projects
- Chromosome Engineering
- Nuclease genome editing (CRISPR/Cas9) *NEW offer *

Validation

- Gene expression validation
- Copy number determination
- Functional validation



Phenotyping

- 150-200 projects / year
- ~ 12 therapeutic areas

8 Platforms

- In vivo disease models

- More than 250 assays available for various functions

Right answer to your scientific project

Therapeutic areas

Psychiatry, Neurology
Cardiac system
Vascular system
Lung exploration functions
Energy metabolism exploration
Oncology
Glucose homeostasis
Bone exploration
Intestinal function
Renal function
Immunology , inflammation
Development and growth

Drug screening:

Target identification / validation
Risk assessments/Side effects

Imaging:

Preclinical in vivo imaging (radiographic, radioisotopic, photoacoustic)
Imaging under BSL3 conditions (optic, confocal..)

In vivo disease models

Lung disease, asthma, inflammation
Intestinal bowel disease (~DSS), peritonitis
Hypertension, Cardiac hypertrophy
Diet induced atherosclerosis
Diet induced obesity, Diabetes
Memory and learning deficits, Alzheimer, ...

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EXCELLENCE IN MOUSE PHENOGENOMICS

TECNIPLAST

innovation through passion℠

Tecniplast, a reference for animal facilities.

HISTORICAL

Tecniplast s.p.a. was founded in **1949** in Varese, near Milan. The company is specialized in the design and manufacture of all species cages and changing stations for animal facilities. Tecniplast Group in Italie is composed of Tecniplast S.p.a et IWT s.r.l companies which design and manufacture the equipment, and bring technical support for Tecniplast France.
Founded in December 2003, Tecniplast France is the preferred commercial and technical contact for any French customer.

- **1949** — Tecniplast foundation
- **1962** — the first moulded plastic cage
- **1972** — Metabolism plastic cage
- **1989** — IVC first generation
- **1993** — IWT foundation
- **2000** — 1340 washing machines
- **2004** — Tecniplast France birth
- **2019** — 900 employees worldwide

CORE VALUES & MISSION OF OUR COMPANY

CORE VALUES

- Innovation
- Passion
- Experience & Competence
- Enduring Responsibility
- Globally reach
- Integrated solution provider

MISSION

Delivering solutions that enhance
- occupational work and safety
- animal well-being
- biomedical research outcome

THE INGREDIENTS OF OUR SUCCESS

- Product portfolio
- Customer support
- Social & Environmental sustainability

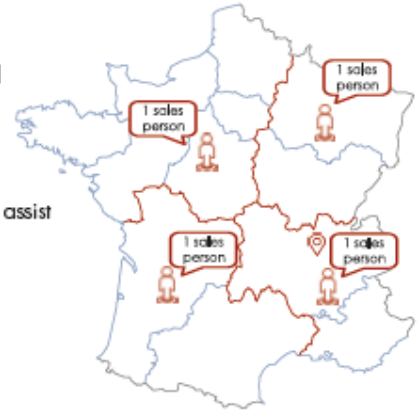
AVAILABLE CERTIFICATIONS

Tecniplast is certified UNI EN ISI 9001:2015 and ISO 14001:2015.
IWT is also certified ISO 9001:2015 et ISO 14001:2004.
The company obtained its first ISO 9001 certification more than 10 years ago.

WHY TECNIPLAST ?

- **Cutting-edge technology** for **first-class products**
- **Eco-designed products** with top quality and ergonomics, thus assuring lower running costs
- **Integrated solutions** from housing to decontamination through logistic material
- **Layout service and work-load analysis** to assist room and cage wash design
- **Solid organization**
- **Training and local service**
- **Automation** as a key for innovation

TPFRANCE



36 employees in France :
- **5** sales person
- **3** project managers
- **1** technical service manager
- **10** technicians

500 m² spare parts internalized stock

a **200 m²** showroom

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PROGRAM IN DETAIL

Tuesday 24- Sept.

2:00 PM	**Secretariat Meeting**	**Room iCS 3013**	
6:00 PM	**END**		

Wednesday 25- Sept.

9:00 AM	**Workshops**		
	Room IGBMC 4004	Andrew Berry, Emily Perry, and Tayebeh Rezaie	Exploring the mouse genome in Ensembl and Previewing GRCm39: assembly updates from the GRC
	Room IGBMC 0075	Thomas Keane	Next Generation Sequencing
	Room CBI 3029	Ann-Marie Mallon	Using International Mouse Phenotyping Consortium (IMPC) data
	Room CBI 1031	Joel Richardson Jason Bubier	Exploring multiple mouse genome with MGI's Multiple Genome Viewer GeneWeaver presentation and tutorial demonstration
	Room IGBMC 3005	C.B. Gurumurthy	Easi-CRISPR: CRISPRing Made Easier
12:00 PM	**Lunch (if ordered)**		
	Trainee Symposium	**Chair Fernando Pardo-Manuel de Villena and Linda Siracusa**	
1:00 PM	TS-01	Kuffler Lauren	Transcriptional effects of genetic-epigenetic interactions on local genes and distant gene networks
1:15 PM	TS-02	Morgan Hugh	Exploring the landscape of subviability in the knockout mouse
1:30 PM	TS-03	Xenakis James	A Statistical Model of Methylation Sequencing Data Identifies Novel Differentially Methylated CpG's and Provides Insights into the Role of Methylation in X-chromosome Inactivation and the Silencing of Transposable Elements
1:45 PM	TS-04	Lewis Lauren	MicroRNA as regulators of 1,3-butadiene-induced strain- and tissue-specific effects in mice.
2:00 PM	TS-05	Mantilla Rojas Carolina	EGFR-independent colorectal tumors progress through enhanced IL10RA signaling
2:15 PM	TS-06	Krayem Imtissal	Strong Epistasis in Genetics of Leishmaniasis - Search for Genes and Mechanisms
2:30 PM	TS-07	Leist Sarah	Deciphering the impact of the host immune response on SARS-CoV susceptibility or resistance using a reduced complexity cross
2:45 PM	TS-08	Mayeux Jessica	Modeling spontaneous systemic autoimmunity using the Collaborative Cross mouse

Wednesday 25- Sept.

3:00 PM	**Break**		
3:30 PM	TS-09	Kimmerlin Quentin	The a4a- and b1-tubulin isotypes work together to sustain efficient platelet biogenesis and hemostasis
3:45 PM	TS-10	Tang Vi	SAR1A rescues the hypocholesterolemia resulting from hepatic Sar1b deletion in mice
4:00 PM	TS-11	Muniz Moreno Maria Del Mar	Network analysis of the brain dysfunction observed in Down syndrome models
4:15 PM	TS-12	Lee Han Kyu	Identification of novel neuroprotective loci modulating ischemic stroke volume in a cross between wild-derived inbred mouse strains
4:30 PM	TS-13	Wells Ann	Natural variation alters Alzheimer's-related gene expression in DO mice
4:45 PM	TS-14	Dai Yichen (Serena)	Weird gene in a weird mammal: A highly divergent pancreatic duodenal homeobox 1 (Pdx1) gene in the fat sand rat
5:00 PM	TS-15	Gazizova Guzel	Regulation of hibernation: promoter expression landscape in skeletal muscle of edible dormouse
5:15 PM	TS-16	May-Zhang Aaron	Identification of discrete subtypes of enteric neurons in humans using cross-species comparison of RNA-Seq data
5:30 PM	TS-17	Noll Kelsey	Role for genetic variation in antibody response to Influenza A Virus
5:45 PM	TS-18	Salvador Anna	Genetic control of hepatic energy metabolism and response to carbohydrate restriction
6:30 PM	**Cocktail reception/dinner**		
8:30 PM	**The Chapman Lecture**	**Chair : Linda Siracusa**	
8 :30 PM	**Oral-01**	**Rudi Balling**	Leaving the comfort zone and why others also only cook with water
9 :45 PM	**Bus Leaves**	**For down town Strasbourg**	

Welcome to IMGC 2019

Come visit us at the Neogen Exhibit

Introducing the new miniMUGA Genotyping array

- 11,000 SNPs for discriminating more than 200 inbred strains and commercially available substrains
- Probabilistic chromosomal sex determination
- Low cost and easy to evaluate report
- Detection of commonly used constructs used for genetically engineered mice

GigaMUGA Genotyping array

- Providing more than 143,000 SNPs allowing for an average number of informative SNPs of greater than 25,000 for most inbred strains
- Ideal for genetic mapping in highly diverse mouse population such as the Diversity Outbred and heterogeneous stocks

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MODERN
FLEXIBLE
COMPLETE

Thursday 26-Sept.			
8:45 AM	**Welcome**	**Yann Hérault – Xavier Montagutelli**	
9:00 AM	**Session I**	**Development, Epigenetics and Stem cells 1**	
		Chair: Xavier Montagutelli - Lauren Tracey	
9:00 AM	Oral-02	Alexandre Reymond	Genome architecture and diseases: the 16p11.2 paradigm
9:30 AM	Oral-03	Fufa Temesgen	Mapping the cis-regulatory landscape of the developing human retinal pigment epithelium for elucidating noncoding ocular disease mechanisms
9:45 AM	Oral-04	Hinttala Reetta	Mouse model for finca (fibrosis, neurodegeneration and cerebral angiomatosis)
10:00 AM	Oral-05	Petkov Petko	Roles of two PRDM9 interactors CXXC1 and EWSR1 in meiotic recombination
10:15 AM	Oral-06	Caldwell Blake	TET2-mediated active DNA demethylation promotes iPSC generation in a MEF reprogramming model
10:30 AM	**Break**		
11 :00 AM	**Session II**	**Development, Epigenetics and Stem cells 2**	
		Chair: Yann Herault - Akira Tanave	
11:00 AM	Selected TS Talk 1		
11:15 AM	Oral-07	Heffner Caleb	A rapid platform for direct modeling of human developmental disorders in mice using CRISPR/Cas9 genome editing.
11:30 AM	Oral-08	Mark Manuel	Retinoic acid: essential for reproduction, not for meiosis
11:45 AM	Oral-09	Kappen Claudia	Transient CRISPR/Cas9 assay of candidate genes for neural tube defects
12:00 PM	Oral-10	Fuchs Helmut	A novel m6A RNA methyltransferase in mammals - characterization of Mettl5 mutant mice in the German Mouse Clinic
12:15 PM	**Mentor Lunch**	**Editorial Board Lunch (Room iCS 3013)**	
1:45 PM	**Session III**	**Human disease models : Neurobehavior**	
		Chair : Michelle Southard Smith - Adelaide Tovar	
1:45 PM	Oral-11	Cordes Sabine	An intersection between an autism spectrum disorder (ASD)-associated microexon splicing program and vertebrate-specific post-translational modification shapes vertebrate behavior
2:00 PM	Oral-12	Hill Sophie	Anti-sense oligonucleotide therapy delays seizure onset and extends survival in a mouse model of Scn8a encephalopathy
2:15 PM	Selected TS Talk 2		Exploring the landscape of subviability in the knockout mouse
2:30 PM	Oral-14	Walter Michael	Pigmentary glaucoma results from mutations in the functional amyloid PMEL
2:45 PM	Oral-15	Koide Tsuyoshi	Behavioral, neurological and genetic bases of tameness in mice
3:00 PM	Oral-16	Binnaz Yalcin	Genetics of mammalian brain morphogenesis
3:15 PM	**Posters (odd) Break**		
5:15 PM	**Panel Discussion**	INFRAFRONTIER	INFRAFRONTIER Sustainability of Mouse Informatics Resources Panel Discussion
6:30 PM	**Buses leave**		
	Optional Tours	**Dinner on Own**	

Friday 27-Sept.			
8:45 AM	**Announcements**		
9 :00 AM	**Session IV**	**Human disease models : Infection and immunology**	
		Chair: Martin Hrabe de Angelis - Callan O'Connor	
9:00 AM	Oral-17	Christine Disteche	Long non-coding RNAs and X chromosome 3D structure and epigenetics
9:30 AM	Oral-18	Gralinski Lisa	Identifying host susceptibility factors to SARS-CoV infection using a Balb/c reduced complexity cross
9:45 AM	Oral-19	Jaubert Jean	A loss-of-function mutation in Itgal contributes to the high susceptibility of strain CC042 to Salmonella infections
10:00 AM	Oral-20	Manet Caroline	Host genetics controls susceptibility to Zika virus in Collaborative Cross mice
10:15 AM	Selected TS Talk 3		
10:30 AM	**Break**		
11:00 AM	**Session V**	**Human disease models : Metabolism and Blood**	
		Chair: Laura Reinholdt - Alexis Bachmann	
11:00 AM	Selected TS Talk 4		
11:15 AM	Selected TS Talk 5		
11:30 AM	Oral-21	Brake Marisa	Analysis of a Sensitized Mouse ENU Screen Identifies Non-ENU Suppressor Variants Introduced Due to Selective Pressure
11:45 AM	Oral-22	Skelly Dan	Diet-driven changes in immune regulation of adipose tissue revealed by single cell transcriptomics
12:00 PM	Oral-23	Iraqi Fuad	Studying the Multimorbidity of Alveolar Bone Changes, intestinal cancer, atherosclerosis, obesity and Impaired Glucose Tolerance in response to High-Fat Diet Consumption using Collaborative Cross Mouse Population
12:15 PM	Oral-24	Tracey Lauren	The pluripotency regulator PRDM14 requires hematopoietic regulator CBFA2T3 to initiate leukemia in mice
12:30 PM	**Lunch**	**Nomenclature lunch (Room iCS 3013**	
2:00 PM	**Session VI**	**Technical Advances and Resources**	
		Chair : Kuniya Abe - Danila Cuomo	
2:00 PM	Oral-25	Bergstrom David	The JAX Genome Editing Testing Center: A Component of the Somatic Cell Genome Editing Consortium
2:15 PM	Oral-26	Ashbrook David	Sequencing the BXD family, a cohort for experimental systems genetics and precision medicine
2:30 PM	Oral-27	Teboul Lydia	Validation of increasingly complex alleles generated by genome editing: employing long read sequencing
2:45 PM	Oral-28	Pavlovic Guillaume	Understanding the variability of the fecal microbiota and large scale evaluation of Host â€“ Microbial genetics interactions: impact of the IMPC knock-out resource for the microbiota community
3:00 PM	Oral-29	Keane Thomas	Reference quality mouse genomes reveal complete strain-specific haplotypes and novel functional loci
3:15 PM	Oral-30	Bult Carol	The Alliance of Genome Resources: Transforming comparative genomics for human and model organisms
3:30 PM	IMGS Business Meeting		
4:30 PM	**Poster Session**	**(Even)/Break**	
6:30 PM	**Buses leave**		
	Optional Tours	**Dinner on Own**	

Saturday 28-Sept.

8:45 AM	**Announcements**		
9:00 AM	**Session VII**	**Technical Advances and Resources 2**	
		Chair : Ruth Arkell - Fernanda Ruiz Fadel	
9:00 AM	Oral-31	Marisa Bartolomei	Regulation of genomic imprinting in development and disease
9:30 AM	Oral-32	Saunders Thomas	Generation and Characterization of Transgenic Rats Carrying Cre Recombinase Knockins at the Dopamine D1 and Adenosine 2a Receptor Loci.
9:45 AM	Oral-33	Solberg-Woods, Leah	Identification of novel genes for adiposity and lipids using outbred heterogeneous stock rats
10:00 AM	Oral-34	Wang, Shur-Jen	Searching diseases and phenotypes for model selection at the Rat Genome Database
10:15 AM	Oral-35	Auerbach, Wojtek	Large humanization in rat ES cells
10:30 AM	**Break**		
11:00 AM	**Session VIII**	**Human disease models : Cancer and environmental factors**	
		Chair: Elizabeth Bryda - Courtney Vaughn	
11:00 AM	Oral-36	Hunter Kent	Aicardi-Goutières Syndrome gene Rnaseh2c is a metastasis susceptibility gene in breast cancer
11:15 AM	Oral-37	Amos-Landgraf James	Bilophila wadsworthia supplementation reduces adenoma burden in the Apc-Min mouse model of colorectal cancer
11:30 AM	Oral-38	Jones Byron	Modeling the Genetics of Gulf War Illness in the Mouse
11:45 AM	Oral-39	Reinholdt Laura	Genetic variation influences pluripotent ground state stability in mouse embryonic stem cells through a hierarchy of molecular phenotypes
12:00 PM	Oral-40	Dumont Beth	Patterns and Mechanisms of Sex Ratio Bias in the Collaborative Cross
12:15 PM	**Lunch**	**Secretariat lunch (Room iCS 3013)**	
2:15 PM	**Session IX**	**Comparative Genomics, Computational Methods & Evolution**	
		Chair : Fernando Pardo-Manuel de Villena - Anu Shivalikanjli	
2:15 PM	Oral-41	Melissa Wilson	Sex-biased genome evolution
2:35 PM	Oral-42	Valdar William	QTL mapping power in the realized Collaborative Cross
2:50 PM	Oral-43	Blake Judith	Comparative Genomics: The Pseudogene Challenge
3:05 PM	Oral-44	Wilming Laurens	Annotating Sequence Variants for Phenotypic Mouse Alleles at Mouse Genome Informatics
3:20 PM	Oral-45	Munger Steven	Learning the ABCs from ESCs to NPCs: Exploiting genetic diversity to elucidate the gene regulatory networks underlying cell differentiation.
3:35 PM	Summary remarks		
3:45 PM	**END**		
4:00 PM	**Buses leave**		
7:00 PM		**Gala Dinner**	

TRAINEE SYMPOSIUM ABSTRACTS

TS-01 : Transcriptional effects of genetic-epigenetic interactions on local genes and distant gene networks

Kuffler Lauren* (1) (2), Skelly Daniel (2), Czechanski Anne (2), Churchill Gary (2), Munger Steven (2), Baker Christopher (2), Reinholdt Laura (3), Carter Gregory (2)

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Modulation of gene expression is fundamental to development, differentiation, and maintenance of homeostasis. Modern genetics has recognized the effects of stable epigenetic factors (or the "epigenotype"), and non-coding regions on gene expression, particularly in those within a gene's “local area”. The interaction between genetic and epigenetic regulatory elements are not systematically understood, and their effects on downstream gene networks are unknown. This project aims to move past isolated genotype or epigenotype influences on expression and explore the extent of genotype-by-epigenotype interaction, its effects on expression, downstream gene networks, and ultimately phenotype. We have worked towards this goal by leveraging genetic and epigenetic data from a panel of Diversity Outbred mouse embryonic stem cells, implementing computational tools to identify local effects of genotype-by-epigenotype interaction. This analysis has revealed significant interactions between genetic variation and areas of open chromatin, which have a quantifiable and predictable effect on transcription of local and downstream genes. The distribution of these interactions map to the boundaries of topologically associated domains. We are preparing to verify the effects of these interactions *in vitro* by manipulating interacting non-coding regions associated with the gene *Duxf3*, which sits at the head of a large but relatively unexplored network of genes that governs the 2-cell-like subpopulation of embryonic stem cells.

*Presenter

TS-02 : Exploring the landscape of subviability in the knockout mouse

Morgan Hugh* (1)

1 - MRC Harwell (United Kingdom)

Subviable knockout mouse lines are those that the homozygous individuals have reduced embryo / perinatal survival. These lines are of particular interest because of the combination of developmental abnormalities and semi-penetrant phenotype, and are enriched for those genes involved with human disease. To examine this phenomenon we have analysed the range of viability present in the International Mouse Phenotyping Consortium (IMPC) dataset of 5022 mouse mutants. We find that 18% of lines show a significant level of subviability, from very few individuals surviving to nearing, but not reaching Mendelian ratios.. An analysis of the adult phenotyping data shows that the lines that exhibit subviability show a different distribution of phenotypes to completely viable lines, with particular enrichment in body composition and hearing phenotypes. Comparing these genes to external datasets shows that this subviable class of genes is of particular relevance to human health.

*Presenter

TS-03 : A Statistical Model of Methylation Sequencing Data Identifies Novel Differentially Methylated CpG's and Provides Insights into the Role of Methylation in X-chromosome Inactivation and the Silencing of Transposable Elements

Xenakis James* (1), Kim Kyungsu (2), Zhabotynsky Vasyl (3), Mi Xinlei (4), Crowley James (5), Sullivan Patrick (6) (7) (5), Pardo-Manuel De Villena Fernando (5) (2)

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Mammalian DNA methylation was first documented in the 1940's, and has since been implicated as a major epigenetic modification in a wide range of cellular processes. While it is essential to mammalian development, aberrant methylation is also associated with disease (e.g., cancer). We applied Reduced Representation Bisulfite Sequencing (RRBS) technology to reciprocal F1 females from two genetically divergent mouse inbred strains (129S1/SvImJ and PWK/PhJ) to dissect the strain and parent-of-origin (PoO) effects on differential methylation. We collected whole-brain DNA from four samples and used Illumina HiSeq 2000 to generate 50 bp single end reads. We used a custom RRBS pipeline to align high-quality reads to the pseudogenomes of 129S1/SvImJ and PWK/PhJ. We then fit a novel statistical model to the RRBS data at each CpG site, treating the number of methylated reads as arising from a beta-binomial distribution, which jointly modeled both strain and PoO effects. We accounted for small-sample type-I error inflation by employing the permutation approach of Devlin and Roeder (1999). Despite the small sample size, we identified differentially methylated CpG sites exhibiting PoO effects near 16 genes, 14 of which are known imprinted genes and two of which are novel (*Mir344i* and *2310015A10Rik*). We also identified 7,425 differentially methylated CpG sites that exhibited significant strain effects. We then used the results to investigate the role of DNA methylation in X-chromosome inactivation and the potential silencing of transposable elements (TE). We identified hundreds of CpG's clustered in dozens of regions of the X chromosome with differential methylation patterns that are indicative of X-inactivation status (including skewed X-inactivation). Further, we associated the observed differential CpG methylation with differential insertion of TE's into the 129S1/SvImJ and PWK/PhJ genomes, likely reflecting the role of DNA methylation in their epigenetic silencing.

*Presenter

TS-04 : MicroRNA as regulators of 1,3-butadiene-induced strain- and tissue-specific effects in mice.

Lewis Lauren* (1), Chappell Grace (1), Blazier John (1), Konganti Kranti (1), Israel Jennier (2), Simon Jeremy (2), Peck Bailey (2), Eklund Karl (2), Furey Terry (2), Rusyn Ivan (1)

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2 - University of North Carolina, Chapel Hill (United States)

1,3-Butadiene is a known rodent and human carcinogen that is both an occupational and environmental health hazard. Genotoxicity is an established mechanism of 1,3-butadiene carcinogenicity; however, it does not explain the tissue-specific tumor development observed in mice. Our previous work demonstrated strain- and tissue-specific alterations in epigenetic effects in response to 1,3-butadiene exposure which may contribute to tissue-specific toxicity. MicroRNA (miRNA) represent another epigenetic mechanism for regulating gene expression and have been implicated in carcinogenesis. In this study we tested the hypothesis that miRNA regulate strain- and tissue-dependent transcriptional and epigenetic responses to 1,3-butadiene exposure in CAST/EiJ and C57BL/6J mice. These mice were exposed to 0 or 625 ppm 1,3-butadiene (6 hr/day, 5 days/week) for 2 weeks. We evaluated changes in mRNA and miRNA expression by sequencing the lung, liver, and kidney tissues. We observed strain- and tissue-specific mRNA and miRNA expression profiles in response to 1,3-butadiene exposure. The miRhub algorithm was used to investigate miRNA as regulators of 1,3-butadiene-induced mRNA expression. We identified 9 miRNA as significant candidates across tissues and strains. In the lung of 1,3-butadiene-exposed C57BL/6J mice, mir-142-5p was significantly decreased and predicted to target significantly upregulated genes involved in chromatin remodeling such as *KDM1B* which is a lysine demethylase for H3K4, a marker of transcription. In addition, mir-142-5p was predicted to bind genes involved in DNA damage repair such as *CtIP*. The results of this study indicate that miRNA may mediate strain- and tissue-dependent variability of 1,3-butadiene-induced epigenetic effects and potentially greater tissue susceptibility to carcinogenesis.

*Presenter

TS-05 : EGFR-independent colorectal tumors progress through enhanced IL10RA signaling

Mantilla Rojas Carolina* (1), Threadgill David (1)

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Epidermal growth factor receptor (EGFR)-targeted therapies have been approved for colorectal cancer (CRC) treatment. However, previous studies have observed that efficacy of anti-EGFR therapy in humans is influenced by the genetic environment on which colonic tumors arise. Mutations in *KRAS* explain some non-responding CRCs, but even in cancers lacking *KRAS* mutations, little is known about which cancers are likely to respond to EGFR targeted treatment. In this study, we used a mouse model with a conditional *Egfr* allele, (*Egfrtm1dwt* also called *Egfrf*) to demonstrate that colorectal tumors can progress through an EGFR-independent mechanism. RNA-seq analysis revealed a group of genes that characterize EGFR-independent colon tumors in mice. One of the top upstream molecules associated with the differentially expressed genes in EGFR-independent colon tumors was IL10RA. Surprisingly, an independent analysis, using a unique mouse model that contains conditionally inactivated *Apc* alleles (*Apctm1Tno* or *Apcf/f)* in combination with a conditionally activatable allele of oncogenic *Kras*(*Krastm4Tyj or KrasLSL-G12D*) also demonstrate that IL10RA was activated in EGFR-independent (*Egfrf/f, Apcf/f, Kras LSL-G12D/+*) when compared to EGFR-dependent (*Apcf/f,Kras LSL-G12D/+*) colon tumors. Quantitative PCR (qPCR) was used to validate the differential expression levels of several genes involved in the IL10RA pathway, including *Sult1a1*, *Il10, Il10ra, Maob, Aadac,* and *Socs3.* In addition, we found anergy-inducing genes to be overexpressed by qPCR in EGFR-independent colon tumors, suggesting that tumor cells without EGFR might escape to cell-mediated immune defense by increasing IL10 production. We also found increased levels of IL10 in serum of animals with EGFR-independent colon tumors. These findings demonstrate the existence of an EGFR-independent mechanism by which CRC can progress, and that EGFR-independent tumor progression might be modulated by the activation of IL10RA. This study will advance our understanding of anti-EGFR resistance in CRC treatment, ultimately contributing to more effective therapies.

*Presenter

TS-06 : Strong Epistasis in Genetics of Leishmaniasis - Search for Genes and Mechanisms

Sohrabi Yahya (1),*Krayem Imtissal (1), Kobets Tatyana (1), Volkova Valeriya (1), Havelková Helena (1), Matyáš Šíma (1), Jarmila Vojtíšková (1), Taťána Jarošíková (2), Slapničkov Martina (1), Aidarova Aigerim (1), Grekov Igor (1), Svobodová Milena (3), Turňová Jana (1), Demant Peter (4), Lipoldová Marie (1)

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3 - Faculty of Science, Charles University (Czech Republic)
4 - Roswell Park Cancer Institute [Buffalo] (United States)

Leishmaniasis, a disease caused by *Leishmania* parasites, ranks as the leading neglected tropical disease in terms of morbidity and mortality. It infects 1 million people in 98 countries causing 30000 deaths annually. Human leishmaniasis exhibits a great diversity of manifestations. Genotype of the infected organism is an important factor that influences susceptibility to and manifestations of this disease. To study human disease using mouse models, several strains are required, which could collectively exhibit different manifestations of human disease. Therefore, we tested strains O20 and B10.O20 as new models of leishmaniasis. B10.O20 originated from resistant strains C57BL/10 (B10) and O20 and it is surprisingly susceptible to *Leishmania major,* exhibiting large skin lesion, high parasite numbers in skin and lymph nodes. Susceptibility to *L. major* was observed only in certain combinations of B10 and O20 genes. Out of 16 recombinant congenic OcB strains that carry different random sets of 12.5 or 6.25 % of B10 genes on the genetic background of O20, only OcB-11 and OcB-31 carried susceptibility-conferring gene combinations. Mapping in F2 hybrids between OcB-31 (or its substrain OcB-43) and O20 revealed five susceptibility loci on chromosomes 2, 3, 5, 9 and 15 that influence development of skin lesions, serum IgE level, and parasite numbers in liver and spleen. Analysis of these loci for polymorphisms between O20 and C57BL/10 that change RNA stability and genes' functions led to detection of 20 potential candidate genes, three out of them are differentially expressed in either spleen and/or skin of mice and correlate with high parasite load in spleen and large lesions. These genes along with the other detected potential candidate genes will be focus of future studies not only in mice but also in humans.
Support: 14-30186S, GACR 16-22346S, and 13-41002P

*Presenter

TS-07 : Deciphering the impact of the host immune response on SARS-CoV susceptibility or resistance using a reduced complexity cross

Leist Sarah* (1), Schäfer Alexandra (2), Jensen Kara (2), Ferris Martin (2), Bell Timothy (2), Hock Pablo (2), Miller Darla (2), Shaw Ginger (2), Pardo-Manuel De Villena Fernando (2), Baric Ralph (2)

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Newly emerging viral pathogens pose a constant and unpredictable threat to human and animal health. Coronaviruses (CoVs) have a penchant for sudden emergence, leading to severe disease as evidenced by severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV). Even though impact of host genetics on susceptibility to infectious diseases has been shown, many critical factors remain to be identified. The Collaborative Cross (CC) a panel of genetically diverse mice offers the possibility to gain insight into the complex interplay between host and pathogen and to identify crucial determinants of pathogenesis.

A panel of 10 CC strains was screened and led to identification of two strains with diverging outcomes after SARS-CoV infection. CC006 is highly susceptible loosing more than 10% of starting body weight within four days after infection whereas CC044 showed a resistant phenotype with no alteration. Surprisingly, both of the mouse strains showed comparable viral titers in lungs on day four. CC006 and CC044 were further characterized including additional immune-related parameters via Flowcytometry. We found large differences in frequency and activation status of a plethora of immune cell populations.

To reduce genetic complexity these two CC strains were chosen for an F2 cross. 400 F2 mice infected with SARS-CoV will be monitored for weight loss and mortality and their lungs harvested for Flowcytometry and viral titer analyses on day four after infection. A second set of 400 F2 mice will be mock infected to analyze differences in baseline quality and quantity of immune cell populations. Both data sets will be used for genetic mapping and identification of candidate genes driving differential immune response profiles in the presence or absence of SARS-CoV. This study will provide powerful insights into the beneficial or detrimental role of the host immune response in the context of SARS-CoV infection.

*Presenter

TS-08 : Modeling spontaneous systemic autoimmunity using the Collaborative Cross mouse

Mayeux Jessica* (1), Mace Parker (1), Kono Dwight (1), Pollard Kenneth (1)

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Human autoimmunity is a complex disease associated with significant genetic heterogeneity. While inbred mouse strains have proven vital for autoimmune disease research, their limited genetic derivation captures only a small portion of the mouse genomic repertoire. Genetic diversity in mice could potentially be substantially expanded by using the large panel of multi-parental recombinant inbred (RI) Collaborative Cross (CC) mice. The CC panel encompasses over 90% of the genetic diversity of the mouse and is the only mammalian resource with genome-wide genetic variation randomized across a large, heterogeneous and reproducible population. Systemic autoimmunity has not been formally described in any CC RI strain, however, a strikingly high percentage of naive Diversity Outbred mice, a genetically heterogeneous stock derived from the same eight CC founder strains, develop spontaneous autoantibodies and a significant percentage are susceptible to silica-induced systemic autoimmunity. Using the CC RI panel as a model to study the range of phenotypes in a complex disease such as systemic autoimmunity, we measured levels of autoantibodies in serum from 35 CC RI strains. We found serum anti-nuclear antibodies (ANAs), a hallmark of systemic autoimmunity, in 11 of the 35 CC RI strains (31%), although only 5 strains (14%) had 50% or more mice that were positive. Interestingly, ANA patterns were similar to those found in humans. Using R/qtl2 and Mega Mouse Universal Genotyping Array SNP information on the CC strains, we mapped a suggestive QTL for ANA positivity to chromosome 4 whose locus overlaps with the proximal end of loci found for idiopathic systemic autoimmune models. These observations support the utility of the CC strains to model complex heterogeneous autoimmune diseases and uncover potentially novel genetic loci linked to autoimmunity.

*Presenter

TS-09 : The a4a- and b1-tubulin isotypes work together to sustain efficient platelet biogenesis and hemostasis

Kimmerlin Quentin* (1), Moog Sylvie (1), Ahmed Muhammad-Usman (1), Brouard Nathalie (1), Eckly Anita (1), Freund Monique (1), Mangin Pierre (1), Strassel Catherine (1), Lanza François (1)

1 - université de Strasbourg, Institut National de la Santé et de la Recherche Médicale, Etablissement Français du Sang - Grand Est, Unité Mixte de Recherche-S 1255, Fédération de Médecine Translationnelle de Strasbourg ; Biologie et Pharmacologie des Plaquettes sanguines : hémostase, thrombose, transfusion (France)

Blood platelets are small non-nucleated cells whose functions are to stop hemorrhages (hemostasis). They are produced by bone marrow megakaryocytes after a profound cytoskeletal reorganization that culminates in the formation of a circular sub-membranous microtubule array known as the platelet marginal band. This unique structure shows no other equivalent in mammals and is thought to arise from a cell-specific combination of a- and b-tubulin isotypes. Previous studies in mice and humans established a central role for b1-tubulin, whose disruption hinders marginal band formation and leads to abnormally large platelets and reduced blood platelet counts (macrothrombocytopenia). Recently, we reported a mouse model carrying a point mutation in a4a-tubulin that phenocopied the defects seen in *Tubb1-/-* mice. Together, these results suggested that a4a- and b1-tubulin were equally important for platelet biogenesis and led us to generate a4a/b1 double knockout mice (DKO). These mice exhibit worsened macrothrombocytopenia in comparison to *Tubb1-/-* and even more so when compared to *Tuba4a-/-* mice, which unexpectedly display near normal platelet parameters. Additionally, profound ultrastructural defects were found in DKO platelets, which were spherical instead of discoid and were devoid of their marginal band. This was accompanied by an impaired megakaryocyte maturation process. Strikingly, DKO mice display a profound bleeding diathesis in contrast to single KO and WT mice. This bleeding disorder could not be explained by defective platelet activation in response to a series of agonists. Follow-up work will evaluate these mice in *in vitro* and *in vivo* models of thrombosis and explore the mechanisms responsible for abnormal marginal band formation at the biochemical and cellular levels. The expected outcome is an improved understanding of the role of microtubules in platelet formation and functions with possible applications to produce platelets in culture.

*Presenter

TS-10 : SAR1A rescues the hypocholesterolemia resulting from hepatic Sar1b deletion in mice

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The transport of secretory proteins from the endoplasmic reticulum to the Golgi is mediated by COPII vesicles. SAR1 is a small GTPase that initiates vesicle formation. Mammalian genomes contain two paralogs for SAR1, SAR1A and SAR1B. In humans, mutations in SAR1B result in chylomycron retention disease (CRD), an autosomal recessive disorder characterized by fat malabsorption and plasma hypocholesterolemia. We generated mice with a conditional Sar1b allele (Sar1b-fl) and demonstrated that mice with germline SAR1B deficiency (EIIa-Cre) die perinatally, with gross appearance and histologic analysis indistinguishable from wild-type (WT) litter mate controls. Mice with liver specific Sar1b deletion (Alb-Cre) exhibited low plasma cholesterol compared to WT litter mate controls (20.6±2.6 and 88.4±4.5 mg/dl, respectively, $p < 0.01$). As expected, the hypocholesterolemia was corrected with delivery of an adenovirus (AV) vector that expresses SAR1B compared to a GFP-expressing AV (GFP-AV) (89.1±7.4 versus 15.1±2.2 mg/dl, respectively, $p<0.01$). To test if SAR1A can similarly rescue the hypocholesterolemia resulting from hepatic SAR1B-deficiency, Sar1bfl/fl Alb-Cre(+) mice were injected with a SAR1A-expressing AV (SAR1A-AV) or GFP-AV as control; cholesterol levels were normalized in mice injected with SAR1A-AV (70.2±9.4 and 15.1±2.2 mg/dl, respectively, $p <0.01$). These results demonstrate that SAR1A can rescue the hypocholesterolemia resulting from SAR1B deficiency in mice. To test if SAR1A rescues the lethality of SAR1B deficient mice, we are generating mice with the Sar1a coding sequence inserted into the endogenous Sar1b locus. These mice should be completely deficient in SAR1B, with SAR1A expressed from its native locus as well as under the regulatory control of the Sar1b gene. Rescue of the lethality of SAR1B deficiency in the latter mice would suggest a functional overlap between the two SAR1 paralogs and that strategies aimed at increasing SAR1A expression might be of therapeutic value in patients with CRD.

*Presenter

TS-11 : Network analysis of the brain dysfunction observed in Down syndrome models

Muñiz Moreno Maria Del Mar* (1), Duchon Arnaud (1), Dubos Aline (1), Marechal Damien (1), Herault Yann (1)

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Down syndrome (DS) is the most frequent intellectual disability (ID) syndrome and is associated with one additional copy of human chromosome 21 (Hsa21). DS affects one out of 700 new-borns and patients have a specific profile, with ID and more than 80 clinical features although the number and severity of the presented features is variable. Nowadays, one of the most accepted theories aiming to explain how DS phenotypes appear considers the existence of a gene dosage imbalance as key to understand these phenotypes [1].
We aim to strengthen our understanding of DS genotype-phenotype relationships to allow the development of better diagnostic tests and therapeutic interventions in preclinical models. For that reason, in collaboration with the Mouse Clinical Institute, animal models carrying specific partial duplications homologous to Hsa21 have being developed [2] and characterized to map which genes or genetic regions showing a dosage imbalance contribute to the observed phenotypes.
We carried on transcriptomics analyses on the hippocampus of several mouse models focusing in the genes/pathways involved in brain dysfunction. Strong pathway connectivity was observed. The gene connectivity was assessed building minimum protein-protein interaction networks. The key hubs and main signalling cascades affected were identified by centrality analyses and the relevance of the connecting nodes was further predicted by Quack[3]. We found a dysregulation of signalling cascades involving DYRK1A or GSK3B previously known, and identified novel ones. Moreover, similarly to the observation in DS patients, where the affectation/severity of the gene dysfunction vary for each patient carrying partial duplication, the animal models show different signalling cascades affected where several members interconnect while the models produced similar phenotypes.
Antonarakis, S.E. (2017). Nature Rev Gen, 18, 147–163.
Herault, Y. *et al*., (2017). Dis Model Mech., 10(10), 1165–1186.
Li T. *et al*., (2018). BioRxiv 196303

*Presenter

TS-12 : Identification of novel neuroprotective loci modulating ischemic stroke volume in a cross between wild-derived inbred mouse strains

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To identify genetic factors involved in cerebral infarction we have attempted a forward genetic approach using quantitative trait locus (QTL) mapping for cerebral infarct volume after middle cerebral artery occlusion, all using common inbred mouse strains. Although in general cerebral infarct volume is inversely correlated with collateral anatomy, we identified several loci that modulate ischemic stroke in a collateral-independent manner. To overcome the limited genetic diversity among classical inbred strains, we have expanded the pool of allelic variation by a survey of the parental mouse strains of the Collaborative Cross that include 3 wild-derived strains. We found that one of wild-derived strains, WSB/EiJ breaks general rule that collateral vessel density inversely correlates with infarct volume. This strain and another wild-derived strain, CAST/EiJ, show the highest collateral vessel densities of any inbred strain we have tested, but infarct volume of WSB is 8.7-fold larger than CAST/EiJ. QTL mapping between these two strains identified 4 new neuroprotective loci modulating cerebral infarct volume while not affecting vascular phenotypes. To identify causative variants in genes mapping within the loci, we surveyed non-synonymous coding SNPs between WSB and CAST and then, using 3 different *in silico* algorithms, predicted the functional consequences of the amino acid substitutions that left 96 genes mapping in one of the four intervals. In addition, we performed RNA sequencing to determine strain-specific gene expression differences in brain tissue between WSB and CAST and identified 220 candidate genes mapping within the loci. Interestingly, combining genes harboring predicted damaging coding SNPs with genes showing at least 2-fold expression difference coding genes in the four intervals left only 15 genes. The identification of the genes underlying these neuroprotective loci will provide new understanding of genetic risk factors of ischemic stroke which may provide novel targets for therapeutic intervention of human ischemic stroke.

*Presenter

TS-13 : Natural variation alters Alzheimer's-related gene expression in DO mice

Wells Ann* (1), Raghupathy Narayanan (1), Robledo Raymond (1), Graber Joel (1), Hibbs Matthew (1), Carter Gregory (1), Chesler Elissa (1)

1 - The Jackson Laboratory (United States)

Multi-parental populations provide a new resource to investigate complex diseases. Diversity Outbred (DO) mice are a heterogenous mouse population created using eight founder strains. Genes identified in the hippocampus of 258 DO mice were grouped into 145 paracliques, which are unique clusters of correlated genes that are closely related. The paracliques were compared with 30 human gene modules related to Alzheimer's disease from the Accelerating Medicines Partnership for Alzheimer's disease (AMP-AD). Gene content overlaps were calculated between the AMP-AD modules and DO paracliques by Jaccard index. In total, 136 paracliques significantly overlapped with the 30 AMP-AD modules. Additionally, we mapped and characterized quantitative trait loci (QTL) to determine if summary eigengenes from each paraclique were associated with genetic factors. Thirty-five out of the 145 paracliques were significantly associated with loci for at least one chromosome. Both SNP associations and database searches were performed to identify potential genes of interest within the QTL. *ADARB2*, a gene that plays a role in contextual learning and memory, was identified within the QTL on chromosome 13 for paraclique 91; however, this gene was not present in the genes that made up paraclique 91 nor any other paraclique. *ADARB2* was a member of an AMP-AD module, associated with astrocytes, that had significant overlap with 9 individual paracliques, sharing 95 genes. Furthermore, variants in *ADARB2*were identified in brain eQTL from Alzheimer's study cohorts, adding to its potential relevance. In sum, this study showcases the potential of utilizing DO mice to translationally investigate complex human diseases.

*Presenter

TS-14 : Weird gene in a weird mammal: A highly divergent pancreatic duodenal homeobox 1 (Pdx1) gene in the fat sand rat

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1 - University of Oxford (United Kingdom)
2 - University of Oxford (United Kingdom)

Strong GC skew in a local genomic region results in conflict between increasing GC levels and potential alteration of conserved amino acids. In most cases, natural selection will purge any deleterious alleles that arise. However, in the gerbil subfamily of rodents, several conserved genes serving key functions have undergone radical alteration in association with strong GC skew. We present an extreme example concerning the highly conserved homeobox gene *Pdx1*, a key gene in initiation of pancreatic organogenesis in embryonic development. In the fat sand rat *Psammomys obesus* and close relatives, we observe a highly divergent *Pdx1* gene associated with high GC content. In this study, we investigate the antagonistic interplay between very rare amino acid changes driven by GC skew and the force of natural selection. Using ectopic protein expression in cell culture, pulse-chase labelling, *in vitro* mutagenesis and drug treatment, we compare properties of mouse and sand rat PDX1 proteins. We find that amino acid changes driven by GC skew resulted in altered protein stability, with a significantly longer protein half-life for sand rat PDX1. We show that both sand rat and mouse PDX1 are degraded through the ubiquitin proteasome pathway. However, *in vitro*mutagenesis reveals that GC skew has caused loss of a key ubiquitination site conserved through vertebrate evolution, and we suggest that sand rat PDX1 may have evolved a new ubiquitination site to compensate. Our results give molecular insight into the conflict between natural selection and genetic changes driven by strong GC skew.

*Presenter

TS-15 : Regulation of hibernation: promoter expression landscape in skeletal muscle of edible dormouse

Gazizova Guzel* (1), Deviatiiarov Ruslan (1), Tyapkina Oksana (2), Cherkasov Alexander (1), Nurullin Leniz (2), Shagimardanova Elena (1), Gusev Oleg (3) (4) (1)

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2 - Federal Research Center "Kazan Scientific Center of the Russian Academy of Science" (Russia)
3 - Omics Science Center, RIKEN (Japan)
4 - KFU-RIKEN Translational Genomics Unit, RIKEN (Japan)

Hibernation is a unique strategy used by many animal species for surviving harsh environment conditions such as low temperature and starvation. Hibernating mammals are able to slow down their metabolism, overcome multiple ischemia-reperfusion cycles and experience long periods of physical inactivity with minimal loss of skeletal muscle mass. Thus, this is a promising model to gain insight into the mechanisms regulating these physiological conditions associated with various pathologies in non-hibernating animals.
A small arboreal rodent, edible dormouse (*Glis glis*), which is capable of dormancy for up to 11 months in a year, was used in this study. In order to identify the activity of the key promoter-level regulatory elements and transcription factors associated with hibernation regulation in edible dormouse CAGE-seq (Cap Analysis of Gene Expression) was applied, along with sequencing and assembling of the genome. In the study two muscle types (“slow” m. Soleus and “fast” m. EDL) in active animals and animals hibernated for 14 days in controlled climate conditions were examined.
We succeeded sequencing of CAGE libraries with depth >10M reads and mapping ratio ~70%. 9489 differential expressed promoters in two muscle types were determined. In results promoter-activity and differential gene expression atlas in skeletal muscles was created. Specific transcription factors and their motifs contributing to the hibernation-associated events were suggested. These data facilitate the reconstruction of regulatory pathways of the protective musculoskeletal adaptation in edible dormice. The study provides the first systematic annotation of promoters' landscape and genes activated in "fast" and "slow" muscle types during hibernation in edible dormice.
The reported study was funded by RFBR according to the research project № 18-34-00657 and was performed according to the Russian Government Program of Competitive Growth of Kazan Federal University.

*Presenter

TS-16 : Identification of discrete subtypes of enteric neurons in humans using cross-species comparison of RNA-Seq data

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The enteric nervous system (ENS), or “second brain,” is the network of neurons and glia in the intestinal wall that coordinates the essential functions of the bowel. To expand our limited understanding of neuronal diversity within the human ENS, we generated a transcriptome catalog of all genes enriched in enteric ganglia from the duodenum, ileum, and colon of 15 healthy human adults using laser capture microdissection (LCM) and RNA-Seq. To avoid cataloging gene signatures from intestinal smooth muscle that tightly ensheaths enteric ganglia, we collected and sequenced intestinal muscle from matched samples and used bioinformatics to remove muscle signatures from enteric ganglia transcriptomes. This process was effective in generating a list of marker genes specific to enteric neurons and glia. We then took advantage of the high similarity between human and mouse ENS to identify putative markers of enteric neuron subtypes in man. Transcriptome profiles from mouse single-nucleus RNA-Seq of enteric neurons were used to identify discrete subtypes of enteric neurons in mice. Using the mouse gene lists, we then identified subtype-specific neuronal markers from the mouse datasets that were enriched in human enteric ganglia. After screening-out genes that were significantly expressed in enteric glia and intestinal smooth muscle, we obtained a distilled set of markers specific to enteric neurons. Discrete subtypes of enteric neurons were then visualized in healthy adult intestinal tissue using *in situ* Hybridization Chain Reaction. Our findings demonstrate the value of cross-species comparative informatics for identification of marker genes for specific neuron populations. The resulting data set is a valuable resource that will facilitate development of additional therapeutics for functional gastrointestinal and motility disorders through the selective targeting and manipulation of discrete neuron subtypes in the human ENS.

*Presenter

TS-17 : Role for genetic variation in antibody response to Influenza A Virus

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Influenza A Virus (IAV) is an enormous public health burden, leading to high morbidity and mortality across the globe. Vaccines for IAV are available but often ineffective; many individuals fail to mount a protective antibody response, leaving them at risk for severe disease. Human studies have shown that host genetic factors play a significant role in regulating the antibody response to infection and vaccination. However, these studies have been severely limited by inability to control important variables such as dose and prior exposure. We have used the Collaborative Cross (CC), a genetically diverse and experimentally tractable mouse genetics reference population, to study the host genetic factors that regulate antibody response to IAV. We infected 110 CC-F1 lines with the pandemic 2009 H1N1 IAV and measured the quantity of IAV-specific antibody at multiple timepoints post-infection. Virus-induced disease was highly variable across strains, which could largely be attributed to variation in the IAV resistance gene *Mx1*. Protective *Mx1* haplotypes (associated with decreased viral load and weight loss) were correlated with decreased antibody responses at day 7 post infection but largely disappeared at later timepoints. Antibody responses were highly variable across lines for different subtypes and timepoints, with heritability estimates ranging from 26-72%. We utilized this heritable variation to map the quantitative trait loci (QTL) underlying the magnitude of antibody response. We mapped 2 highly significant ($p<0.05$) QTL, *Ari2* and *Ari3* (antibody response to influenza), as well as 9 significant ($p<0.1$) QTL across other isotypes and timepoints, including *Ari1*. *Ari1* was mapped for IgG2a/IgG2c at day 7 post infection. Notably, *Ari2*, which was mapped for IgG3 at day 10, was also widely associated with IgM and other IgG isotypes at days 7 and 10 post-infection. *Ari2* haplotype was also correlated with antibody response to SARS-Coronavirus (but not Chikungunya virus), suggesting that *Ari2* is broadly involved in the early antibody response to respiratory viruses. *Ari3*, which was mapped for change in IgG2b between days 15 and 45, showed a strong association with IgG2b at day 15 individually. Candidate genes for *Ari1* and *Ari2* include viral pathogenesis and immune genes that have also been identified in human studies of infectious diseases. Haplotype of the IAV resistance gene *Mx1,* which is a strong driver of viral titer, weight loss, and mortality, was associated with antibody response only at day 7.

*Presenter

TS-18 : Genetic control of hepatic energy metabolism and response to carbohydrate restriction

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The application of genomic approaches to understand unique responses to diet effects has been understudied when compared to genomic characterization of complex disease. In order to advance precision dietetics, we are establishing a predictive measure for responsiveness to carbohydrate consumption. Our laboratory has previously demonstrated the effects of inter-individual response to diet in a study using four inbred mouse strains: C57BL/6J (B6), FVB/NJ (FVB), A/J, and NOD/ShiLtJ (NOD). Increased body fat gain and other negative health effects were observed in B6 mice consuming an American diet (high fat, high carbohydrate) and but not in B6 mice on a ketogenic diet (high fat, no carbohydrate). The negative health effects observed in FVB mice exposed to the American diet persist in FVB mice exposed to the ketogenic diet. This suggested that the individual response to a high fat diet is more dependent upon the presence or absence of carbohydrates than exposure to the high fat diet alone for B6 mice, whereas FVB mice showed no differential responsive when carbohydrates were restricted. Consequently, B6 mice are predicted to respond to a dietary intervention restricting carbohydrate consumption while FVB should be non-responsive. Analysis of the liver transcriptomes suggests that hepatic energy metabolism is a major determinant of response or non-response to carbohydrate restriction. An intercross (F2) population was generated to further investigate the divergence observed in hepatic energy metabolism.Half of the F2 mice were placed on American diet and half on ketogenic diet for three months before characterizing changes to body composition and weight gain. Genetic analysis in each of the F2 populations revealed quantitative trait loci (QTL) on Chr 7 (American) and 5 (ketogenic). We are systematically investigating the effects of the ketogenic diet on glucose metabolism and liver health as it relates to hepatic energy metabolism in these mice.

*Presenter

MAIN SYMPOSIUM ABSTRACTS

Oral-01 : Leaving the comfort zone and why others also only cook with water

The Chapman Lecture
Balling Rudi* (1)

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Verne Chapman was the mentor of my mentor, Janet Rossant. Both were extremely generous, in giving credit as well as in sharing ideas. My time in Toronto as a postdoc and my visits to Verne Chapman at Roswell Park in Buffalo during that time set me on a path in genetics and in developmental biology. I fell in love with both. In my presentation I would like to outline the challenges that we still face in analyzing biological systems, which are highly complex, adaptive and nonlinear. I will describe the need for interdisciplinarity, including its joys and frustrations that come along with it. I will use the LCSB as an example how we try to cope with the avalanche of data, the need for data integration and the importance to move from correlation to causality. I will share some recent insight into the pathogenesis of Parkinson's disease that tries to “Connect the dots” and come up with a hypothesis suggesting that between many of our chronic, age related diseases there might be “Common mechanisms at play”.

*Presenter

Oral-02 : Genome architecture and diseases: the 16p11.2 paradigm

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Copy number changes in 16p11.2 contribute significantly to neuropsychiatric traits. Besides the 600 kb BP4-BP5 (breakpoint) CNV found in 1% of individuals with autism spectrum disorders and schizophrenia and whose rearrangement causes reciprocal defects in head size and body weight, a second distal 220kb BP2-BP3 CNV is a likewise potent driver of neuropsychiatric, anatomical and metabolic pathologies. These two CNVs-prone regions at 16p11.2 are reciprocally engaged in complex chromatin looping and concomitant expression changes, as well as genetic interaction between genes mapping within both intervals, intimating a functional relationship between genes in these regions that might be relevant to pathomechanism.
These recurrent pathogenic deletions and duplications are mediated by a complex set of highly identical and directly oriented segmental duplications. This disease-predisposing architecture results from recent, *Homo sapiens*-specific duplications (i.e. absent in Neandertal and Denisova) of a segment including the *BOLA2* gene, the latest among a series of genomic changes that dramatically restructured the region during hominid evolution. Our results show that *BOLA2* participates in iron homeostasis and a lower dosage is associated with anemia. These data highlight a potential adaptive role of the human-specific expansion of *BOLA2* in improving iron metabolism.
Finally, we combined phenotyping of carriers of rare copy variant at 16p11.2, Mendelian randomization and animal modeling to identify the causative gene in a Genome-wide association studies (GWAS) locus for age at menarche. Our interdisciplinary approach allowed overcoming the GWAS recurrent inability to link a susceptibility locus with causal gene(s).

*Presenter

Oral-03 : Mapping the cis-regulatory landscape of the developing human retinal pigment epithelium for elucidating noncoding ocular disease mechanisms

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Mutations in genes expressed in the retina and retinal pigment epithelium (RPE) are associated with many inherited and degenerative eye diseases with effects ranging from partial or total loss of vision at birth to progressive childhood- or adult-onset blindness. While coding mutations in critical eye development genes are commonly implicated as the cause of ocular malformations, challenges remain to identify noncoding disease-causing variation and determine the role of regulatory elements in cell identity and function. Using a multidimensional epigenomic profiling approach, we mapped the regulatory state changes occurring during neural retina induction, retinal differentiation, and RPE specification from differentiating human induced pluripotent stem cells (hiPSCs). Integrative analysis of these maps revealed dynamic chromatin transitions and highlighted enhancers at known RPE-specific genes as well as putative cell-type specific enhancer loci. Furthermore, transcription factor motif enrichment analysis of chromatin state and gene expression changes between iPSC and iPSC-derived RPE identified a variety of transcriptional cis-regulatory networks underlying RPE specification. Next, we used whole genome sequencing to evaluate families with congenital ocular malformations without causal variants in protein coding regions. By filtering genetic variants based on RPE-specific regulatory maps, we narrowed the scope from millions of variants across the genome to <3% of putative “active” genomic space. We linked a novel hereditary macular dysplasia to an insertional translocation of a 339 kb gene desert fragment with putative enhancer-like activities during specific periods of retinal development. We then developed a model using patient-derived iPSC to generate RPE for mapping perturbed developmental gene regulation at this locus. In summary, these data increase our understanding of the cis-regulatory networks underlying RPE development and open new avenues for identification and prioritization of noncoding disease-causing variants in ocular tissues.

*Presenter

Oral-04 : Mouse Model for FINCA (Fibrosis, Neurodegeneration, and Cerebral Angiomatosis)

Hiltunen Anniina (1), Pietilä Ilkka (1), Kangas Salla (1), Vuolteenaho Reetta (1), Tuominen Hannu (1), Kaarteenaho Riitta (1), Hallman Mikko (1), Uusimaa Johanna (1), Hinttala Reetta*(1)

1 - University of Oulu (Finland)

Discoveries of recessive mutations as causes of familial multiorgan diseases have provided molecular basis of an increasing number of diseases and tools to study novel cellular pathways underlying their pathogenesis. We have recently identified harmful compound heterozygous variants in the *NHLRC2* gene, causing a novel fatal multiorgan disease in humans. We have characterized and named the disease as FINCA based on the unique histopathological findings of the patients, such as fibrosis, neurodegeneration, and cerebral angiomatosis. The children were born healthy, but at the age of 2 months, they started to manifest progressive multi-organ symptoms resembling no previously known disease. The disease course was highly progressive and the patients died before the age of two years. Function of NHLRC2 is currently unknown even though it is widely expressed in human and mouse tissues. NHLRC2 is conserved across the species, the mouse protein being 84 % similar to human NHLRC2.

We use mouse as a model to study the function of NHLRC2 and the disease pathomechanism of FINCA *in vivo*. Heterozygous C57BL/6N-*Atm1Brd Nhlrc2tm1a(KOMP)Wtsi/Atm1Brd Nhlrc2tm1a(KOMP)Wtsi* mice were obtained from Infrafrontier-EMMA repository. Homozygous *Nhlrc2* KO turned out to be lethal early in development, failing to develop morula- stage and placentation. Next, we generated a knock-in (KI) mouse model carrying the FINCA point mutation, c.G442T; p.Asp148Tyr. We used CRISPR/Cas9 gene editing and homology directed repair template to introduce the desired point mutation. We crossed the C57BL/6N-*Nhlrc2em1Rthl* mice with KO mice to produce compound heterozygous genotype mimicing the genotype in patients. Our recent phenotyping data derived from the FINCA mice has brought encouraging first observations of features similar to the FINCA disease.

As a conclusion, we show for the first time that dysfunction of NHLRC2 leads to FINCA in humans and that the underlying pathomechanism can be studied using mouse as a model organism.

*Presenter

Oral-05 : Roles of two PRDM9 interactors CXXC1 and EWSR1 in meiotic recombination

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In mice and humans, meiotic recombination occurs at 1-2 kb long recombination hotspots, whose position and activity are determined by PRDM9, a meiosis-specific DNA-binding protein that trimethylates histone-3 at lysines 4 and 36. In male germ cells of mice, PRDM9 trimethylates histone 3 at about 5000 sites per cell; of these, ~300 acquire DNA double-strand breaks, and these in turn are repaired to yield only ~24 crossovers. Using yeast two-hybrid assay, we identified CXXC1 and EWSR1 as two of the proteins that interact most strongly with PRDM9. Both proteins interact with the KRAB domain of PRDM9. To explore te functions of these proteins in meiosis, we used germ cell specific conditional knockouts (*Cxxc1loxP/Δ;Stra8-Cre* and *Ewsr1loxP/Δ;Stra8-Cre*) mouse models. To our surprise, CXXC1 was completely dispensable for fertility. In contrast, male *Ewsr1* CKO mice were sterile, with a histological phenotype consistent with prophase I arrest. The CKO mice showed dramatic reduction of the number and activity of H3K4me3 marks at meiotic hotspots and asymmetric trimethylation at the weakest hotspots. The positions of DSB were shifted towards closed chromatin, resulting in a decrease of crossover number from ~24 to ~18, a number insufficient for proper chromosomal pairing and subsequent segregation. In addition to binding PRDM9, EWSR1 also binds to the meiotic-specific cohesin REC8. Since REC8 and PRDM9 do not bind directly to each other, EWSR1 provides a physical link between hotspot-bound PRDM9 and the chromosomal axis, thereby ensuring proper positioning of activated hotspots on the chromosomal axis for DSB initiation. Physically, our results support a model in which binding of EWSR1 both stabilizes PRDM9 dimer binding at hotspots, ensuring proper H3K4/K36 trimethylation, and incorporates activated hotspots into the forming chromosomal axis. In the absence of EWSR1, PRDM9-dependent trimethylation only occurs at the strongest hotspots, which failure affects all subsequent recombination processes.

*Presenter

Oral-06 : TET2-mediated active DNA demethylation promotes iPSC generation in a MEF reprogramming model

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In cell culture, somatic differentiation can be reversed through the overexpression of *Oct4*, *Sox2*, *Klf4*, and *c-Myc* (OSKM) to generate induced pluripotent stem cells (iPSCs). This process is dependent on enzymes of the Ten-eleven Translocation (TET) family, which promote active DNA demethylation. Active DNA demethylation can proceed through two distinct pathways: active modification with passive dilution (AM-PD) or active modification with active removal (AM-AR). Recent evidence suggests that AM-PD demethylation may be insufficient for iPSC reprogramming, indicating the two DNA demethylation pathways are not functionally equivalent. In order to test the influence of different modes of DNA demethylation on iPSC reprogramming, we performed OSKM induction on mouse embryonic fibroblasts (MEFs) overexpressing wild-type *Tet2-WT*, catalytically inactive *Tet2-HxD*, or hypomorphic *Tet2-T1285E*, which is competent for AM-PD but not AM-AR demethylation. Our results demonstrate that overexpression of *Tet2* leads to an increase in iPSC reprogramming efficiency, and that this effect is dependent upon TET2's AM-AR activity. Furthermore, this increased reprogramming efficiency correlates with an increased rate of DNA demethylation at Klf4 target sites. These experiments suggest that the AM-PD and AM-AR DNA demethylation pathways have non-redundant functions in regulating iPSC reprogramming, and represent the first evidence of biological activity specifically attributable to one mode of active DNA demethylation.

*Presenter

Oral-07 : A rapid platform for direct modeling of human developmental disorders in mice using CRISPR/Cas9 genome editing.

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Advances in sequencing technology continue to increase the rate at which putative genetic mutations are identified for human diseases. Despite these rapid improvements in gene discovery, ascribing a causal relationship between a particular genetic variant and a disease is often challenging. Animal models provide powerful tools to support gene discovery and investigate the mechanisms of disease, with the mouse providing the ideal mammalian system to model developmental disorders. While CRISPR/Cas9 genome editing has simplified and accelerated mouse model creation, timelines are still often on the order of a year, and thus can be incompatible with the needs of human gene discovery programs. To address this issue, we have developed a rapid platform to directly evaluate the causality of novel genes/variants for developmental disorders, leveraging the high-throughput mouse embryo phenotyping platform built for the KOMP2/IMPC program. We demonstrate that modelling a possible disease mutation via direct phenotypic analysis of F0 (“founder”) mouse embryos generated by CRISPR/Cas9 can be achieved in a matter of weeks. In proof-of-principle studies, we show that we can efficiently generate and definitively identify expected morphological phenotypes in a mosaic population of edited embryos. Our platform can generate both knockout (null) and precision knock-in (missense) alleles in a single experiment, creating an allelic series to support our understanding of variant function. Finally, we apply our platform in support of multiple human disease gene discovery efforts, demonstrating the value of our approach. Together with current experiments to increase the efficiency in generation of precision knock-in alleles, our platform has the potential to improve the speed and utility of the mouse as a tool to validate and model novel variants for human disease.

*Presenter

Oral-08 : Retinoic acid: essential for reproduction, not for meiosis

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Recent studies, published in prestigious scientific journals, have concluded that all-trans retinoic acid (ATRA) played a crucial role in controlling the entry into meiosis of germ cells (GC) in female fetuses through inducing *Stra8,* an essential gatekeeper of meiotic initiation. ATRA, the active metabolite of vitamin A, is synthesized in its target tissues by 3 retinaldehyde dehydrogenases (RALDH), encoded by the *Aldh1a1*, *Aldh1a2* and *Aldh1a3* genes. ATRA acts through binding to nuclear receptors of which there are 3 isotypes, RARA, RARB and RARG. We have generated mutant mice that no longer express any RAR in fetal tissues by conditional somatic mutagenesis: *UbcCreERT2Rara/b/g* mutants reproduce the set of severe congenital abnormalities characteristic of the fetal vitamin A deficiency syndrome and also present in knockout fetuses carrying deletions of *Rara* and *Rarb*, *Rara* and *Rarg* and *Rarb* and *Rarg*. However, against all expectations, expression of *Stra8* and other meiotic markers is only slightly delayed in *UbcCre ERT2Rara/b/g* female fetuses. In male mice, where entry into meiosis occurs after birth, deletion of the 3 *Aldh1a1* genes specifically in the seminiferous epithelium of the testis blocks the ATRA-dependent critical step of premeiotic CG differentiation, but not the entry into meiosis. Taken together, our results indicate that impairment of the ATRA signaling pathway does not induce the meiotic arrest that was expected from literature data. We conclude that ATRA, although instrumental to reproduction in both males and females, is not required for meiosis entry and progression of GC to the zygotene stage.

*Presenter

Oral-09 : Transient CRISPR/Cas9 assay of candidate genes for neural tube defects

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Our laboratory is interested in the molecular mechanisms that confer elevated risk for neural tube defects to offspring from pregnancies affected by maternal diabetes and obesity. The exposure to these conditions alters expression of multiple genes in the developing embryo, creating molecular scenarios that are difficult to model in the one-by-one approach of conventional gene mutagenesis. We therefore plan to employ CRISPR/Cas9 technology to target multiple genes simultaneously. Since neural tube defects arise around midgestation, the phenotypic analysis of embryos does not as such require establishment of permanent mouse lines, thus enabling us to pursue a transient transgenic strategy.

Here we will report on our efforts to establish proof-of-concept for this approach, by targeting genes with known roles in developmental abnormalities, such as *T/*brachyury, *Lrp6*, *Mesp2*, *Map4k4* and *Axin2*. We will show examples of morphological defects that arose consistently from independent targeting events in each of these genes. The successful establishment of this approach now enables us to 1) assay any heretofore uncharacterized gene for potential roles in embryonic development, as well as in surviving adults; 2) assay for interactions of multiple genes in specific developmental defects; and 3) superimpose targeting of individually sub-symptomatic genes (alone or in combination) with metabolic exposures to more closely reflect the multifactorial origins of birth defects and complex human disorders and diseases.

*Presenter

Oral-10 : A novel m6A RNA methyltransferase in mammals - characterization of Mettl5 mutant mice in the German Mouse Clinic

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To date the regulatory roles of RNA modifications are well appreciated. Extensive research is ongoing to identify novel types, sites and substrates for many of them with m6A being the most studied. Three enzymatic complexes involved in the deposition of m6A into RNA have been identified in the recent years in mammals. We identified METTL5 as an enzyme with methyltransferase activity towards adenosine in a systematic screen for a collection of potential methyltransferases with an in vitro methyltransferase assay. We generated a Mettl5-KO mouse using CRISPR/Cas technology and systematically characterized it in the German Mouse Clinic phenotyping screen. Homozygous Mettl5 mice are subviable, and less than 12.5% of mice born reach weaning age. Weight monitoring in the age between 5 and 15 weeks showed significantly lower body mass in Mettl5 -/- mice compared to controls. Snout deviations were observed in X-ray and microCT images. The analysis detected nasal bones with abnormal growth patterns in about half of Mettl5 -/- animals as a feature with incomplete penetrance. 8-week-old Mettl5 homozygous mice were hypoactive and hypoexploratory during a 20-minute open field test. In OCT images of retinas we detected abnormal retrolental tissue present in the eyes of 16-week-old Mettl5 mice, due to alterations in hyaloid vascular system regression. The phenotype was asymmetrically, as we observed always more severe alterations in the right eye. Further alterations of homozygous Mettl5 mutants were observed in neurological functions and the immune system as well as reproduction organs. Heterozygous animals presented with no or very mild phenotypic deviations.
In summary, we identified a novel m6A RNA methyltransferase and demonstrated its implication in cellular and vital functions adding to the complexity of epitranscriptome regulators. The observed phenotypic alterations in Mettl5-KO mice support the correlation of METTL5 in patients with microcephaly, intellectual disability and growth retardation.

*Presenter

Oral-11 : An intersection between an autism spectrum disorder (ASD)-associated microexon splicing program and vertebrate-specific post-translational modification shapes vertebrate behavior

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Our ability to engage in social interactions significantly influences the quality of our lives. This is most apparent when this facility is compromised, as in autism spectrum disorder (ASD) and Cri du Chat Syndrome (CdCS). We have shown that a neuronal-specific alternative splicing network of microexons (short 3-27 nt exons) is misregulated and expression of the vertebrate-specific neuronal microexon regulator SRRM4/nSR100 reduced (Irimia et al., Cell, 2014) in a substantial proportion of ASD brains Moreover, misregulation of this nSR100-dependent splicing network is controlled by neuronal activity and mutant mice with reduced nSR100 levels display hallmark ASD features. Thus, misregulation of an nSR100-dependent splicing network controlled by changes in neuronal activity is causally linked to an important subset of autism cases (Quesnel-Vallieres et al., Mol. Cell, 2016).
Together with alternative splicing, dynamic and reversible post-translational modifications, such as ubiquitination, further shape our nervous system and may be of critical importance in CdCS. The addition and removal of ubiquitin chains can determine protein subcellular localization, stability and/or activity. Linear ubiquitin (Met1Ub) chains, in which one ubiquitin is fused to the starting methionine of another, emerged evolutionarily alongside increasingly nuanced social interactions in vertebrates. Linear ubiquitin chains are added to proteins by the linear ubiquitin assembly complex (LUBAC) and can be removed by OTULIN (also known as GUMBY/FAM105b), a deubiquitinase dedicated to the cleavage of linear ubiquitin chains (Rivkin et al, Nature 2013). Haploinsufficiency of *OTULIN* is associated with the anti-social behaviors in CdCS patients. We have identified neuronal OTULIN client proteins and a critical intersection between microexon splicing and linear ubiquitination that illustrates how variations in the levels of one or a few nSR100 regulated microexons or OTULIN client proteins can have dramatic consequences. Thus, these vertebrate-specific post-transcriptional and post-translational programs contribute to the molecular basis for fluid situation-appropriate behaviors.

*Presenter

Oral-12 : Anti-sense oligonucleotide therapy delays seizure onset and extends survival in a mouse model of Scn8a encephalopathy

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The gene *SCN8A* encodes the voltage-gated sodium channel Nav1.6, which is localized at the axon initial segment and at nodes of Ranvier in the CNS and PNS. Exome sequencing has identified several hundred *de novo* mutations of *SCN8A* in patients with epileptic encephalopathy, a disorder characterized by early onset seizures, developmental delay and cognitive impairment. Many patients with *SCN8A* encephalopathy are nonambulatory and nonverbal, and the condition is resistant to standard anti-epileptic drugs. Patient mutations in *SCN8A*result in gain-of-function changes in the biophysical properties of Nav1.6 that lead to elevated channel activity and resulting neuronal hyperactivity. In order to dissect pathogenic mechanisms and test therapeutic interventions, we generated two mouse models expressing patient mutations (*Wagnon et al, HMG 2015; Bunton-Stasyshyn et al, Brain 2019*). We are currently studying the effectiveness of anti-sense oligonucleotides (ASOs) to compensate for neuronal hyperactivity by reducing Nav1.6 mRNA abundance. Mice are treated by intracerebroventricular injection of an ASO that decreases the abundance of the *Scn8a* transcript by 50%. We observe a dose-dependent increase in seizure-free survival of the mutant mice, from 2 weeks for untreated mice to 9 weeks in mice receiving two treatments of ASO. The treated mice did not exhibit the side effects that can result from further reduction of Nav1.6 function, such as muscle wasting and ataxia. The data thus far have demonstrated the potential utility of ASO therapy for treatment of this intractable childhood epilepsy.

*Presenter

Oral-14 : Pigmentary glaucoma results from mutations in the functional amyloid PMEL

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Pigmentary glaucoma (PG) is the most common secondary glaucoma making it a major cause blindness worldwide. Recently, we have reported that mutations in the melanosome structural protein premelanosome protein (PMEL) underlie PG, the first known genetic cause of this form of blindness in humans. Functional analysis of non-synonymous PMEL missense mutations found in patients revealed 7/9 mutations displayed defects in proteolytic cleavage and/or melanosome fibril formation. CRISPR-Cas9 disruption of the homolog *pmela*in zebrafish caused profound pigmentation defects and glaucoma-like phenotypes further supporting PMEL's role in PG. However, the mechanism by which PMEL mutations cause glaucoma is yet to be elucidated. PMEL is a rare protein that forms functional amyloid fibers at normal physiological conditions; indeed PMEL fibers constitute the scaffold in melanosomes upon which melanin is synthesized and deposited. We hypothesize that PMEL mutations are gain-of function mutations that switch PMEL from a functional to a pathological amyloid. In the eye, the trabecular meshwork located in the anterior segment, is the primary drainage route of aqueous humor. We now show that PMEL containing cellular debris is phagocytosed by ocular trabecular meshwork cells which may compromise cell survival. As loss of trabecular meshwork cells results in IOP homeostasis deregulation, these findings could reveal one of the initiating steps of pigmentary glaucoma pathogenesis.

*Presenter

Oral-15 : Behavioral, neurological and genetic bases of tameness in mice

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Tameness is a behavioral characteristic with two potential components: reluctance to avoid humans (passive tameness) and motivation to approach humans (active tameness). To quantify these two different components of tameness separately in mice, we established three behavioral tests: the ‘active tameness', ‘passive tameness', and ‘stay-on-hand' tests. We previously analyzed with the tameness tests for two groups of mouse inbred strains: domesticated strains (laboratory strains) and wild strains. We found that most of the domesticated strains showed significantly greater passive tameness than wild strains, whereas there was no significant difference in active tameness. The results suggested that domesticated strains were predominantly selected for passive tameness over the course of their domestication but no attempts were made to select for active tameness in mice. Therefore, we tried to elucidate genetic and neural mechanism underlying active tameness by conducting selective breeding using genetically diverse wild-derived heterogeneous stock (WHS) made from eight wild inbred strains. As a result, the selected groups exhibit significantly higher active tameness than control groups, and following genetic study revealed that at least two closely linked loci on Chromosome 11 associate with increased active tameness. Further behavioral studies revealed that selected groups exhibit higher social interaction behavior comparing the control groups. Our current attempts to analyze c-Fos positive neurons and RNA transcriptome will provide information for neural and molecular bases of active tameness in mice.

*Presenter

Oral-16 : Genetics of mammalian brain morphogenesis

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Brain morphogenesis is an important process contributing to higher-order cognition, however our knowledge about its biological basis is largely incomplete. Here, I will first present the analysis of 118 neuroanatomical parameters in 1,566 mutant mouse lines obtained through collaboration with the Sanger Institute Mouse Genetics Project, a partner of the International Mouse Phenotyping Consortium, and the identification of 198 genes whose disruptions yield NeuroAnatomical Phenotypes (NAPs). Second, I will talk about groups of functionally similar NAP genes that participate in pathways involving the cytoskeleton, the cell cycle and the synapse, displaying distinct fetal and postnatal brain expression dynamics and importantly, their disruption that can yield convergent phenotypic patterns. Finally, I will show the relevance of this resource to human neurodevelopmental diseases. Indeed, 17% of human unique orthologues of mouse NAP genes are known loci for cognitive dysfunction. The remaining 83% constitute a vast pool of genes newly implicated in brain architecture, providing the largest study of mouse NAP genes and pathways. This offers a complementary resource to human genetic studies and predict that many more genes could be involved in mammalian brain morphogenesis.

*Presenter

Oral-17 : Long non-coding RNAs and X Chromosome 3D structure and epigenetics

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The mammalian X Chromosome is regulated by molecular mechanisms that evolved to help maintain a balanced expression throughout the genome and between males and females. X inactivation silences one X Chromosome in females by repressive epigenetic mechanisms that involve long non-coding RNAs, histone modifications, DNA methylation, chromatin condensation, and nuclear positioning. We will discuss our new findings on the role of specific elements in regulation of epigenetic features, location, and 3D structure of the inactive X Chromosome, based on allelic studies in hybrid mice. In particular, we have found that the lncRNA locus *Dxz4* controls in cis the bipartite 3D structure of the inactive mouse X Chromosome. Surprisingly, the lncRNA *Firre* exerts trans-acting effects to maintain heterochromatic features of the inactive X. Loss of *Firre* RNA results in a dramatic loss of H3K27me3 and of components of the PRC2 complex on the inactive X, as well as in disruption of its perinucleolar location. Importantly, these features are partially restored by ectopic expression of a mouse or human cDNA transgene, strongly supporting a conserved trans-acting role of *Firre* RNA in maintaining the heterochromatin environment. Finally, we will discuss the fact that the silencing of the X Chromosome is incomplete and some genes escape X inactivation, which can result in sex differences that vary between cell/tissue types.

*Presenter

Oral-18 : Identifying host susceptibility factors to SARS-CoV infection using a BALB/c reduced complexity cross

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Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) was identified in 2002 as the etiologic agent of a global outbreak of atypical pneumonia and acute respiratory distress syndrome. Host factors contributing to either survival or progression to severe disease remain unknown. To address this question, we used a systems genetics approach driven by the serendipitous observation that BALB/cJ mice are resistant to infection with SARS-CoV while BALB/cByJ mice are extremely susceptible. Taking advantage of recent genotyping advances and the close genetic relationship between these substrains, we designed an F2 cross between BALB/cJ and BALB/cByJ to map host alleles that guide the response to SARS-CoV infection. We observed that susceptibility to SARS-CoV infection was dominant and that weight loss and pulmonary hemorrhage were significantly correlated ($p<0.001$). We identified two quantitative trait loci that governed day four weight loss, located at Chr15 32.3-81.3Mb and Chr5 117Mb-151Mb. The Chr15 QTL region includes 189 novel variants between BALB/cJ and BALB/cByJ in 103 genes or intergenic regions and the Chr5 QTL includes 225 novel variants. Testing additional BALB/c substrains reduced the number of possible candidate genes in both loci by over 80%. Currently we are narrowing the QTL intervals using PCR based fine mapping, generating congenic mice, examining the expression levels of high priority candidate genes such as *Sla*, *Ext1* and *Sumf2* and by challenging select knockout mice. Given the small number of possible causative variants we anticipate identifying both the genes and the causative mutations that dictate the varying BALB/c responses to SARS-CoV infection. Analysis of the early response to infection in susceptible and resistant BALB/c substrains indicates that aberrant immune signaling is likely to be responsible for the differential infection outcome. In addition to improving our understanding of SARS-CoV pathogenesis, this work highlights the care that must be taken in comparing phenotypes between mouse substrains.

*Presenter

Oral-19 : A loss-of-function mutation in Itgal contributes to the high susceptibility of strain CC042 to Salmonella infections

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Salmonella are intracellular bacteria responsible of foodborne infections and a major threat for human populations worldwide. Mouse models have been extensively used to model distinct aspects of the human *Salmonella* infections *in vivo* and have led to the identification of several host susceptibility genes. We have investigated the susceptibility of Collaborative Cross strains in two experimental models of *Salmonella* infections: i) using *S.* Typhimurium as a model of human typhoid fever, ii) using *S.* Enteritidis which models human *Salmonella*carriage. In both models, strain CC042 displayed extreme susceptibility with very high bacterial loads and mortality. Mice showed lower spleen weight and decreased splenocyte numbers before and after infection, affecting mostly CD8+ T cells, B cells, macrophages and monocytes. Uninfected mice also had lower thymus weight with reduced (CD4+, CD8+) double positive thymocytes. Analysis of bone marrow resident hematopoietic progenitors showed a strong bias against MPP4 which leads to T, B and NK cells and granulocyte-macrophage progenitors. An F2 cross between CC042 and C57BL/6N identified two QTLs on Chromosome 7 (*Salmonella* Typhimurium susceptibility locus, *Stsl6* and *Stsl7*), with WSB-derived susceptible alleles. A private variant in the integrin alpha L (*Itgal*) gene is carried by CC042 in the *Stsl7* QTL region. A quantitative complementation test confirmed the effect of *Itgal*loss of function in a (B6xCC042)F1 background, but not in a pure C57BL/6 background. These results underline the utility of the Collaborative Cross to dissect host genetic control of susceptibility to infections.

*Presenter

Oral-20 : Host genetics controls susceptibility to Zika virus in Collaborative Cross mice

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Zika virus (ZIKV), an emerging mosquito-borne flavivirus, has been responsible for worldwide epidemics over the past decade. The recent explosive spread of ZIKV has been associated with the emergence of rare but severe neurological complications and congenital afflictions among infected populations. This variability in disease severity and pathogenesis is due to multiple factors, which likely include host genetic determinants. Our aim is to identify host genetic factors, which control increased susceptibility to ZIKV infection. To this end, we are using the Collaborative Cross (CC), a powerful resource for systems genetics approaches. We investigated the influence of genetic background on susceptibility to ZIKV in 35 CC strains in which type I interferon response was blocked by a monoclonal antibody.

The genetic diversity of the CC panel enabled phenotypes ranging from complete resistance to severe symptoms and death, with large variations in the peak and kinetics of plasma viral load. To gain understanding of the underlying mechanisms, we performed a detailed phenotyping study on a few strains of interest. The severity of brain lesions varied from mild to severe encephalitis and correlated with plasma viral load. We investigated the replication rate of ZIKV in primary cultured cells and found that it was increased in the most susceptible strain, providing one putative mechanism for the differences of susceptibility between strains. Finally, we identified, in three contrasted CC strains, correlated susceptibility to Zika, Dengue and West-Nile infections, suggesting shared mechanisms of response to these flaviviruses. However, genetic analysis did not reveal a role for *Oas1b* in the susceptibility to ZIKV, while it is a major restriction factor of WNV.

Our results demonstrate the critical importance of the host's genome-wide genetic variation on its susceptibility to ZIKV infection and provide new mouse models to investigate the mechanisms of human ZIKV disease and other flaviviral infections.

*Presenter

Oral-21 : Analysis of a Sensitized Mouse ENU Screen Identifies Non-ENU Suppressor Variants Introduced Due to Selective Pressure

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Factor V Leiden (FVL) is an incompletely penetrant thrombosis susceptibility variant common in humans. To identify modifiers of FVL (*F5tm2Dgi*), we performed a sensitized mouse ENU mutagenesis screen for mutations suppressing the *F5tm2Dgi/F5tm2Dgi Tfpitm1Gjb*/+ perinatal lethal thrombotic phenotype. Although we identified thrombosuppressor mutations in two of our 22 independent *MF5L* mouse lines, the others are still unknown. The highly penetrant (77.2%) *MF5L16* mouse line produced a large multigenerational pedigree containing 136 viable *F5tm2Dgi/F5tm2DgiTfpitm1Gjb*/+ mice. The *in vitro* Prothrombin Time (PT) assay revealed a potent antithrombotic effect in *MF5L16 F5tm2Dgi/F5tm2Dgi Tfpitm1Gjb*/+ mice compared to *F5tm2Dgi*/+ *Tfpitm1Gjb*/+ and *Tfpitm1Gjb*/+ control mice (q<0.01). To identify the *MF5L16* suppressor, four mice were analyzed by whole genome sequencing (WGS). A total of 44 candidate ENU mutations were identified. Sanger resequencing analysis determined that 22 were false-positive calls. Seven arose in and were introduced into *MF5L16* by *F5tm2Dgi/F5tm2Dgi* breeders. Three arose on the *Tfpitm1Gjb* mouse background. The remaining 12 candidates could not be analyzed as they were in repetitive/low complexity regions. Due to the lack of ENU-induced mutations segregating in *MF5L16*, the seven mutations entering the pedigree from the *F5tm2Dgi/F5tm2Dgi* breeders were analyzed in all 136 *MF5L16* mice. A mutation in an intergenic region on Chromosome 18 was significantly associated with survival of *F5tm2Dgi/F5tm2Dgi Tfpitm1Gjb*/+ mice (p=0.0031). Two mutations within intronic regions on Chromosome 9 and 13 were significantly associated with survival when co-inherited with the Chromosome 18 mutation (p=0.000113). These results suggest that additional suppressor mutants arising from selective pressure in the *F5tm2Dgi/F5tm2Dgi* mice used as the sensitizing phenotype were superimposed upon the ENU mutagenesis screen. Our work illuminates an additional layer of complexity arising during the analysis of genetically sensitized ENU screens. In addition, the genetic interactions between these thrombosuppressor mutations could explain the complexity of human thrombosis.

*Presenter

Oral-22 : Diet-driven changes in immune regulation of adipose tissue revealed by single cell transcriptomics

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Obesity is reaching near-epidemic levels worldwide. Visceral white adipose tissue (vWAT), a component of total body fat, is not merely an inert lipid storage compartment but is also an important endocrine organ harboring a diverse population of immune cells. Visceral obesity is associated with a state of chronic low-grade inflammation which contributes to a range of pathologies including type 2 diabetes and cardiovascular disease. We used single cell transcriptomics to deeply profile visceral adipose tissue and constructed an immune-focused vWAT cell atlas using data from >15,000 cells. Our approach employs cell sorting via flow cytometry to ensure inclusion of certain rare vWAT immune cell types while maintaining the ability to quantify changes in composition within broad classes of the immune hierarchy. We used this strategy to profile vWAT from mice fed chow or high-fat diet for eight weeks. Mice fed high-fat diet were heavier, had significantly impaired glucose regulation, and showed marked changes in vWAT cell composition and transcriptional profiles. We identified over twenty clearly discernable cell types present in mice fed both diets. Notably, single cell profiling revealed strong diet-driven shifts in macrophage cell state. We present insights into the biogenesis and function of high-fat diet macrophage subsets, building on previously known properties of adipose tissue macrophages. Harmonization of vWAT single cell transcriptional profiles with data from other tissues revealed novel links to macrophage states in other diseases, including shared activation pathways. Finally, we discuss insights into adipose tissue homeostatic immune constituents gained from single cell transcriptomics of genetically diverse mouse strains whose susceptibility to obesity and related sequelae varies dramatically. These results provide a framework for characterizing changes in visceral adipose immune cell networks brought about by diet, genetic background, or drug treatment, and for interpreting how these factors may impact obesity-associated inflammatory processes.

*Presenter

Oral-23 : Studying the Multimorbidity of Alveolar Bone Changes, intestinal cancer, atherosclerosis, obesity and Impaired Glucose Tolerance in response to High-Fat Diet Consumption using Collaborative Cross Mouse Population

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Obesity and Type 2 diabetes (T2D) were shown an association with the pathogenesis and development of alveolar bone loss in periodontitis and intestinal cancer development. To dissect the host susceptibility loci underlying these diseases, we used collaborative cross (CC) mouse population, induced by High-Fat Diet (HFD). A cohort of mice from 8 week old mice of CC lines were assessed in this study, divided into four groups; 1) control group - mice maintained on chow for 12 weeks; 2) bacterial challenge - mice maintained on chow diet and infected orally with *P.gingivalis* & *F.nucluatum* for 12 weeks; 3) dietary challenge - mice maintained on HFD (42% Fat) for 12 weeks; and 4) dietary challenge and bacterial challenge- mice maintained on HFD and infected orally for 12 weeks. Body weight and intraperitoneal glucose tolerance test (IPGTT) was assessed at different time points during the experiment, and at terminal point, polyp counts in the small and large intestines were assessed, and the maxillary jaws were harvested and bone volume was quantified by micro-CT technique. Results have shown that the level of alveolar bone varies between the different CC lines in all the experimental groups. Furthermore, some CC lines showed a significant alveolar bone loss following both bacterial and dietary challenges, while others did not. Significant negative correlation between glucose tolerance ability (IPGTT values) and bone volume among mice of the dietary challenge group. Data analysis reveals significant positive correlation with sex bias between body weight gain and polyp counts. T2D and polyp counts showed significant negative correlations in male's small intestines, except the colon where correlations were positive but did not reach the significant level. Our results may provide a novel basis for the development of alternative therapeutic targets to control periodontitis and intestinal cancer development among T2D patients.

*Presenter

Oral-24 : The pluripotency regulator PRDM14 requires hematopoietic regulator CBFA2T3 to initiate leukemia in mice

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Prdm14 is a pluripotency regulator central to embryonic stem cell identity and primordial germ cell specification. Genomic regions containing PRDM14 are often amplified leading to mis-expression in human cancer. Prdm14 expression in mouse hematopoietic stem cells (HSCs) leads to progenitor cell expansion prior to the development of T-cell acute lymphoblastic leukemia (T-ALL), consistent with PRDM14's role in cancer initiation. Here, we demonstrate mechanistic insight into PRDM14-driven leukemias in vivo. Mass spectrometry revealed novel PRDM14-protein interactions including histone H1, RNA binding proteins and the master hematopoietic regulator CBFA2T3. In mouse leukemic cells, CBFA2T3 and PRDM14 associate independently of the related ETO family member CBFA2T2, PRDM14's primary protein partner in pluripotent cells. CBFA2T3 plays crucial roles in HSC self-renewal and lineage commitment, and participates in oncogenic translocations in acute myeloid leukemia. These results suggest a model whereby PRDM14 recruits CBFA2T3 to DNA, leading to gene mis-regulation causing progenitor cell expansion and lineage perturbations preceding T-ALL development. Strikingly, Prdm14-induced progenitor cell expansion and resulting T-ALL does not occur in mice deficient for Cbfa2t3, demonstrating that Cbfa2t3 is required for leukemogenesis. Moreover, T-ALL develops in Cbfa2t3 heterozygotes with a significantly longer latency, suggesting that PRDM14-associated T-ALL is sensitive to Cbfa2t3 levels. Our study highlights how an oncogenic protein uses a native protein in progenitor cells to initiate leukemia, providing insight into PRDM14-driven oncogenesis in other cell types.

*Presenter

Oral-25 : The JAX Genome Editing Testing Center: A Component of the Somatic Cell Genome Editing Consortium

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The JAX Genome Editing Testing Center (JAX-GETC) is working at the intersection of genome editing technologies and gene therapy platforms to achieve fundamental breakthroughs in the treatment of genetic disease. To accomplish this mission, the JAX-GETC is building novel mouse reporter platforms for robust and sensitive detection of editing activity, and will be using these models to support the evaluation of new delivery technologies and editors, *in vivo*. Drawing upon JAX's unique expertise and unparalleled mouse genetic resources, the Center leadership has assembled a talented, multi-functional team organized into discrete components. The three research components—the Animal Model Production Unit, the Gene Editing Testing Core, and the Animal Model Resource Core—build on existing research and management teams, and are supplemented with collaborating teams that bring unique resources and skills to the overall Center.
The aims of the JAX-GETC are, first, to develop a mouse model resource (including a panel of reporter models) to robustly monitor genome editing activity and cell-type specificity, *in vivo*. In addition, the JAX-GETC will develop a scalable platform to support the delivery of editing components and the analysis of editing outcomes. Third, we will contribute to the Somatic Cell Genome Editing (SCGE) consortium by deploying systems to share both data and animal resources. Last, the Center aims to leverage the scale of our mouse modeling capabilities, our *in vivo* manipulation platforms, and our expertise, to develop a framework for future collaborative expansion.
The successful completion of these aims will advance the goals of the SCGE program, which are to improve genome editing technologies, to translate this technology into clinical applications, and to maximize gene editing's potential to treat as many diseases as possible.

*Presenter

Oral-26 : Sequencing the BXD family, a cohort for experimental systems genetics and precision medicine

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6 - Ecole Polytechnique Fédérale de Lausanne (Switzerland)

The BXD mouse family is the most deeply phenotyped mammalian model system, with more than 7000 classical phenotypes and over 100 ‘omics datasets publicly available in GeneNetwork.org. GeneNetwork is both a data repository and an open source toolkit allowing examination of complex interactions between gene variants, phenotypes from different biological levels, and environmental factors.
The family consists of ~150 inbred strains, each of which is homozygous for a unique mosaic of alleles from the C57BL/6J and DBA2/J parents. We have carried out 40X sequencing of 152 BXD strains, and their parents, using a Chromium linked-read strategy, with mean fragment length of 44kb.
We have increased the number of known, segregating, small variants in the BXD to >6 million, and are working on large structural variants. Most variants segregate with an ~50/50 allele frequency, making them ideal for mapping and for massive parallel whole phenome mapping, aka PheWAS (systems-genetics.org).
We have produced a draft ‘infinite marker map', intended to identify every recombination event in the family. This draft map shows an improvement in both mapping power and precision.
We also confirmed ~1300 regions of the genome showing ‘epoch' effects. These variants occurred in the parental strains over the 40 years between the first and last set of BXD strains being produced, and therefore show a distinct segregation pattern in the family. These allow causal variants to be rapidly discovered.
Identification of private variants has allowed predictions of variants causing strains to be outliers for phenotypes in GeneNetwork. We show three genes which are candidates for an abnormal memory and anxiety phenotype in BXD74.
This family is an excellent resource for testing networks of causal and mechanistic relations among millions of molecular and organismal traits, including, addiction, neurodegeneration, and longevity. Full sequencing of all lines has only increased its usefulness.

*Presenter

Oral-27 : Validation of increasingly complex alleles generated by genome editing: employing long read sequencing

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Mouse models are valuable tools to understand genes functions, genetic diseases and to develop and test new therapeutic treatments *in vivo*. The ability to introduce tailored modifications within the mouse genome is essential to generate them. The CRISPR/Cas9 system has brought new perspectives for the generation of mouse models in a more efficient and precise fashion, at reduced price, all within a shorter time scale. We are developing protocols for the production of increasingly complex alleles. Alongside the generation of mutants, their validation represents a new challenge that is essential to meet to ensure research reproducibility. We will present our recent developments of processes for genome engineering. We will summarise our findings on unexpectedly large deletions produced by CRISPR/Cas9 activity. We will also show the results of a new pilot for the use of the long-read sequencing for founder screening and model validation. With new processes for allele validation, we uncover further variability in the outcome of applying CRISPR/Cas9 to the modification of mouse early embryos. This includes discrete sequence changes, the generation of larger than expected deletions and chromosomal rearrangements. We will show how extensive validation recognises unwanted variants at early stages of the mutagenesis process and reduces the number of animals used for genome engineering.

*Presenter

Oral-28 : Understanding the variability of the fecal microbiota and large scale evaluation of Host – Microbial genetics interactions: impact of the IMPC knock-out resource for the microbiota community

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The International Mouse Phenotyping Consortium (IMPC) is an international scientific endeavor that is creating and characterizing knockout mutation for every protein coding gene in the mouse genome. In addition to generating and phenotyping approximately 20,000 models, one of our consortium's challenges is to guarantee the reproducibility of the generated data. As it is becoming increasingly evident that changes to the gut microbiota (GM) can have significant effects on animal models and their expressed phenotypes, we evaluated the variability of the GM and its impact on IMPC phenotyping results. C57BL/6N wild type mice used as control in IMPC phenotyping protocols were analyzed for their GM content. The GM composition is stable in the different institutes for more than 2 years and no strong correlation between GM content and phenotyping deviation was observed. Our results suggest that 1) the GM composition somehow correlates with the global animal health sanitary status and 2) the wild type GM has a minor impact on phenotyping variability. Moreover, because hundreds of C57BL/6N mice were analyzed for their GM content at 16 week of age, we were able to define the first GM reference range in an animal facility.
To evaluate Host – Microbial genetics interactions, hundreds of IMPC knock-out mice are now starting to be analyzed using 16S metagenomics. Comparing knock-out GM content to the wild type GM reference range already allowed us to detect subtle changes in microbiome composition in knock-out mutants while eliminating non-significant variations.

*Presenter

Oral-29 : Reference quality mouse genomes reveal complete strain-specific haplotypes and novel functional loci

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Previously we reported full-length draft de novo genome assemblies for 16 widely used inbred mouse strains and find extensive strain-specific haplotype variation. We identified and characterised 2,567 regions on the current mouse reference genome exhibiting the greatest sequence diversity. These regions are enriched for genes involved in pathogen defence and immunity and exhibit enrichment of transposable elements and signatures of recent retrotransposition events. Combinations of alleles and genes unique to an individual strain are commonly observed at these loci, reflecting distinct strain phenotypes. Advances in third generation long read sequencing technologies (Pacific Biosciences and Oxford Nanopore) mean that it is now possible to efficiently create reference quality mammalian genomes. We report the first results of long read resequencing and de novo assembly of the sixteen inbred mouse strains. We show that these technologies can create accurate and complete representation of many of the most complex regions of the mouse genome, illustrating striking coding and regulatory variation.

*Presenter

Oral-30 : The Alliance of Genome Resources: Transforming comparative genomics for human and model organisms

Bult Carol* (1), Blake Judith (1), Cherry J. (2), Calvi Brian (3), Mungall Chris (4), Howe Kevin (5), Perrimon Norbert (6), Shimoyama Mary (7), Sternberg Paul (8), Thomas Paul (9), Westerfield Monte (10)

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4 - Lawrence Berkeley National Laboratory [Berkeley] (United States)
5 - European Bioformatics Institute (United Kingdom)
6 - Harvard University [Cambridge] (United States)
7 - Medical College of Wisconsin (United States)
8 - California Institute of Technology (United States)
9 - University of Southern California (United States)
10 - University of Oregon [Eugene] (United States)

The Alliance of Genome Resources (a.k.a., the Alliance), formed by the major Model Organism Databases (MODs) and the Gene Ontology Consortium (GOC), seeks to realize the full potential of model organism data resources for comparative genomics and functionalization of the human genome, The six MODs (Saccharomyces Genome Database, WormBase, FlyBase, Zebrafish Information Network, Mouse Genome Database, Rat Genome Database) and the GOC have a long history of expediting discoveries in genome biology through the integration of heterogeneous genetic, genomic, and phenotype data, and with information from disparate sources such as the scientific literature, unpublished data from individual researchers, and diverse publicly available data archives, into expertly curated community database resources. The full significance and impact of the MODs and GOC for comparative biology have been negatively impacted in the past by the lack of unified data access mechanisms and user interfaces. Now the Alliance provides integrated access to genetic, genomic, and phenotype data generated by multiple research communities about biological systems in model organisms that can reveal new insights into the mechanisms underlying human biology and disease (https://alliancegenome.org).
The Alliance is committed to the development of shared modular infrastructure, including common tools for data acquisition and curation, common mechanisms for data access, and unified user interfaces and analysis tools. We provide access to the collected knowledge about model organisms and human gene function in both browsable and computation-ready formats. Prior to the Alliance, it would have required countless hours for individual researcher to assemble relevant function, phenotype, and disease data from each resource on their own. In this presentation, we will demonstrate how Alliance resources provide unprecedented support for the comparison of gene function, expression, phenotype, and models of human disease among diverse model organisms.

*Presenter

Oral-31 : Regulation of genomic imprinting in development and disease

Bartolomei Marisa* (1)

1 - University of Pennsylvania (United States)

Imprinted genes, which are unique to mammals, are monallelically expressed in a parent-of-origin specific manner. Most imprinted genes reside in clusters that are located throughout the mammalian genome. The clusters contain an imprinting control region (ICR), which harbors allele-specific methylation and governs the imprinting of the entire domain. Although most imprinted clusters use long non-coding RNAs to regulate imprinted gene expression, a few are regulated by CTCF and allele-specific insulator function. One such cluster harbors the *H19*and *Igf2* imprinted genes, and is controlled by an ICR that contains multiple CTCF binding sites. Gain of maternal methylation and loss of paternal hypermethylation of the *H19*/*IGF2*ICR are associated with the human growth disorders Beckwith-Wiedemann Syndrome (BWS) and Silver-Russell Syndrome (SRS), respectively. A second imprinted locus, *Grb10*, also uses an ICR with CTCF binding sites to regulate an unusual allele and tissue-specific imprinting pattern. Using gene targeting and genome editing, we have generated cell lines and mice to study imprinting mechanisms. We have also studied the mechanism governing imprint establishment in the germline using mice harboring mutations in epigenetic regulators.

*Presenter

Oral-32 : Generation and Characterization of Transgenic Rats Carrying Cre Recombinase Knockins at the Dopamine D1 and Adenosine 2a Receptor Loci.

Saunders Thomas* (1), Pettibone Jeffrey (2), Hughes Elizabeth (1), Ferrario Carrie (1), Berke Joshua (2), Filipiak Wanda (1)

1 - University of Michigan Medical school (United States)
2 - UCSF Center for Integrative Neuroscience (United States)

CRISPR/Cas9 technology was used to generate transgenic rats carrying Cre recombinase at the dopamine D1 receptor (*Drd1a*) or adenosine 2a receptor (*Adora2a*). The use of CRISPR permits the precise introduction of Cre transgenes in the genome. This approach results in expression patterns that precisely follow endogenous gene expression patterns. The use of CRISPR/Cas9 is an important advance over the use of large (~200 kb) bacterial artificial chromosome (BAC) transgenes to direct Cre recombinase expression. The random integration of BAC transgenes into the genome and the variability in numbers of BAC transgenes affect the fidelity with which proteins are expressed from BAC transgenes. Long Evans rats, a preferred strain for cognition research, were used for genomic modification with CRISPR/Cas9. The iCre coding sequence was placed immediately before the termination codons of *Drd1a*or *Adora2a*genes. The function of the receptors was preserved by inserting the P2A self-cleaving peptide sequence between the receptor coding sequences and the iCre coding sequence. After the transgenic rat lines were established, whole-genome sequencing was used to verify the absence of off-target hits, gene expression patterns were characterized by in situ hybridization, protein function was demonstrated by *in vivo*viral vector mediated transfection. Functional Cre expression in the striatal direct and indirect pathways was observed in the D1-Cre and A2a-Cre rats. Both rat lines show normal locomotor activity and learning in simple instrumental and Pavlovian tasks. These new D1-Cre and A2a-Cre rat lines will be used to study normal brain functions and neurological and psychiatric pathophysiology.

*Presenter

Oral-33 : Identification of novel genes for adiposity and lipids using outbred heterogeneous stock rats

Solberg Woods Leah* (1), Le Thu (2), Keele Gregory (3), Holl Katie (4), Seshie Osborne (1), Tschannen Michael (4), Craddock Ann (1), Hawkins Greg (1), Valdar William (5), Mott Richard (2)

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2 - University College London, Department of Genetics, Evolution and Environment, London (United Kingdom)
3 - The Jackson Laboratory, Bar Harbor, ME (United States)
4 - Medical College of Wisconsin, Milwaukee, WI (United States)
5 - UNC at Chapel Hill, Chapel Hill, NC (United States)

Obesity is a major risk factor for multiple diseases and is in part heritable, yet the majority of causative genetic variants remain unknown. We set out to fine-map multiple metabolic traits and identify underlying candidate genes using outbred heterogeneous stock (HS) rats. We measured body weight, fat pad weight, fasting and post-prandial glucose and insulin, and fasting cholesterol and triglycerides in 1,519 adult males. Rats were genotyped using low coverage whole genome sequencing followed by imputation using STITCH. RNAseq was run in liver and adipose tissue in over 400 of these rats. Physiological quantitative trait loci (pQTLs) were identified using both SNP-based (miQTL) and haplotype-based (R/qtl2) methods, taking into account the complex family structure of the HS. Expression QTLs (eQTLs) were identified using Matrix eQTL, a SNP-based approach, followed by mediation analysis. We identified 31 QTLs, five of which were pleiotropic. Only eight QTLs were in common between SNP and haplotype-based methods. We identified 1,595 and 1,327 cis-eQTLs for adipose and liver tissue, respectively, 300 of which were shared between tissues. Using mediation analysis, we identified *Krtcap3* as a mediator within a pleiotropic QTL on Chr 6 for epididymal and retroperitoneal fat pad size and fasting triglycerides. Adipose *Grk5* was a mediator of a QTL on Chr 1 for epididymal and retroperitoneal fat pad size and *Snx10* was a mediator of a QTL on Chr 4 for fasting cholesterol. In other regions we identified multiple genes as mediators. This study identifies novel regulators of adiposity and lipids and reinforces the power of outbred rat models for genetic mapping and gene identification of metabolic traits.

*Presenter

Oral-34 : Searching diseases and phenotypes for model selection at the Rat Genome Database

Wang Shur-Jen* (1), Smith Jennifer (2), Laulederkind Stanley (2), Zhao Yiqing (3), Hayman Thomas (2), Thota Jyothi (2), Tutaj Monika (2)

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2 - Marquette University and Medical College of WI (United States)
3 - Mayor Clinic (United States)

The laboratory rat (*Rattus norvegicus*) has been the model organism of choice for the study of complex diseases for more than 150 years. The Rat Genome Database (RGD) has been storing and standardizing genomic, genetic, phenotype/disease and strain data for the laboratory rat since 1999. These data are curated with controlled vocabularies and can be visualized using different searching/browsing tools and analyzed by the RGD tool suite. The manual disease curation project has sequentially targeted 12 major disease areas (https://rgd.mcw.edu/wg/portals/), and the data are aggregated into portals where related data are integrated. Another useful portal is the Phenotype and Models Portal (https://rgd.mcw.edu/wg/physiology/). It houses the quantitative phenotype tools where phenotype values of individual measurements and calculated expected ranges for strain groups are available. The PhenoMiner tool is the search platform for all phenotype values of rats curated from published literature, imported from other resources or submitted by researchers. These curated PhenoMiner data are then used to calculate the expected ranges of a given phenotype for a designated strain group. Currently, the expected ranges are available for inbred strains. An automatic meta-analysis pipeline is under development to allow for updates of these ranges and bringing in new data sets from different strain types. In addition to querying by phenotype measurements, the calculated expected ranges can also be visualized by strain groups. Damaging variants for sequenced strains are listed under the corresponding group along with phenotypes. Linking phenotype values and genomic variations using the Expected Ranges tool will provide a useful approach to understanding the complexities of physiological genomics.

*Presenter

Oral-35 : Large humanization in rat ES cells

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Rats have been used for laboratory studies for over 100 years and, prior to the discovery of mESC, were much more frequently used than mice. In many cases mice harboring human disease mutation do not replicate same phenotype. In those cases, rat might be a better model. Although the development of rat ESC (rESC) was reported 10 years ago only a small number of reports using rESC have been published. Instead, CRISPR/Cas9-based editing in one cell embryos has become a more common approach. However, there are important limitations to gene editing technologies in embryos, the most notable being the difficulty of inserting or replacing DNA sequences larger than about 10 kb. We report here that we have generated germline competent ES cell lines from several strains of rats. These rESC lines maintain their germline transmitting potency after serial targeting with BAC-based targeting vectors. When combined with CRISPR/Cas9 to produce double-stranded breaks in the region of interest, we achieved high targeting efficiency (up to 60%) and we were able to replace entire rat genes spanning up to 101 kb with the human orthologue.

*Presenter

Oral-36 : Aicardi-Goutières Syndrome gene Rnaseh2c is a metastasis susceptibility gene in breast cancer

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1 - National Cancer Institute (United States)

Breast cancer is the second leading cause of cancer-related deaths in the United States, with the majority of these deaths due to metastatic lesions rather than the primary tumor. Thus, a better understanding of the etiology of metastatic disease is crucial for improving survival. Using a haplotype mapping strategy in mouse and shRNA-mediated gene knockdown, we identified *Rnaseh2c*, a scaffolding protein of the heterotrimeric RNase H2 endoribonuclease complex, as a novel metastasis susceptibility factor. We found that the role of *Rnaseh2c* in metastatic disease is independent of RNase H2 enzymatic activity, and immunophenotyping and RNA-sequencing analysis revealed engagment of the T cell-mediated adaptive immune response. Furthermore, the cGAS-Sting pathway was not activated in the metastatic cancer cells used in this study, suggesting that the mechanism of immune response in breast cancer is different from the mechanism proposed for Aicardi-Goutières Syndrome, a rare interferonopathy caused by RNase H2 mutation. These results suggest an important novel, non-enzymatic role for RNASEH2C during breast cancer progression and add *Rnaseh2c* to a panel of genes we have identified that together could determine patients with high risk for metastasis. These results also highlight a potential new target for combination with immunotherapies and may contribute to a better understanding of the etiology of Aicardi-Goutières Syndrome autoimmunity.

*Presenter

Oral-37 : Bilophila wadsworthia supplementation reduces adenoma burden in the Apc-Min mouse model of colorectal cancer

Amos-Landgraf James* (1)

1 - Rat Resource and Research Center, University of Missouri (United States)

Human studies have recently associated certain intestinal microbial communities with the presence of colorectal cancer (CRC). Previously, we colonized the familial colon cancer mouse model (*ApcMin*) with distinct complex gut microbiotas (GMs), and found that mice colonized with a simplified GM developed fewer adenomas, while a more complex GM resulted in higher adenoma numbers. Characterization of the two GMs via 16S rRNA microbial profiling revealed increased relative abundance of sulfidogenic *Bilophila* species associated with higher adenoma numbers in *ApcMin* mice. To directly assess the effects of *Bilophila* on adenoma initiation and progression, dams and their *ApcMin* offspring harboring a lower complexity GM with no detectable *Bilophila* were gavaged with 10^7-10^8 colony forming units (CFUs) of the human isolate *Bilophila wadsworthia*. To assess colonization of *B. wadsworthia*, we sequenced the 16S rRNA bacterial gene in post-gavage fecal samples and small intestinal (SI) epithelium and found significantly increased levels of the bacteria in both. Additionally, 16S rRNA sequencing determined that supplementation with *B. wadsworthia* induced a shift in the complex GM, driven primarily by the addition of *B. wadsworthia* and concurrent loss of *Prevotella* sp. At 3 months of age, we found that relative to controls, *ApcMin* mice treated with *B. wadsworthia* developed significantly fewer and smaller adenomas, resulting in an overall lower adenoma burden. To determine whether mice treated with *B. wadsworthia* exhibit a different immunophenotype, we quantified expression of the Type 1 T helper cell-specific transcription factor *Tbx21* in ileal scrapes. We observed increased expression of *Tbx21* in *B. wadsworthia*-treated mice, suggesting immune-mediated adenoma suppression in treatment groups. These results suggest that *B. wadsworthia* has a protective role in both initiation and progression of CRC, and may modulate disease susceptibility in *ApcMin* mice through direct host-microbe interactions, or indirectly through broader GM community changes.

*Presenter

Oral-38 : Modeling the Genetics of Gulf War Illness in the Mouse

Jones Byron* (1), O'callaghan James (2), Miller Diane (2), Zhao Wenyuan (1), Xu Fuyi (1), Lu Lu (1)

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2 - Health Effects Laboratory, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Morgantown, West Virginia (United States)

In 1991, the USA and allies sent 900,000 troops to Kuwait to defend against Iraqi invasion. Of the troops sent, 25-30% returned with a chronic illness that included general malaise, GI and neurological complaints. Most of those afflicted are still experiencing symptoms nearly 30 years later. O'Callaghan and Miller proposed that the illness was based on neuroinflammation caused by exposure to organophosphorus (OP) compounds combined with high circulating glucocorticoids and developed a mouse model accordingly. The model consists of exposing mice to corticosterone in the drinking water for 7 days and on the 8th day, administering an OP (diisopropylflurophosphate- DFP), as a surrogate of nerve agent sarin. Indices of neuroinflammation are changes in expression of proinflammatory cytokine genes in the frontal cortex and hippocampus. Jones expanded the model to include 30 BXD inbred strains to show genetic variability in susceptibility to the effects of the treatment. We showed wide genetic variability in the effect of the treatment on expression of IL1B, IL6 and TNF. Mapping the variability in IL1B, we nominated *Spon1* as candidate gene. We then performed RNA-seq analysis genome wide. The data showed both *Il1b* and *Spon1* as well as several other proinflammatory cytokine genes were responsive to the treatment, thus supporting our hypothesis that Gulf War Illness is based, at least in part, on neuroinflammation and shows wide variability in susceptibility to the effects of the chemicals to which the troops were exposed. Supported in part by DoD Grant GWI160086.

*Presenter

Oral-39 : Genetic variation influences pluripotent ground state stability in mouse embryonic stem cells through a hierarchy of molecular phenotypes

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1 - The Jackson Laboratory (United States)
2 - Predictive Biology (United States)
3 - National Toxicology Program, the National Institute of Environmental Health Sciences (United States)

Before widespread adoption of 2i culture conditions, stable mESC lines could only be derived from a limited set of inbred mouse strains. We and others employed 2i culture approaches (inhibition of ERK1/2 and GSK3) to overcome inbred strain derivation recalcitrance, however the underlying cause of recalcitrance remains a mystery. Moreover, in our work with genetically diverse, germ line competent mESCs we have observed significant intrastrain variability in morphology, growth rate, plating efficiency, and gene expression in the presence of 2i+LIF in undefined (serum) culture conditions. These observations suggest that mESCs from different inbred strains have distinct responses to the cell culture environment that may influence the stability of the pluripotent ground state *in vitro*, and ultimately impact cellular trajectories during *in vitro* differentiation. To identify the underlying genetic factors influencing this variability, we used a systems genetics approach. We profiled gene expression and chromatin accessibility in 185 genetically heterogeneous mESCs from the Diversity Outbred mouse population. We mapped thousands of loci affecting chromatin accessibility and/or transcript abundance, including eleven instances where distant QTL co-localized in clusters. For one cluster we identified *Lifr* transcript abundance as the causal intermediate regulating 122 distant genes enriched for roles in maintenance of pluripotency. Joint mediation analysis implicated a single enhancer variant ~10kb upstream of *Lifr* that alters chromatin accessibility, influences *Lifr* transcript abundance, and precipitates a cascade of molecular events affecting expression of pluripotency markers. We validated this hypothesis using reciprocal allele swaps, revealing mechanistic details underlying ground state stability of mESCs *in vitro*, and potentially mESC derivation recalcitrance.

*Presenter

Oral-40 : Patterns and Mechanisms of Sex Ratio Bias in the Collaborative Cross

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Mendel's laws of segregation predict a 1:1 ratio of males to females, but deviations from this expectation are common in nature. Sex ratio bias (SRB) may often reflect sex differences in viability or survival, but can also arise from genetic conflict between loci on the X and Y over transmission to the next generation. Sex chromosome conflicts are commonly observed in crosses between incipient species and they may play a role in the emergence of intrinsic reproductive barriers. The Collaborative Cross (CC) founder strains include representatives from three distinct *Mus musculus* subspecies, leading us to hypothesize that this diverse population may harbor significant, but heretofore underappreciated, SRB. To explore this possibility, we analyzed breeding records for 48 CC strains maintained in The Jackson Laboratory's Repository over the two-year period from January 2016 to December 2018. Remarkably, one-third (n = 16) of CC lines exhibit significant SRB at weaning, with more male-biased (n = 11) than female-biased strains (n = 5). We show that these pervasive sex biases persist across multiple strain breeding environments, are stable over time, and are not explained by differences in neonatal mortality. Given the absence of significant SRB in the inbred CC founders and their F1 hybrids, we hypothesize that recessive epistatic allele combinations only realized in mosaic CC mice drive these widespread trends. Current functional investigations are exploring the underlying genetic and molecular mechanisms of SRB in several of the most extremely sex-biased CC strains. Taken together, our findings reveal the scope of SRB in the CC population, implicate genetic mechanisms of sex ratio control, and establish the CC as a powerful resource for investigating sex chromosome genetic conflict in action.

*Presenter

Oral-41 : Sex-biased genome evolution

Wilson Melissa* (1)

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The human sex chromosome evolved from a pair of homologous autosomes, and are unlike any other pair of chromosomes within the human genome. While many parts of the X and Y chromosomes have diverged from one another, there are still some regions that share significant sequence homology, and others, the pseudoautosomal regions, that still undergo homologous recombination in genetic males. This unique evolutionary history results in technical challenges for genome alignment analysis of NGS data. I will present an overview of the evolutionary history of the human X and Y, and then present new methodology to improve genomic and transcriptomic analyses of the sex chromosomes. Additionally, I will discuss a new theory for how evolution may have shaped sex-specific differences in immune function, facilitated by the evolution of our sex chromosomes.

*Presenter

Oral-42 : QTL mapping power in the realized Collaborative Cross

Keele Greg (1) (2), Crouse Wesley (1), Kelada Samir (1), Valdar William* (1)

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2 - The Jackson Laboratory (United States)

The Collaborative Cross (CC) is a mouse genetic reference population whose range of applications includes quantitative trait loci (QTL) mapping. The design of a CC QTL mapping study involves multiple decisions, including which and how many strains to use, and how many replicates per strain to phenotype, all viewed within the context of hypothesized QTL architecture. Until now, these decisions have been informed largely by early power analyses that were based on simulated, hypothetical CC genomes. Now that more than 50 CC strains are available and more than 70 CC genomes have been observed, it is possible to characterize power based on realized CC genomes. We report power analyses from extensive simulations and examine several key considerations: 1) the number of strains and biological replicates, 2) the QTL effect size, 3) the presence of population structure, and 4) the distribution of functionally distinct alleles among the founder strains at the QTL. We also provide general power estimates to aide in the design of future experiments. All analyses were conducted with our R package, SPARCC (Simulated Power Analysis in the Realized Collaborative Cross), developed for performing either large scale power analyses or those tailored to particular CC experiments.

*Presenter

Oral-43 : Comparative Genomics: The Pseudogene Challenge

Blake Judith* (1), Bult Carol (1), Zhu Sophia (1), Mitchell Cailey (1), Drabkin Harold (2), Mukherjee Gaurab (1), Mcandrews Monica (2), Dolan Mary (2)

1 - The Jackson Laboratory (United States)
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The concept of a pseudogene, that being a "*sequence that closely resembles a known functional gene at another locus within a genome that is non-functional as a consequence of (usually several) mutations that prevent either its transcription or translation (or both)* [SO:0000336]", becomes ever more complicated as precise genetic engineering techniques utilize annotated genomic sequences to enable development of new animal models. Within bioinformatics data resources, the pseudogene designation can be sub-divided into multiple categories such as 'unitary pseudogenes' where a protein-coding gene occurs in one taxon (say human) but there is no equivalent gene in another taxon (say mouse)1. Another example is 'polymorphic pseudogenes' where, when comparing multiple fully sequenced genomes (say 17 strains of mice), a genome feature may be classified as a protein-coding gene in some strains and as a pseudogene in other strains.
Here we investigate the pseudogene category of genome features as represented in human and mouse genomes with the intent to clarify and refine genome feature classifications for comparative functional genomic investigations. We report on current understanding of these features utilizing GENCODE, NCBI, MGI, UniProt, SO, and other relevant resources. We evaluate some of the complexities generated by definition and nomenclature assertions, and provide some specific use cases where features currently classified as pseudogenes are reported in RNA_seq and other HT functional data streams.
1 A classic example of a unitary pseudogene is the human *GULOP* pseudogene which partially codes for gulonolactone (L-) oxidase. While being pseudogenic in human, this gene corresponds to functional orthologs in many other mammalian species, such as mouse, where the mouse *Gulo* gene encodes for L-gulono-gamma-lactone oxidase that catalyzes the last step of ascorbic acid biosynthesis.

*Presenter

Oral-44 : Annotating Sequence Variants for Phenotypic Mouse Alleles at Mouse Genome Informatics

Wilming Laurens* (1), Law Meiyee (1), Beal Jon (1), Campbell Jeffrey (1), Corbani Lori (1), Baldarelli Richard (1), Richardson Joel (1), Smith Cynthia (1), Bult Carol (1)

1 - The Jackson Laboratory (United States)

The power of the mouse as a model for human disease can only be fully exploited if researchers are able to find suitable mouse models for their human disease of interest. Many human diseases are ultimately caused by simple genomic mutations (single or multiple nucleotide variations (SNVs, MNVs) small insertions or deletions (indels)). However, the large number of genetic variants uncovered from individual patients presents challenges in identifying the causal gene or genomic regions. Although the Mouse Genome Informatics (MGI) database provides gene and genotype connections to phenotype annotations, the sequence context of the genome variants for phenotypic alleles is not yet available.

To provide researchers with a searchable, structured dataset of mouse mutations for comparative analysis, we have undertaken a variant annotation project aimed at annotating, initially, mouse SNVs, MNVs and small indels. These variants, characterized by their genomic position and altered sequence, are associated with phenotypic alleles (both synthetic and spontaneous) in the MGI database (www.informatics.jax.org). Variant attributes include variant type (insertion, substitution, etc.) and molecular consequence (in-frame insertion, stop codon gain, etc.). Data will be available in Human Genome Variation Society (HGVS) notation to represent transcript and protein contexts. This data will be accessible from MGI and the Alliance of Genome Resources (Alliance; www.alliancegenome.org) in March 2020. Additional variants from large sequencing and mouse mutagenesis projects will be added to augment the curated data. By tying variant data and associated phenotype data to the genome, researchers will be able to search using one or more human variants and find models with variants/mutations that result in the same amino acid change, have the same variant effect (missense, etc.), have the same functional impact (pathogenic, etc.), occur in the same protein domain(s), or have the same mode of inheritance (recessive, dominant, etc.), resulting in phenotypes similar to a patient.

*Presenter

Oral-45 : Learning the ABCs from ESCs to NPCs: Exploiting genetic diversity to elucidate the gene regulatory networks underlying cell differentiation.

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1 - The Jackson Laboratory (United States)
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Pluripotent stem cells (PSCs) provide an important model for human disease and offer the promise of personalized regenerative medicine. However, phenotypic heterogeneity represents a challenge to fulfilling this promise, as populations of cells with similar identities are required to maximize therapeutic effect and minimize negative side effects. Phenotypic variation has recently been attributed to underlying genetic variation in PSCs, impacting multiple aspects of human stem cell biology including stability of the pluripotent state *in vitro* as well as their response to directed differentiation and subsequent cell fate diversification.
We recently took advantage of mouse embryonic stem cell (mESC) lines derived from the powerful Diversity Outbred (DO) heterogenous stock to show that genetic variation biases ground state pluripotency through direct effects on gene expression and chromatin accessibility. These regulatory variants likely impact individual cell types and differentiation potential; however, the downstream impacts of regulatory variation in mESCs on differentiation to specific lineages are not well understood. To address this, we expanded our multi-omic analysis to include neural progenitor cells (NPCs) differentiated from the same DO mESC lines. We identified thousands of loci genome-wide that affect gene expression in one or both cell types. The effects of local regulatory variants are often detected in both the mESC and NPC transcriptomes, while most *trans* effects from distant variants are cell type-specific. Joint mediation analysis across cell types identified transcriptional signatures in NPCs that appeared to stem from regulatory variants acting earlier to bias the ESC transcriptome. We are in the process of validating these predictions with allele swap experiments. Together, these studies reveal the complex regulatory architecture that drives differentiation of pluripotent stem cells to diverse cell types, and provide a blueprint to modify the genome to precisely direct cell differentiation in diverse individuals.

*Presenter

POSTER ABSTRACTS

P01 : Comprehensive analyses of naive-to-primed pluripotency transition in mice

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Implantation to uterus, a vital process specific to mammals, triggers new relationships between embryos and their mother, leading to a new phase of development. For example, pluripotential cells in the peri-implantation embryos undergo naïve-to-primed transition, accompanied with large-scale changes in epigenomic status. In female mammals, one of the two X chromosome is randomly inactivated so that expression levels of X-linked genes are compensated between XX female and XY male. Although this random X chromosome inactivation (XCI) occurs at peri-implantation stage, the precise timing of its initiation *in vivo* or *in vitro* has not been understood fully. Here we examined the expression of *Xist* and *Tsix*, non-coding RNAs involved in XCI, in peri-implantation embryos using whole-mount 3D RNA-FISH (Shiura and Abe, Sci. Rep. 2019). The results demonstrate that imprinted *Xist* expression disappears by embryonic day (E) 4.5 and that random XCI is initiated already in some cells of E4.75 embryos, coincident with the moment of implantation.
In parallel with this *in vivo* study, we have established a robust *in vitro* system for analysis of naïve-to-primed transition by modifying the efficient EpiSC derivation method using Wnt inhibitor (Sugimoto et al, Stem Cell Rep. 2015). Taking advantage of this system, we performed single cell analysis of the transition process and identified two novel cellular states in addition to the known naïve and primed statuses. One is characterized by global down regulation of thousands of genes, coincided with initiation of random XCI, and the other represents self-renewing pluripotent stem cell (PSC) population with intermediate phenotype between the naïve and the primed PSCs.
Combined, these results will serve as a basis for future functional studies of naïve-to-primed transition process as well as XCI and also provide new insights into pluripotency spectrum in mammals.

*Presenter

P02 : Hepatic gene expression variations in response to high fat diet-induced diabetes using next-generation RNA-sequencing in Collaborative Cross mouse population

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6 - Universitat Pompeu Fabra (UPF), Barcelona. (Spain)
7 - Centre for Genomic Regulation (CRG), Barcelona. (Spain)
8 - Department of Vertebrate Genomics, Max Planck Institute for Molecular Genetics, Germany (Germany)
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Aims: Hepatic gene expression is known to differ between healthy and type 2 diabetes (T2D) and Metabolic syndrome (MetS) conditions. Identifying these variations will provide better knowledge of the development of gene-targeted therapies. The aim of this study is to assess diet-induced hepatic gene expression of susceptible versus resistant CC lines to T2D development.
Methods: Next generation RNA-sequencing (RNAseq) for 84 livers of diabetic and non-diabetic mice of 43 different CC lines (both sexes) following 12 weeks on High-Fat (42 % fat) Dietary challenge. The analysis was performed for joint sexes and separately, per line in healthy and diabetic mice.
Results: Hepatic gene expression differs in diabetic versus non-diabetic mice with significant sex effect. In overall population (regardless of sex) 601 genes were differentially expressed (DE), while in females only group, 718 genes, and 599 genes in males only group. Top prioritized DE candidate genes in diabetic versus non-diabetic conditions were; *Lepr*; *Ins2*; *Mb*; *Ckm*; *Mrap2* and *Ckmt2* for the overall population. Females only-group top prioritized DE candidate genes were; *Hdc*; *Serpina12*; *Socs1*; *Socs2*;*Mb*, while for males only group; *Serpine1*; *Mb*; *Ren1*; *Slc4a1*;*Atp2a1*. Data analysis for sex-differences revealed 193 DE genes in health (Top candidate: *Lepr; Cav1; Socs2; Abcg2; Col5a3*), and 389 genes DE between diabetic females versus males (Top candidate: *Lepr; Clps; Ins2; Cav1; Mrap2*).
Conclusions: Our findings emphasize the complexity of T2D and MetS to be significantly controlled by complex genetic components of the host. As well, we demonstrate the significant sex-differences, between males and females during health and increasing to extent levels during disease/diabetes. Altogether, opening the venue for further studies targeting for the discovery of effective sex-specific and personalized preventions and therapies.

*Presenter

P03: Generation and validation of increasingly complex alleles introduced by genome editing

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Mouse models are valuable tools to understand gene function, genetic disease mechanisms and to develop and test new therapeutic treatments *in vivo*. The CRISPR/Cas9 system can be utilised as a genome-engineering tool and has brought new perspectives in the generation of mouse models of human disease. The use of this system allows for the introduction of targeted point mutations and other subtle modifications into the mouse genome in a time-efficient and cost-effective manner. We will present our recent developments of processes for genome engineering. As the CRISPR/Cas9 system becomes better understood and communicated, the requests for mouse models of human disease become ever more complex. These include flanking a target exon with FLOX sites, large megabase deletions of DNA sequence containing multiple genes and humanising sections of a gene to better mimic a disease model in humans. Alongside the generation of these mutants, their validation represents a new challenge. With new processes for allele validation, we uncover further variability in the outcome of applying CRISPR/Cas9 to the modification of mouse early embryos. We will demonstrate how we have used droplet digital PCR (ddPCR) to identify discrete sequence changes, the generation of larger than expected deletions and chromosomal rearrangements. Extensive validation in this manner recognises unwanted variants at early stages of the mutagenesis process, which reduces the number of animals required for genome engineering and contributes to experimental reproducibility of the model.

*Presenter

P04 : Validation of a new rat Down syndrome model overexpressing DYRK1A: YaH-Rur6647-4497-DUP

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Down syndrome (DS) is the most common form of mental retardation and dysmorphism in humans, affecting about 1 newborn each 700 births. This syndrome results from the presence of an additional copy of chromosome 21 (Hsa21). Among the genes in Hsa21, *DYRK1A* gene (dual specificity tyrosine regulated kinase 1A) stands as one of the most studied driver candidate genes of the observed neurological phenotypes in DS. Indeed, overdose of this gene has been reported in both, DS patients and mice models overexpressing DYRK1A, where deficits in learning, memory, cognition, endocytosis and synaptic function have been observed (Duchon et al. 2016).
DYRK1A kinase has been extensively studied in DYRK1A overexpression mouse models however this model has certain limitations like their low learning and memorizing abilities. Therefore, it is necessary to use another model like the rat, which will be more appropriate for study of pathologies like DS. Compare to mice, rat is genetically closer to humans and their behavior shows closer similarities too. Indeed, rats have greater social, learning and memorization skills and the presence of conserved Hsa21 syntenic region over two chromosomes in rats compared to the syntenic region in mouse conserved in three chromosomes, makes of the rat a strong model to study intellectual disabilities syndromes. That is the reason why this project aims to validate a new rat model overexpressing DYRK1A and created using CRISPR-Ca9 system. To validate this new model, we first analysed DYRK1A expression at the molecular (RNA and protein) and biochemical (kinase activity) levels. Then, we studied the consequences of DYRK1A overexpression on a behaviour context, focusing specifically on memory and learning skills. In the future, this line will be used to test new pharmacological inhibitors of DYRK1A and could provide a better understanding of DYRK1A overexpression consequences over another resourceful pre-clinical rodent model.

*Presenter

P05 : Transcriptomic adaptation to high-fat diet of the gastro-intestinal tract in the BXD mouse genetic reference panel

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Digestion, absorption, excretion and protection are the major physiological functions of the gastro-intestinal tract (GIT). To perform its metabolic role, the GIT has evolved to have a large surface area that is in direct contact with the external environment. In this project, we decided to explore gene-by-environment interactions in the GIT by focusing on transcriptomic data collected in genetically diverse mouse BXDs, which are recombinant inbred lines derived from C57BL/6J and DBA/2J strains. These mice were fed a conventional chow diet (CD) or high-fat diet (HFD). First, we defined the conserved and global transcriptional adaptions of two different sections (ileum and colon) to HFD by using a combination of differential expression, gene set enrichment and principal component analysis. Second, we explored quantitative trait-transcript (QTT) associations, to define gene sets and metabolic phenotypes that are highly correlated. Third, expression quantitative trait locus (eQTL) analysis was performed to pinpoint genetic variants that control variation in transcript levels and could mediate regulation of metabolic traits. Altogether, this study can be used as a resource for better identifying GIT transcriptional players regulating the development of obesity and its associated comorbidities.

*Presenter

P06 : A spontaneous rhesus macaque model of heritable colorectal cancer associated with mutations in DNA Mismatch Repair (MMR) genes: An improved animal model of Lynch Syndrome in humans

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Colorectal cancer (CRC) is the third most common cancer in the US. Most CRC cases arise on a sporadic background, but Lynch Syndrome (LS) is the most common hereditary condition predisposing to CRC. LS is secondary to germline mutations in one of four DNA mismatch repair (MMR) genes: *MLH1, MSH2, MSH6* or *PMS2*. Heterozygous carriers have high life-time risk to develop cancers commonly located in the proximal colon or ileocecal valve, as well as extracolonic tumors. Since 2001, 65 cases of spontaneous CRC have been diagnosed among rhesus macaques (*Macaca mulatta*) at the Keeling Center for Comparative Medicine and Research (KCCMR). Rhesus CRC commonly presents as anemia, weight loss, diarrhea and a palpable abdominal mass. Histopathology of these tumors closely resembles human Lynch Syndrome. We previously reported 2 potential causative germline mutations identified by whole genome sequencing (WGS) 20 of the 65 total CRC cases: a premature stop codon in *MLH1* and; a missense mutation in *MSH6*, predicted to be highly deleterious (Combined Annotation-Dependent Depletion score of 22.8). Human LS exhibits microsatellite instability (MSI). Initial studies in rhesus CRC cases indicate high MSI in some but not all cases. We draw three conclusions from these data: a) approximately half of KCCMR rhesus CRC cases can be described as LS based on the damaging mutations in *MLH1* or *MSH6* and clinicopathologic presentation; b) further analyses are needed to determine if other molecular changes may underlie CRC in cases not attributable to *MLH1* or *MSH6* variants; c) because attempts to model Lynch Syndrome in rodents by disrupting MMR genes do not generate pathology that parallels human LS, this spontaneous rhesus macaque model, due to natural mutations in MMR genes and displaying nearly identical pathology, will be uniquely valuable in efforts to develop improved immune therapies and prevention strategies.

*Presenter

P07 : Collection, Identification, and Modeling of De Novo Mutations Occurring Within an 80-Pair FVB/NJ Mouse Breeding Colony.

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Approximately 20-30 million Americans are affected by Mendelian genetic disorders with broad clinical consequences. While many of these maladies run in families, and are heritable from one generation to the next, many others are not. These non-heritable diseases arise sporadically among children of healthy parents and within families with no prior history of the illness, by spontaneous *de novo* mutation. In additional to rare diseases, *de novo* mutations have been implicated in a subset of more commonly occurring neurodevelopmental diseases including autism-spectrum disorders, intellectual disability, and schizophrenia. To model the appearance of *de novo* mutation as it manifests among neonates in the human population, and to expand upon the technologies of mutation detection, we have established a standing colony of 80 breeding pairs of FVB/NJ mice producing a large and continuous population of neonatal animals.

To date (June 20, 2019) 18,750 neonates have been recorded. Of these, 276 aberrant (deceased, distressed, or dysmorphic) neonates have been euthanized and/or collected for micro-CT analysis. To date, 176 have actually been scanned.

Whole genome sequences have been obtained for 100 of these aberrant neonates along with 50 unaffected control mice. SNP and INDEL variants have been identified among the 100 aberrant neonate genomes and filtered/sorted as follows: Called variants did not appear in dbSNP, or among known FVB/NJ-specific SNPs; called variants occurred in two or fewer experimental strains; called variants did not occur among control strains; called variants were classified as having a High, Moderate, or Low predicted impact (snpEFF).

Four hundred thirty-six (436) mutational events were identified across 89 strains and 389 loci (342 unique events, 47 events occurring in two strains). Variants with the highest likelihood of causation are being modeled by conditional CRISPR knockin to create a strain/phenotyping platform of recurrent "*de novo*" mutations.

*Presenter

P08 : Targeted improvements to the first pass annotation of the mouse reference genome.

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Since 2012, the GENCODE consortium have been producing reference quality annotation of protein-coding genes, pseudogenes, long non-coding RNAs and small RNAs in Mouse to provide this foundational resource. The GENCODE consortium includes both experimental and computational biology groups who generate primary data, create bioinformatic tools and provide analysis to support annotation and automated analyses to improve and extend the GENCODE gene annotation.
GENCODE annotators have completed the initial pass of the Mouse genome which involved “walking” each BAC clone on each chromosome and annotating each gene locus in turn. The first pass annotation was released in GENCODE M21, April 2019. New data, sequencing technology and analysis methods mean that we are often able to improve the annotation at each locus in terms of accuracy, and depth in terms of identifying new splicing isoforms. The focus is now is a more targeted approach to ensure efficiency when further improving the annotation, with a view towards performing a comparative analysis between Human and Mouse in the near future. Comparison between Human and Mouse orthologs often aids annotation at both loci. The use of a sequence conservation analysis, PhyloCSF, has enabled us to rapidly identify novel as yet unannotated exons, and assess coding capacity which aids in the decision between making a protein coding, lincRNA or pseudogene annotation. Despite the many similarities the genomes of Mice and Humans are different in their gene content. Mouse has a very large repertoire of Olfactory receptor genes and many Vomeronasal receptors. We have used organ-specific RNAseq datasets to annotate these gene families in much more detail than was previously possible.
GENCODE mouse gene sets are released approximately four times a year. Ensembl/GENCODE gene annotations are accessible via the Ensembl and UCSC genome browsers, the Ensembl FTP site, Ensembl Biomart, Ensembl Perl and REST APIs and gencodegenes.org.

*Presenter

P09 : Final content, comprehensive validation, and updated report for the MiniMUGA genotyping array

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At the 32nd IMGC in 2018, we reported on the initial version of the MiniMUGA genotyping array, outlining its design goals and preliminary performance metrics. Since then, we have added 954 markers, bringing the total number of markers in the final version of the MiniMUGA array to 11,125. Of these new markers, 905 are SNPs designed to be informative for one of 41 mouse substrains. The remaining 49 markers are designed to detect 7 common genetic constructs. For validation and reference purposes we genotyped 7,605 samples: 5,769 with the initial version of the array and 1,836 with the final version of the array. Based on this data set, we 1) fined-tuned chromosomal sexing capabilities, 2) refined the detection of 17 different genetic constructs, 3) increased the number of mouse inbred strains with consensus genotype calls to 241, and 4) extensively characterized and validated 2,308 diagnostic markers for 43 mouse inbred substrains and 663 markers for 10 mouse strain groups. Finally, we have incorporated all of these improvements into an updated sample report designed to be easily interpreted by a non-specialist. Importantly, the first section of the report provides a complete descriptive summary of quality, inbreeding, chromosomal sex, genetic background, and presence of genetic constructs for each genotyped sample. The final version of MiniMUGA is now available to the public. We wish to thank the Mutant Mouse Resource and Research Centers (MMRRC) for providing many mouse samples used for development and validation.

*Presenter

P10 : Mouse Phenome Database: An integrative database and analysis suite for curated primary mouse phenotypic data

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The Mouse Phenome Database (MPD; phenome.jax.org) is a widely used resource that provides access to primary experimental data, protocols and analysis tools for mouse phenotyping studies. Data are contributed by investigators around the world and represent a broad scope of phenotyping endpoints and disease-related characteristics in naïve mice and those exposed to drugs, environmental agents or other treatments. MPD was re-engineered to facilitate interactive data exploration and quantitative analysis. We are curating data from inbred strains and other reproducible strains, including KOMP mice, Collaborative Cross (CC), CC-RIX, and founder strains. We are also collecting primary data from mapping populations, including advanced high-diversity mouse populations such as Diversity Outbred mice. We are developing a new data submission interface for data contributors so that they, as domain experts, may annotate their own data with relevant ontology terms and provide detailed information for protocols and animal environmental conditions as required by the ARRIVE guidelines. New tools and analyses are under continual development and include a polygenic traits selection tool and replicability analysis. We have also implemented a linear mixed model based GWAS analysis that culminates in the ability to perform GWAS meta-analyses based on a user selected collection of traits or by leveraging ontology terms. Global application of this strategy across the database results in many SNP-to-trait mappings supported by multiple research studies. Through collaborative and integrative efforts with other genomic data resources, such as GeneWeaver, SNP results from a meta-analysis can be leveraged for cross-species analysis, allowing users to identify mouse traits or experimental assays most relevant for studying human disease. Furthermore, it will provide a means for users to compare mouse regulatory mechanisms associated with phenotypes in MPD and empirical human datasets present in GeneWeaver.

*Presenter

P11 : GeneWeaver: an online platform for cross-species analysis and heterogeneous data integration.

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Systems genetics has been an effective strategy for gene discovery and for finding the relations among traits and their mechanisms in genetic reference populations. Integrative functional genomics combines data from diverse experimental paradigms to find the common and distinct biological mechanisms of biological traits within and across species. As these methods have evolved, so too have the software systems that support interactive user initiated analyses. Flexible tools have made rapid interrogation of integrative genetic and genomic data resources possible. GeneWeaver is a database and a suite of tools for integrative functional genomic analysis. GeneWeaver allows users to integrate heterogeneous functional genomics data in an interactive manner. The repository contains over 150,000 gene sets consisting of over 80,000 genes from ten species derived largely from empirical functional genomics studies such as gene expression microarrays, RNA-sequencing experiments, QTL mapping and GWAS. In addition GeneWeaver contains data aggregated from public resources such as ontological annotations by term from GO, Disease Ontology and Mammalian Phenotype Ontology (MP); pathway databases [e.g. Kyoto Encyclopedia of Genes and Genomes (KEGG) and Pathway Commons (PC)]; and curated repositories (e.g. Comparative Toxicogenomics Database and Molecular Signature Database). These sets of genes together with user provided datasets, can be analyzed with the built-in tools, such as Hierarchical similarity Graph tool, Jaccard Similarity and MSET. GeneWeaver was recently redesigned and now includes an advanced curation interface, and access using an API. Recently published applications of GeneWeaver applied to research fields ranging from aging, cutaneous biology, pain and addiction demonstrate the utility and flexibility of this resource. NIDA DA P50 039841 Research Center of Excellence for Systems Neurogenetics of Addiction (EJC); NIAAA R01 AA 018776 Data structures algorithms and tools for ontological discovery(EJC);

*Presenter

P12 : Cytometer: Computerised segmentation of white adipocytes in full size H&E histology images using convolutional neural networksâ€‹.

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Changes in adipocyte size distribution and number in white adipose tissue (WAT) affect fat storage in subcutaneous and visceral depots of the body, altering the risk of coronary artery disease, hypercholesterolemia and type 2 diabetes. Assessing small subpopulations can indicate an early onset of disease and provide a richer picture than overall statistics, but it also requires large numbers of cells for statistical significance. Manual segmentation is unfeasible, and automatic segmentation needs to tackle the large size of histology images (over 80,000 x 40,000 pixels); discriminate WAT from other types of tissue; white adipocytes presenting as a thin membrane surrounding an empty untextured area; torn membranes and other histology artifacts; and cell overlap.

We propose a deep learning pipeline for white adipocyte segmentation from full resolution H&E histology images, trained and validated on a hand traced dataset of 2,074 mouse cells that we produced for this work. The pipeline features convolutional neural networks (CNNs) to first estimate membrane detection using a distance transformation as a learned intermediate data representation. Second, morphological operators are used to produce an initial segmentation. Third, a CNN classifies each segmentation as WAT or otherwise, and finally, another CNN corrects the segmentation to account for cell overlaps. In addition, we propose a windowing algorithm to process full size images in small, adaptively overlapping tiles.

We also propose statistical methods to compare cell area populations rather than just median cell values, as this can provide size-dependent insights, e.g. increase in the number of small precursor cells.

Finally, we save our segmentation results for display on the DeepZoom platform AIDA, which enables comfortable navigation of large histology images in a regular web browser, and manual correction of the segmentations.

*Presenter

P13 : Effect of various H19/Igf2 imprinting dysregulation on mouse embryonic development

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In mammals, a small number of genes are expressed in a parent-of-origin-specific manner. Aberrant expression of these genes is associated with human imprinting disorders such as Beckwith-Wiedemann syndrome (BWS) and Silver-Russell syndrome (SRS). Cis-regulatory elements, called imprinting control regions (ICRs), mediate this allele-specific gene regulation. The *H19/Insulin-like growth factor 2 (Igf2)* ICR [**IC1**] interacts with the zinc-finger protein CTCF. CTCF binds to unmethylated maternal IC1 and acts as an insulator to block shared enhancers from interacting with the *Igf2* promoter, allowing the enhancers to interact with the *H19* promoter. Paternal IC1 is DNA methylated, preventing binding of CTCF and letting the enhancers interact with the *Igf2* promoter. In human, various mutations of IC1 have been reported to be associated with BWS and SRS cases.

Although the mechanism of *H19/Igf2* imprinting is conserved in mouse and human, mouse IC1 (mIC1) differs from human IC1 (hIC1) in several aspects. This complicates studying human genetic mutations of IC1 using mouse models. To better model human BWS/SRS mutations in mouse, we have generated a mouse model with hIC1 replacing the endogenous mIC1 [**H19hIC1**]. The paternal transmission of hIC1 resulted in loss of DNA methylation which led to increased *H19* expression and ablated *Igf2* expression, and perinatal lethality and decreased embryonic weights. To examine if increased *H19* expression is responsible for this lethality, we have generated *H19* null mice [**H19ΔH19**]. Lethality and decreased weight were not rescued in H19ΔH19/hIC1 mice. Although the previously increased *H19* expression was mostly reduced, the *Igf2* expression remained very low in H19ΔH19/hIC1 embryos. To test if low *Igf2* expression is causing the lethality, we used another mouse model with IC1 deletion [**H19Δ3.8**]. Surprisingly, H19Δ3.8/hIC1 neonates were rescued from lethality and decreased weight. *Igf2* and *H19* expression was comparable between H19Δ3.8/hIC1 neonates and their wild-type littermates depending on tissues.

*Presenter

P14 : Development and characterisation of pain-related sodium channel CRISPR-Cas mouse model for Scn10aG1662S

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Neuropathic pain is defined as pain arising as a consequence of a lesion or disease affecting the somatosensory system and it affects 5% of the general population and 40% of patients with neurological diseases. Treatments are inadequate with less than 50% of patients achieving 50% of pain relief at best. Neuropathic pain is characterized by the presence of allodynia and hyperalgesia and can be provoked in animal models. The voltage-gated sodium channel Nav1.8 is known to function in the transmission of pain signals induced by cold, heat, and mechanical stimuli. Previous studies have identified an allele of Scn10a encoding the α-subunit of Nav1.8. The purpose of this current study is the creation and characterisation of the first Knock-In mouse model that recapitulates gain-of-function mutation in Nav1.8 sodium channel (Gly1662Ser). This mutation was found in patients suffering from painful neuropathy. The mouse models are created using CRISPR-Cas technology, introducing the endonuclease Cas9, double guide RNA and a specific oligonucleotide sequence that bear the mutation. The KI mice will be analysed for pain sensitivity and behaviour. The results of this analysis can be used to really assess the relation between gain or loss of function in the Nav1.8 and the nociceptive abilities. The findings may be useful in treating medical conditions related to neuropathic pain.

*Presenter

P15 : Development and refinement of a high throughput pipeline for the generation of KO mice by CRISPR/Cas9 genome editing

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The development of CRISPR/Cas9 tools has revolutionised the genome editing field, allowing for the generation of genetically modified mice with increased ease and efficiency. Through our evolving processes, we provide a genome engineering service with the ability to produce and validate a variety of different KO and KI models. This has led to the development of a high throughput pipeline for the efficient generation of KO mice which supports the generation of over 100 KO projects a year as part of the IMPC effort. This has been achieved through reviewing and optimising all steps of the production line. We have transitioned from pronuclear injections, through cytoplasmic injections to electroporation of CRISPR reagents, which has simplified and sped up the delivery of these reagents into 1-cell embryos. Our validation procedures have been improved with the combination of Digital Droplet PCR and traditional Sanger sequencing of the target locus to provide a dual confirmation of the KO, as well as checking for random integration(s) of the excised fragment. This has been of significance as we have demonstrated the introduction of much larger deletions than were expected, likely due to MMEJ.

*Presenter

P16 : Assessment of dietary effects on lead accumulation in a population-based mouse model

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Blood lead (Pb) levels (BLLs) have been declining in the US for decades. Nonetheless, lead exposure is an ongoing public health issue. Lead poisoning impacts many developmental and biological processes, most notably intelligence, behavior, and overall life achievement.Whether through contaminated water, lead-based paint, or a combination of sources, the main source of lead exposure is through the diet. Some dietary nutrients, such as iron and calcium, can interfere with the intestinal absorption of lead. Moreover, there is a considerable variation in the susceptibility to harmful effects of lead exposure in the general population. The variety of different outcomes may be due to both nutritional and genetic factors. To specifically address the influence of both genetic background and nutrition on lead accumulation, we are utilizing the Collaborative Cross (CC), a mouse reference population which allows modeling of the genetic diversity found in human populations. To this purpose, adult CC females from different CC lines receive either mouse chow or American diet – a dietary pattern characterized by high intake of sugar and fat – and lead (0.1%) through drinking water *ad libitum*. CC lines show significant variation in BLLs depending on genetic background, diet, and genetic background-by-diet interactions. We are also assessing differences in lead distribution patterns and in the microbiome across exposed strains. Using this model, we aim to elucidate mechanisms by which genetics and diet contribute to lead accumulation and provide prevention strategies and dietary interventions to reduce adverse effects of lead exposure.

*Presenter

P17 TS-14 : Weird gene in a weird mammal: A highly divergent pancreatic duodenal homeobox 1 (Pdx1) gene in the fat sand rat

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Strong GC skew in a local genomic region results in conflict between increasing GC levels and potential alteration of conserved amino acids. In most cases, natural selection will purge any deleterious alleles that arise. However, in the gerbil subfamily of rodents, several conserved genes serving key functions have undergone radical alteration in association with strong GC skew. We present an extreme example concerning the highly conserved homeobox gene *Pdx1*, a key gene in initiation of pancreatic organogenesis in embryonic development. In the fat sand rat *Psammomys obesus* and close relatives, we observe a highly divergent *Pdx1* gene associated with high GC content. In this study, we investigate the antagonistic interplay between very rare amino acid changes driven by GC skew and the force of natural selection. Using ectopic protein expression in cell culture, pulse-chase labelling, *in vitro* mutagenesis and drug treatment, we compare properties of mouse and sand rat PDX1 proteins. We find that amino acid changes driven by GC skew resulted in altered protein stability, with a significantly longer protein half-life for sand rat PDX1. We show that both sand rat and mouse PDX1 are degraded through the ubiquitin proteasome pathway. However, *in vitro*mutagenesis reveals that GC skew has caused loss of a key ubiquitination site conserved through vertebrate evolution, and we suggest that sand rat PDX1 may have evolved a new ubiquitination site to compensate. Our results give molecular insight into the conflict between natural selection and genetic changes driven by strong GC skew.

*Presenter

P18 : Somatic mutation and epilepsy: a mouse model.

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The role of post-zygotic somatic mutation in the etiology of seizure disorders is not well characterized. The significant increase in incidence of epilepsy above the age of 70 years could be related to the increase in somatic mutation with age. We are studying a mouse model that permits quantitation of expression of one specific epileptogenic somatic mutation in adult mice, and comparison of expression level with occurrence of seizures. In the conditional mouse, expression of the *SCN8A* encephalopathy patient mutation p.Arg1872Trp (R1872W) is activated by Cre recombinase (Bunton-Stasyshyn et al, BRAIN 2019). This mutation impairs closing of the sodium channel Nav1.6, resulting in neurological hyperexcitability. Heterozygous adult mice carrying the conditional allele and the CAG-CRE-ER transgene (JAX 004682) were treated with varying doses of tamoxifen. Activation of the R1872W mutant allele was quantitated by RT-PCR of exon 26 from whole brain RNA followed by targeted deep sequencing on the Illumina MiSeq sequencer. With the highest dose of tamoxifen, approximately 80% activation of the mutant allele was obtained. All of the mice treated with the highest dose exhibited spontaneous seizures, beginning between two and five weeks after tamoxifen. The activation of the mutant allele was directly proportional to tamoxifen dose, and varied from 2% to 80% in our study. At the lower levels of activation of the mutant allele, spontaneous seizures were not observed, indicating that there is a high threshold for epileptogenesis. Experiments are in progress to determine whether the lower levels of mutant expression lead to increased susceptibility to seizure induction. The absence of spontaneous mutations in mice with a significant load of mutant sodium channels suggests that there may be a high threshold for seizure induction. (Supported by NIH R01 NS34509).

*Presenter

P19 : Optimizing PCR for mouse genotyping: recommendations for reliable, rapid, cost effective and high-throughput genotyping protocol for any mutation

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Genotyping consists of searching for a DNA sequence variation localized at a well-defined locus in the genome. It is an essential step in animal research as it allows to identify animals that will be bred to generate and maintain a colony, euthanized to control the available space in the animal facility or used in experiment protocols.Because of its high sensitivity and its low tolerance to inhibitors, PCR is subject to frequent false positive, i.e. amplification of a contaminant, misidentification of the animals during tissue sampling or downstream treatments and false negative, i.e. no amplification, results. PCR can also fail to correctly amplify some templates like GC-rich sequences or secondary structures. Although genotyping is routinely performed in research laboratories, the establishment of reliable, rapid and cost effective genotyping protocols for every mutation is generally low on the list of priorities of scientific researchers. Inconclusive genotyping can thus result in irreproducible results and losing or contaminating a mouse line. In our institute, 7 to 12% of animals genotyped per year were re-sampled and analyzed a second time. We found that 5 % result in a different genotype.
Based on our expertise in high throughput genotyping (60,000 animals per year for hundreds of different genetic markers or gene mutations), we describe here some recommendations for fast, sensitive, easy and cost-effective PCR genotyping to characterized the genotype of mice. The large amount of data generated in recent years has enabled us to discuss optimization of parameters to improve reliability of each assay and propose recommendations for reproducibility and reduction of inconclusive genotyping occurrences.

*Presenter

P20 : The Study of the Neuroepigenetic Regulation of Imprinted Gene Grb10

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Imprinted genes are a subset of mammalian genes that are exclusively expressed from either the maternal or paternal chromosome. Dysregulation of imprinted gene expression is associated with various human disorders, including the stunted growth disorder Silver-Russell syndrome (**SRS**). This disorder is associated with the abnormal inheritance of two maternal copies or alleles of the imprinted gene Growth Factor Receptor Bound Protein-10 (**GRB10**). Although most somatic cells express *GRB10* exclusively from the maternal allele, alternative promoters on the paternal allele drive *GRB10* expression only in neurons. However, the regulatory elements that coordinate this remarkable epigenetic "switch" of *GRB10* expression in development are unknown. This proposal will test the requirement of (1) allele-specific DNA methylation sequences and (2) zinc-finger protein **CTCF** binding in normal neuronal *GRB10* expression using relevant mouse models and CRISPR-edited neurons. By analyzing these epigenetic elements in a neuronal differentiation system and *in vivo*, we are the first to demonstrate how *GRB10* is epigenetically regulated. These findings will elucidate the mechanisms for allele and tissue-specific gene expression in the brain. Our results may also provide insight into the molecular basis of SRS, which could prompt epigenetic etiology screening and therapeutic options.

*Presenter

P21 : Assessing the effects of mixed-oral bacteria on the severity of type 2 diabetes using the collaborative cross mouse model

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Background: Heritability plays a central role in the pathogenesis of Type 2 diabetes (T2D) and infectious diseases. Our studies demonstrated utilization of genetically highly diverse inbred lines of mice, namely Collaborative Cross (CC), for dissecting host susceptibility for development of T2D and periodontitis, showing significant variations following high-fat (42% fat) diet (HFD).
Aims: Assess the effects of oral-mixed infection on development and severity of diet-induced T2D using the CC lines.
Materials & Methods: 221 mice of 10 CC lines (both sexes) challenged for 12 weeks HFD or Standard diet since the age of 8 wks. old. At week 5, mice were infected with *Porphyromonas gingivalis (Pg)* and *F. nucleatum (Fn)* strain. Biweekly body weight (BW) recorded; glucose tolerance ability assessed 3-time point during the experiment.
Results & conclusions: Males were more susceptible to HFD than females, showing the higher area under the curve (AUC) for the glucose tolerance test, 60057 (±3992.57) min*mg/dL for males versus 41672 (±1722.50) min*mg/dL. HFD induced impaired glucose tolerance more than standard diet for both sexes without infection. Interestingly, in some CC lines, the combination of HFD with infection have worsen the impairment of glucose tolerance to greater levels in both males (60057 vs. 50972 min*mg/dL) and females (41672 vs. 37282 min*mg/dL). Altogether, our results demonstrate a high contribution of heritability to host response towards infection cross diet cross-sex interactions.

*Presenter

P22 TS-09 : The a4a- and b1-tubulin isotypes work together to sustain efficient platelet biogenesis and hemostasis

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Blood platelets are small non-nucleated cells whose functions are to stop hemorrhages (hemostasis). They are produced by bone marrow megakaryocytes after a profound cytoskeletal reorganization that culminates in the formation of a circular sub-membranous microtubule array known as the platelet marginal band. This unique structure shows no other equivalent in mammals and is thought to arise from a cell-specific combination of a- and b-tubulin isotypes. Previous studies in mice and humans established a central role for b1-tubulin, whose disruption hinders marginal band formation and leads to abnormally large platelets and reduced blood platelet counts (macrothrombocytopenia). Recently, we reported a mouse model carrying a point mutation in a4a-tubulin that phenocopied the defects seen in *Tubb1-/-* mice. Together, these results suggested that a4a- and b1-tubulin were equally important for platelet biogenesis and led us to generate a4a/b1 double knockout mice (DKO). These mice exhibit worsened macrothrombocytopenia in comparison to *Tubb1-/-* and even more so when compared to *Tuba4a-/-* mice, which unexpectedly display near normal platelet parameters. Additionally, profound ultrastructural defects were found in DKO platelets, which were spherical instead of discoid and were devoid of their marginal band. This was accompanied by an impaired megakaryocyte maturation process. Strikingly, DKO mice display a profound bleeding diathesis in contrast to single KO and WT mice. This bleeding disorder could not be explained by defective platelet activation in response to a series of agonists. Follow-up work will evaluate these mice in *in vitro* and *in vivo* models of thrombosis and explore the mechanisms responsible for abnormal marginal band formation at the biochemical and cellular levels. The expected outcome is an improved understanding of the role of microtubules in platelet formation and functions with possible applications to produce platelets in culture.

*Presenter

P23- TS-06 : Strong Epistasis in Genetics of Leishmaniasis - Search for Genes and Mechanisms

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Leishmaniasis, a disease caused by *Leishmania* parasites, ranks as the leading neglected tropical disease in terms of morbidity and mortality. It infects 1 million people in 98 countries causing 30000 deaths annually. Human leishmaniasis exhibits a great diversity of manifestations. Genotype of the infected organism is an important factor that influences susceptibility to and manifestations of this disease. To study human disease using mouse models, several strains are required, which could collectively exhibit different manifestations of human disease. Therefore, we tested strains O20 and B10.O20 as new models of leishmaniasis. B10.O20 originated from resistant strains C57BL/10 (B10) and O20 and it is surprisingly susceptible to *Leishmania major,* exhibiting large skin lesion, high parasite numbers in skin and lymph nodes. Susceptibility to *L. major* was observed only in certain combinations of B10 and O20 genes. Out of 16 recombinant congenic OcB strains that carry different random sets of 12.5 or 6.25 % of B10 genes on the genetic background of O20, only OcB-11 and OcB-31 carried susceptibility-conferring gene combinations. Mapping in F2 hybrids between OcB-31 (or its substrain OcB-43) and O20 revealed five susceptibility loci on chromosomes 2, 3, 5, 9 and 15 that influence development of skin lesions, serum IgE level, and parasite numbers in liver and spleen. Analysis of these loci for polymorphisms between O20 and C57BL/10 that change RNA stability and genes' functions led to detection of 20 potential candidate genes, three out of them are differentially expressed in either spleen and/or skin of mice and correlate with high parasite load in spleen and large lesions. These genes along with the other detected potential candidate genes will be focus of future studies not only in mice but also in humans.
Support: 14-30186S, GACR 16-22346S, and 13-41002P

*Presenter

P24 : Identifying the Genomic Switch for Cell Type-Specific B4galnt2 Expression in Mice

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Von Willebrand factor (VWF) is a circulating multimeric glycoprotein that plays a prominent role in hemostasis by binding to and activating platelets and also serving as a plasma carrier molecule for factor VIII (the hemophilia A gene). Quantitative and qualitative defects in VWF can be due to mutations in the *Vwf* gene or modifications of VWF. VWF deficiency causes the most common inherited bleeding disorder in humans, von Willebrand disease (VWD). Type 1 VWD is characterized by a quantitative reduction of plasma von Willebrand factor (VWF) to 10-45% its normal circulating levels. Circulating human VWF levels are sensitive to modification by glycosyltransferases such as ABO. VWD is also common in mice. Using inbred mice, we mapped the cause of mouse VWD to a 42 kilobase (kb) cis-regulatory locus of the beta-1,4-N-acetyl-galactosaminyltransferase 2(*B4galnt2)* gene on Chromosome 11, called *Mvwf1*. This region controls *B4galnt2* expression, switching it from intestinal epithelium to endothelial expression in at least 13 inbred mouse strains with VWD. Endothelial *B4galnt2* post-translationally modifies VWF, resulting in its clearance from the plasma. We sought to precisely map the genomic switch for *B4galnt2* expression within the *Mvwf1* locus. The wild-derived LEWES/EiJ mouse strain has endothelial specific *B4galnt2* expression, while the C57BL/6J (B6) strain has intestinal epithelial expression. Comparative Sanger sequencing analysis of the *Mvwf1* locus in B6 and LEWES/EiJ uncovered 560 single nucleotide polymorphisms and 505 indels, resulting in 2.5% sequence divergence. We next used a deep convolutional neural network approach to analyze the *Mvwf1* region in both strains in order to identify a sub-region most likely responsible for the expression switch. This sub-region lies 1.2kb from the *B4galnt2* transcription start site. In future studies we will perform CRISPR/Cas9 genome editing to evaluate the accuracy of the model and confirm the polymorphisms responsible for the switch in *B4galnt2* expression.

*Presenter

P25- TS-12 : Identification of novel neuroprotective loci modulating ischemic stroke volume in a cross between wild-derived inbred mouse strains

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To identify genetic factors involved in cerebral infarction we have attempted a forward genetic approach using quantitative trait locus (QTL) mapping for cerebral infarct volume after middle cerebral artery occlusion, all using common inbred mouse strains. Although in general cerebral infarct volume is inversely correlated with collateral anatomy, we identified several loci that modulate ischemic stroke in a collateral-independent manner. To overcome the limited genetic diversity among classical inbred strains, we have expanded the pool of allelic variation by a survey of the parental mouse strains of the Collaborative Cross that include 3 wild-derived strains. We found that one of wild-derived strains, WSB/EiJ breaks general rule that collateral vessel density inversely correlates with infarct volume. This strain and another wild-derived strain, CAST/EiJ, show the highest collateral vessel densities of any inbred strain we have tested, but infarct volume of WSB is 8.7-fold larger than CAST/EiJ. QTL mapping between these two strains identified 4 new neuroprotective loci modulating cerebral infarct volume while not affecting vascular phenotypes. To identify causative variants in genes mapping within the loci, we surveyed non-synonymous coding SNPs between WSB and CAST and then, using 3 different *in silico* algorithms, predicted the functional consequences of the amino acid substitutions that left 96 genes mapping in one of the four intervals. In addition, we performed RNA sequencing to determine strain-specific gene expression differences in brain tissue between WSB and CAST and identified 220 candidate genes mapping within the loci. Interestingly, combining genes harboring predicted damaging coding SNPs with genes showing at least 2-fold expression difference coding genes in the four intervals left only 15 genes. The identification of the genes underlying these neuroprotective loci will provide new understanding of genetic risk factors of ischemic stroke which may provide novel targets for therapeutic intervention of human ischemic stroke.

*Presenter

P26- TS-04 : MicroRNA as regulators of 1,3-butadiene-induced strain- and tissue-specific effects in mice.

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1,3-Butadiene is a known rodent and human carcinogen that is both an occupational and environmental health hazard. Genotoxicity is an established mechanism of 1,3-butadiene carcinogenicity; however, it does not explain the tissue-specific tumor development observed in mice. Our previous work demonstrated strain- and tissue-specific alterations in epigenetic effects in response to 1,3-butadiene exposure which may contribute to tissue-specific toxicity. MicroRNA (miRNA) represent another epigenetic mechanism for regulating gene expression and have been implicated in carcinogenesis. In this study we tested the hypothesis that miRNA regulate strain- and tissue-dependent transcriptional and epigenetic responses to 1,3-butadiene exposure in CAST/EiJ and C57BL/6J mice. These mice were exposed to 0 or 625 ppm 1,3-butadiene (6 hr/day, 5 days/week) for 2 weeks. We evaluated changes in mRNA and miRNA expression by sequencing the lung, liver, and kidney tissues. We observed strain- and tissue-specific mRNA and miRNA expression profiles in response to 1,3-butadiene exposure. The miRhub algorithm was used to investigate miRNA as regulators of 1,3-butadiene-induced mRNA expression. We identified 9 miRNA as significant candidates across tissues and strains. In the lung of 1,3-butadiene-exposed C57BL/6J mice, mir-142-5p was significantly decreased and predicted to target significantly upregulated genes involved in chromatin remodeling such as *KDM1B* which is a lysine demethylase for H3K4, a marker of transcription. In addition, mir-142-5p was predicted to bind genes involved in DNA damage repair such as *CtIP*. The results of this study indicate that miRNA may mediate strain- and tissue-dependent variability of 1,3-butadiene-induced epigenetic effects and potentially greater tissue susceptibility to carcinogenesis.

*Presenter

P27 : Characterization of the CHMP2Bintron5 Knock-in mice: a new model of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD)

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Amyotrophic Lateral Sclerosis (ALS) is as a fatal progressive and idiopathic neurodegenerative Motor Neuron Disease (MND). As a MND, ALS affects mainly motor neurons in the cortex, brainstem and spinal cord, leading to denervation of neuromuscular junctions and paralysis. The incidence of ALS is around 2-3 per 100 000 person-years. Among them, 15% of ALS patients develop Frontotemporal Dementia (FTD) another neurodegenerative disease. Faintly higher than ALS, the incidence of FTD is 3-4/100 000 person-year. Characterized by defects of cognitive ability FTD is the second commonest form of pre-senile dementia after Alzheimer's disease. Interestingly, 15% of FTD patients are also diagnosed for ALS.
Charged Multivesicular Body Protein 2B (CHMP2B) is the first gene reported linked to both ALS and FTD. To better understand the mechanisms leading to these diseases and mimic patient's situation we have developed a new mouse model with a knock-in of the CHMP2BI5 , a missens mutation of *CHMP2B* found in patients. The objective of the study is to determine whether the presence of a single copy of the mutation is sufficient to drive ALS and/or FTD symptoms.
To answer this question, we characterized this new transgenic line with complementary approaches including behavioral, functional, biochemical and histological analyses. The preliminary results obtained indicated that our animal model did develop some symptoms related to ALS, FTD or both of them.

*Presenter

P28 : Exploring genes, phenotypes and pathways across the 3D genome

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The 3D structure of the genome is thought to be important in gene regulation as distal regulatory elements affect target genes by making direct physical contact with them via chromatin looping. Recently chromosome conformation capture techniques have identified areas of the genome with a high degree of self-interaction/looping, these regions are called topologically associating domains (TADs). TADs co-localise regulatory elements, such as enhancers with target genes whilst also insulating regulatory elements from non-target genes. They fall within large chromatin compartments which vary extensively between tissues with large areas of the genome switching between the active and inactive compartments. It is thought that single or series of TADs constitute the unit of compartment switching leading to speculation that genes within the same TAD may be phenotypically or functionally linked. However, a comprehensive comparison of the phenotypes, disease associations and pathways of genes within the same TADs has not yet been undertaken. In this work I investigate possible links between TADs and phenotypes and further investigate the function of the 3D genome, using publicly available mouse Hi-C datasets from ESC, liver, and cardiacmyocytes. TADs are called in these datasets using two detection algorithms and functional analysis conducted using GO semantic similarity. Moreover, I have started to develop an analysis framework to detect significant associations between TAD distribution, gene content and functional characteristics genome wide.
The results indicate that most TADs contain few genes and there is no correlation between the size of the TAD and the number of genes it contains. There is a trend for a larger proportion of pairs of genes within the same TAD to have highly similar functional annotations compared to pairs of genes within random TADs. These results together with future analysis will seek to formally establish if there is a link between TADs and phenotypes.

*Presenter

P29 : Comparative transcriptomic analysis of three different mouse models of cystic kidney disease

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Cystic kidney diseases (CKD) encompass heterogeneous disorders causing end stage renal disease affecting children and adults. CKD show a broad range of clinical variability but the underlying molecular mechanisms leading to this phenotypic range are poorly understood. It has been suggested that cystogenic processes share partially overlapping pathological mechanisms because CKD-associated proteins co-localize at the primary cilium, which is thought to play a central pathogenic role. With our study, we aim to elucidate the transcriptional changes preceding and accompanying cyst growth.

This study compares three mouse models of CKD: The autosomal dominant polycystic kidney disease (ADPKD) model C57BL/6J-*Pkd1*$^{tm1.1Pcha}$ and the nephronophthisis (NPH) models FVB/NJ-*Invs*^{inv} and C57BL/6J-*Nek8*^{jck}. The timepoints of analysis are matched for the stage of disease, including a timepoint preceding cyst development. The kidneys were collected at P10, P20, and P30 for C57BL/6J-*Pkd1*$^{tm1.1Pcha}$, at P0 and P7 for FVB/NJ-*Invs*^{inv}, and at P5, P10, and P15 for C57BL/6J-*Nek8*^{jck} and homogenized in Trizol. Total RNA was prepared, and samples were sent for mRNA sequencing. Additionally, we snap-froze kidneys in liquid nitrogen for nuclei preparation and single-cell RNA sequencing (in progress).

mRNA sequencing revealed differential gene expression for FVB/NJ-*Invs*^{inv} and later stage C57BL/6J-*Pkd1*$^{tm1.1Pcha}$ mice; these were comparable between the two models, including gene sets previously known to be affected in CKD. However, the analysis of the C57BL/6J-*Nek8*^{jck} and early stage C57BL/6J-*Pkd1*$^{tm1.1Pcha}$ RNA data showed few differentially expressed genes. This finding emphasizes the necessity of utilizing single-cell RNA sequencing to detect the signal in specific pre-cystic cell lineages within an otherwise essentially normal whole kidney.

By comparing transcriptional changes at the single-cell level over the course of cystogenesis in three different genetic models, we aim to provide new insights into potential cyst causing mechanisms, which may facilitate the establishment of curative treatment for the severe disorders of CKD.

*Presenter

P30 : Homepage of RIKEN BioResource Research Center

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1 - RIKEN BioResource Research Center (Japan)

The RIKEN BioResource Research Center (BRC) is a global not-for-profit bioresource center providing biological materials (experimental mice, Arabidopsis thaliana as a laboratory plant, cell culture lines derived from humans and animals, microorganisms, and associated genetic materials), technical services, and educational programs to private enterprises and academic organizations.
Development of the data dissemination and sharing infrastructures for meta-information of bioresources including mouse strains is one of the significant issues for research resource centers. In 2018, RIKEN BRC have launched the Integrated Bioresource Information Division committing to offer bioresource-related information worldwide for promotions of research and development that facilitates the use and application of bioresources. The Integrated Bioresource Information Division has three missions: 1) Development of homepage contents which plays crucial roles to promote uses of bioresource, by carrying resource catalog, window of the collection and distribution of resources as well as advertisement of resources to potential users. 2) Promotion of the data integration and standardization. Data integration of bioresource data with meta-information such as use cases and quality of bioresources also is significant issue for facilitation of application of bioresources. Especially, phenotype data is important for researchers to choose appropriate experimental materials for their studies. Data standardization is also important for wider dissemination of bioresource data across databases and linking bioresource data with related data such as genome, human health and environments. 3) Big data analysis to discover novel biological functions or principles of life systems applying large-scale data analysis technologies with mathematical analysis.
Mouse strain is one of major resources in RIKEN BRC, which plays crucial roles for biomedical researches. In this poster, we introduce RIKEN BRC's website (https://brc.riken.jp) focusing how to access mouse strain related information.

*Presenter

P31- TS-08 : Modeling spontaneous systemic autoimmunity using the Collaborative Cross mouse

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Human autoimmunity is a complex disease associated with significant genetic heterogeneity. While inbred mouse strains have proven vital for autoimmune disease research, their limited genetic derivation captures only a small portion of the mouse genomic repertoire. Genetic diversity in mice could potentially be substantially expanded by using the large panel of multi-parental recombinant inbred (RI) Collaborative Cross (CC) mice. The CC panel encompasses over 90% of the genetic diversity of the mouse and is the only mammalian resource with genome-wide genetic variation randomized across a large, heterogeneous and reproducible population. Systemic autoimmunity has not been formally described in any CC RI strain, however, a strikingly high percentage of naive Diversity Outbred mice, a genetically heterogeneous stock derived from the same eight CC founder strains, develop spontaneous autoantibodies and a significant percentage are susceptible to silica-induced systemic autoimmunity. Using the CC RI panel as a model to study the range of phenotypes in a complex disease such as systemic autoimmunity, we measured levels of autoantibodies in serum from 35 CC RI strains. We found serum anti-nuclear antibodies (ANAs), a hallmark of systemic autoimmunity, in 11 of the 35 CC RI strains (31%), although only 5 strains (14%) had 50% or more mice that were positive. Interestingly, ANA patterns were similar to those found in humans. Using R/qtl2 and Mega Mouse Universal Genotyping Array SNP information on the CC strains, we mapped a suggestive QTL for ANA positivity to chromosome 4 whose locus overlaps with the proximal end of loci found for idiopathic systemic autoimmune models. These observations support the utility of the CC strains to model complex heterogeneous autoimmune diseases and uncover potentially novel genetic loci linked to autoimmunity.

*Presenter

P32 : More Informative Nomenclature for Protein Domain-Containing Gene Models

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Mouse Genome Informatics (MGI, www.informatics.jax.org) is the authoritative source for official nomenclature for the mouse. The Mouse Genome Nomenclature Committee (MGNC) works with other nomenclature committees and model organism databases, (especially the HUGO Human Gene Nomenclature Committee (HGNC) and the Rat Genome Database (RGD)), subject matter experts, and interested scientists to develop nomenclature in accordance with our guidelines. The guidelines (www.informatics.jax.org/mgihome/nomen/index.shtml) for mouse gene symbols require that each symbol be unique and, ideally, informative.

Gene models, a specific subset of named genetic features, are computationally predicted genes imported to MGI from NCBI and Ensembl. MGI imports the models and gives them unique symbols (such as *Gm50139* and *0610040J01Rik*) which are disseminated to other databases. The models can be protein coding, various types of non-coding RNAs, or pseudogenes. The current project aims to provide more informative symbols to gene models that contain UniProt protein domains. We searched MGI for gene models with symbols including “Gm” or “rik” that possess Consensus CDS (CCDS) IDs and UniProt IDs. This search returned 622 unique genes with 611 UniProt domains.

This poster describes the process used to identify candidate protein domain-containing models for renaming, the different domains they contain and the process for renaming the models. For example, *5830473C10Rik* was changed to *Albfm1*, albumin superfamily member 1, because it contains an ALB/AFP/VDB domain. Blast and Blat were used to check for orthologous human genes but none were found in this case. When human orthologs are found, HGNC is consulted so nomenclature can be assigned in parallel.

*Presenter

P33 : The touch screen system, interesting potentials for evaluation of cognitive abilities

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The touch screen system constitute an increasingly popular method of assessing cognitive functions in rodents. This system has a high translational potential considering its similarity to human CANTAB tests (Cambridge Neuropsychological Test Automated Battery). It has also the advantage to be low stress while using appetitive motivation and requires minimal experimenter involvement. Different protocols can be used for evaluation of various neuropsychological constructs, including attentional processes, different aspects of learning and memory abilities, or cognitive flexibility, altered in several psychiatric and neurodegenerative diseases (e.g., Alzheimer's disease, schizophrenia, Huntington's disease, frontotemporal dementia).
We have established two cognition evaluating protocols and analyzed the performance of C57BL/6J and C57BL/6N strains, known to show genetic variation and different behavioral traits. We'll describe results of this study as well as advantages and drawbacks of this technology.

*Presenter

P34 : Studying of genetic susceptibility of intestinal cancer developments in response to high-fat diet induced obesity and type 2 diabetes in the collaborative cross mouse

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Background: Colorectal cancer (CRC) incidence is affected by risk factors including obesity, unhealthy diet, and smoking. Conclusive evidence have proven that we can reduce the colorectal cancer (CRC) mortality through detection and treatment of early-stage CRCs and the identification and removal of polyps**.** High fat diet (HFD) plays part in the disease risk for both type 2 diabetes (T2D) and intestinal cancer through biological mechanisms including inflammation**.** For studying systems genetics of the CRC development influenced by HFD and T2D, we use the next generation of mouse genetic reference population, the collaborative cross (CC), which is a large panel of recombinant inbred strains.
Aims:We aim to study genetic factors underline intestinal cancer development associated with diabetes and obesity in response to a high-fat diet, on the same host genetic background.

Materials & Methods: A cohort of mice of different CC mouse lines were maintained on 42% HFD for 12 weeks period. Body weight was be determined bi-weekly and body response to glucose load by a 3 hours glucose tolerance test (GTT) at weeks zero, 5 and 12 during the experiment. After three months, we terminated the mice and extracted the small intestines and colon for assessing Polyp counts, as an indicator for intestinal cancer development susceptibility**.**
Results & conclusions: Our initial results have indicated that there is a variation in polyps' number, with variation spectrum between 3 and 12 total polyps. There is also a significant correlation between T2D, obesity and intestinal cancer development. The current data in combination with the future expected data promise to provide a significant resource for conducting gene mapping and elucidate the nature of the genes involved in resistance and rate of development of Intestinal Cancer and T2D induced by high fat and obesity.

*Presenter

P35- TS-11 : Network analysis of the brain dysfunction observed in Down syndrome models

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Down syndrome (DS) is the most frequent intellectual disability (ID) syndrome and is associated with one additional copy of human chromosome 21 (Hsa21). DS affects one out of 700 new-borns and patients have a specific profile, with ID and more than 80 clinical features although the number and severity of the presented features is variable. Nowadays, one of the most accepted theories aiming to explain how DS phenotypes appear considers the existence of a gene dosage imbalance as key to understand these phenotypes [1].
We aim to strengthen our understanding of DS genotype-phenotype relationships to allow the development of better diagnostic tests and therapeutic interventions in preclinical models. For that reason, in collaboration with the Mouse Clinical Institute, animal models carrying specific partial duplications homologous to Hsa21 have being developed [2] and characterized to map which genes or genetic regions showing a dosage imbalance contribute to the observed phenotypes.
We carried on transcriptomics analyses on the hippocampus of several mouse models focusing in the genes/pathways involved in brain dysfunction. Strong pathway connectivity was observed. The gene connectivity was assessed building minimum protein-protein interaction networks. The key hubs and main signalling cascades affected were identified by centrality analyses and the relevance of the connecting nodes was further predicted by Quack[3]. We found a dysregulation of signalling cascades involving DYRK1A or GSK3B previously known, and identified novel ones. Moreover, similarly to the observation in DS patients, where the affectation/severity of the gene dysfunction vary for each patient carrying partial duplication, the animal models show different signalling cascades affected where several members interconnect while the models produced similar phenotypes.
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*Presenter

P36- TS-17 : Role for genetic variation in antibody response to Influenza A Virus

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Influenza A Virus (IAV) is an enormous public health burden, leading to high morbidity and mortality across the globe. Vaccines for IAV are available but often ineffective; many individuals fail to mount a protective antibody response, leaving them at risk for severe disease. Human studies have shown that host genetic factors play a significant role in regulating the antibody response to infection and vaccination. However, these studies have been severely limited by inability to control important variables such as dose and prior exposure. We have used the Collaborative Cross (CC), a genetically diverse and experimentally tractable mouse genetics reference population, to study the host genetic factors that regulate antibody response to IAV. We infected 110 CC-F1 lines with the pandemic 2009 H1N1 IAV and measured the quantity of IAV-specific antibody at multiple timepoints post-infection. Virus-induced disease was highly variable across strains, which could largely be attributed to variation in the IAV resistance gene *Mx1*. Protective *Mx1* haplotypes (associated with decreased viral load and weight loss) were correlated with decreased antibody responses at day 7 post infection but largely disappeared at later timepoints. Antibody responses were highly variable across lines for different subtypes and timepoints, with heritability estimates ranging from 26-72%. We utilized this heritable variation to map the quantitative trait loci (QTL) underlying the magnitude of antibody response. We mapped 2 highly significant ($p<0.05$) QTL, *Ari2* and *Ari3* (antibody response to influenza), as well as 9 significant ($p<0.1$) QTL across other isotypes and timepoints, including *Ari1*. *Ari1* was mapped for IgG2a/IgG2c at day 7 post infection. Notably, *Ari2*, which was mapped for IgG3 at day 10, was also widely associated with IgM and other IgG isotypes at days 7 and 10 post-infection. *Ari2* haplotype was also correlated with antibody response to SARS-Coronavirus (but not Chikungunya virus), suggesting that *Ari2* is broadly involved in the early antibody response to respiratory viruses. *Ari3*, which was mapped for change in IgG2b between days 15 and 45, showed a strong association with IgG2b at day 15 individually. Candidate genes for *Ari1* and *Ari2* include viral pathogenesis and immune genes that have also been identified in human studies of infectious diseases. Haplotype of the IAV resistance gene *Mx1,* which is a strong driver of viral titer, weight loss, and mortality, was associated with antibody response only at day 7.

*Presenter

P37 : High content screening of toxic response phenotypes in cells derived from the Diversity Outbred mouse population.

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Genetic variation has a significant influence on susceptibility to chemical exposures, therefore toxicological studies using isogenic strain backgrounds cannot fully capture the range of potential physiological responses observed in the human population. With segregating genetic variation derived from 8 distinct, diverse isogenic strains, the Diversity Outbred (DO) mouse population captures ~90% of the genetic diversity found in the *Mus musculus* species. As a platform for cellular systems toxicology, cells derived from DO mice offer an opportunity to explore a range of cell autonomous response phenotypes *in vitro* and to correlate these endpoints with physiological responses from parallel *in vivo* studies in the context of integrated systems genetics studies. Here we present our initial efforts to develop this approach in the context of arsenic (As) exposure. The cell autonomous genotoxic effects of As are the indirect result of DNA repair inhibition and increased oxidative stress. Taking advantage of this, we are creating a panel of primary fibroblasts from a DO population that will be exposed to As in a parallel, *in vivo* study. To optimize our screening capabilities, we have tested both ELISA-based and high content screening assays for assessment of cytotoxic and genotoxic responses in these cells. Our initial data demonstrate that image-based high content cellular screening outperforms ELISA based assays by providing multidimensional data at single cell resolution. Our data also reveal compelling interindividual variation in genotoxic response to *in vitro* As exposure across a range of doses. Taking advantage of the mapping power made possible by the genetic architecture of the DO population, our long term goals are to use these *in vitro* phenotypes to map the underlying genetics of As sensitivity. Gene discoveries from the parallel *in vivo* and *in vitro* arms of the study and will be integrated and validated using CRISPR/Cas9 gene editing.

*Presenter

P38 : The role of PRDM9 zinc finger sequence in mouse hybrid sterility

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The hybrid sterility is a process of reproductive isolation between closely related species in some cases manifested by asynapsis of orthologous chromosomes and male meiotic failure.
Studies with two mouse inbred strains representing two mouse subspecies showed that the heterozygosity of *Prdm9* gene in their F1 hybrid male offspring is the major reason for the observed sterility and meiotic chromosome synapsis failure. *Prdm9* is defining the hotspot placement in meiotic recombination by posting trimethylation marks on lysine residues of histone 3. However, its exact role in molecular mechanism of hybrid sterility is not clear. To find the connection between meiotic recombination, meiotic chromosome synapsis and hybrid sterility, we study the role of different combinations of *Prdm9* alleles in F1 mouse hybrid fertility by using the *Prdm9* alleles obtained from natural mouse populations.
Our main approach is to combine the information about the DNA sequence of the zinc fingers of the used *Prdm9* alleles with their phenotype representation like meiotic asynapsis rate, testes weight, sperm count, etc. We find correlation between certain *Prdm9* alleles and meiotic phenotypes whose uniqueness or general distribution will be discussed further.

*Presenter

P39 : Physiological role of APP during aging: behavioral and molecular study in a new model of knock-out rat

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The *Beta-Amyloid Precursor Protein* (APP), precursor of the amyloid-beta (Aβ) peptide, is implicated in Alzheimer disease (AD). In early onset AD, the *App* gene is mutated, resulting in increased production of Aβ. Accumulation of Aβ results in amyloid plaques, one of the characteristics of AD. APP has been mostly studied in the context of AD. However, this protein has also many physiological functions for which the mechanisms are not understood. Different models of knock-out mice (KO) for *App* showed an implication of APP in synaptic plasticity, neuronal morphology and cognitive functions. Since inter-species differences may exist, it is interesting to confirm these results in an organism as the rat. Thus, we created a new model of rat KO for the *App* gene. At 2 and 12 months, we evaluated anxiety and locomotion. We also tested spatial memory and behavioral flexibility in the Morris Water Maze (MWM). The expression of different markers was assessed by western blot in the hippocampus. Our results show the emergence of cognitive deficits with aging. At 12 months, homozygous rats exhibited a slower learning and a flexibility deficit in the MWM. Therefore, the APP protein participates in the maintenance of cognitive functions over aging. At the molecular level, there was no impact of the KO on the expression of APLP1, a protein of the same family as APP. Surprisingly, the expression of APLP2, another protein of this family, was decreased at 12 months. The lack of APP had also an impact on the expression of the synaptic marker PDS-95, with a decrease at 12 months. GFAP tended to be decreased in homozygous at 2 months and S100B, another astrocytic marker, is decrease at 12 months. These data point to relatively subtle cognitive alterations in APP KO rats, in parallel with weak alterations at the molecular level.

*Presenter

P40 : Baseline cardiac phenotypes vary across a diverse population of mice: implications for cardiotoxicity risk assessment

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Cardiotoxicity is often the most sensitive parameter for determining threshold exposure levels of toxicants, but relatively few environmental chemicals have been tested successfully for cardiotoxicity. This is due, in part, to incomplete, although ongoing, development of models of cardiotoxicity, both *in vitro* and *in vivo*. Simplistic *in vitro* models lack receptor diversity, while *in vivo* models usually make use of a homogenous population. Of those chemicals tested, translating findings from current models to human risk assessment is challenging due to the lack of genetic diversity represented in these models, as well as limited epidemiological data to validate translation to humans. Animal models have been the gold standard for risk assessment, and with the use of individuals from a genetically diverse mouse reference population, the Collaborative Cross (CC), we can model the genetic diversity present in the human population. In 31 strains of mice, electrocardiogram measurements indicate a high strain-dependent variability ranging from 300 BPM to 800 BPM as well as significant differences in QT interval duration. Comparing cardiac high frequency ultrasounds acquired in both conscious and unconscious mice, strain-dependent effects of isoflurane on cardiac function were observed. Results demonstrate inter- and intrastrain variability in unexposed mice as well as in their response to chemicals. While the goal is to create a powerful diverse testing panel whose baseline phenotypes are characterized before and after exposure to several chemicals, these baseline measurements are crucial for identifying the ideal model for testing toxicity, ultimately allowing more informative risk assessments.

*Presenter

P41 : Mapping tolerance of intraspecific variation across the human and mouse genomes

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Regional differences in population-wide variation across the genome can be explained in part by constraint due to purifying selection, and provide a framework for interpreting the functional importance of genomic elements. Here, we use a sliding window approach to quantify intraspecific constraint across the human and mouse genomes. We highlight the relative enrichment and depletion of genomic annotations across the most and least constrained regions of the genomes, and show constraint is closely correlated between protein-coding regions and cis regulatory elements for both species. Furthermore we compare constraint across syntenic regions, and for pathogenic variants in human with an orthologous position in the mouse. Our results have implications for inferring when the mouse may be sufficiently analogous to serve as a model for human disease.

*Presenter

P42 : Development of a new mouse model of neuropathic chronic itch and investigation for therapeutic approach

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Pruritus is very common, irritating sensation that provoke the desire to scratch and extremely complicated syndrome. There are various factors that are involved for the onset of pruritus including environmental factors, genetics, hypersensitivity of itch related sensory nerves, dysfunction of skin and immune system. It could be sever and more devastating when this sensation is persistent and lingering along with skin inflammation and malfunction of nerve cell. Prevalence of neuropathic itch is still not well known. However, recently similar abnormalities associated to skin collagen VI especially COL6A5 gene have been reported. Unfortunately, due to lack of any available mice mode progress hasn't made in this area. Therefore, we developed new mice model that recapitulates Col6a5 mutation causing human neuropathic chronic itch using CRISPR-Cas technology. To characterize this newly developed mice model pathological symptoms, disease progression, behavior abnormalities, skin innervation assessment and electrophysiological measurements of nerve conductance work is ongoing. With observed phenotypic results numerous further test will be performed to develop this model for not only better understanding of pathogenesis but also for development of precise drug in future.

*Presenter

P43 : GRCm39 is coming: Updates to the mouse genome reference assembly

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The Genome Reference Consortium (GRC) provides updates to the mouse reference genome assembly, a resource critical to murine research. Since the 2012 release of GRCm38, the latest coordinate-changing update, the GRC has generated a total of 6 publicly available non-coordinate-changing assembly releases, the latest in 2017. These updates cumulatively include 65 fix and 9 novel patch scaffolds, which respectively represent corrections to the GRCm38 chromosomes and strain-specific alternate sequence representations for selected genome regions.

To evaluate the improvements that will be reflected in GRCm39, the GRC generated and analyzed a non-public version of the reference known as “GRCm38B”. GRCm38B represents the genome updates generated as patches together with additional curations made since the last patch release. In GRCm38B, 322 reported genome issues were resolved, 70% of which addressed gaps and clone problems. GRCm38B analyses demonstrate including of 254 new components, as well as the removal of ~200Kb of over-expanded sequence. GRCm38B is more contiguous than GRCm38, with >60% increase in both contig and scaffold N50. GRCm38B has 5 chromosomes comprised of a single scaffold and 11 chromosomes comprised of 2 scaffolds. Alignment of RefSeq-transcripts to GRCm38B show improved representation for >50 genes. Since analyses of GRCm38B, we have continued curation efforts, resolving an additional 40 genome issues, in some cases using sequences from the recently-released “Eve” assembly (GCA_003774525.2) to correct errors or close gaps. We will present data from our most recent analyses and curation, including our review of reference bases that are consistently different in 17 other mouse strains. Finally, we will present the results of recent RefSeq curation activities in mouse annotation and review resources, tools and mechanisms for contacting the GRC. Upon the release of GRCm39, planned for late 2019/early 2020, curation of the mouse genome reference assembly will be limited to the resolution of community-reported issues.

*Presenter

P44 : The Multiple Genome Viewer: a browser for exploring and comparing genomes

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The availability of annotations for the sequenced genomes of 19 mouse genomes represents an unprecedented opportunity to investigate the relationship between genotype and phenotype in the laboratory mouse. To provide the research community with new tools to explore multiple genomes at one time, MGI and MouseMine implemented new user interfaces to take advantage of these data, including the Multiple Genome Viewer (MGV). MGV supports browsing and comparing multiple genomes simultaneously. With it, users are able to explore the annotated mouse genomes in a coordinated, parallel fashion not possible in other browsers. Key features include a highly interactive display (organized as a stack of horizontal strips, one per selected genome, with vertical connectors between the same/equivalent gene in each genome); the ability to find “equivalent” regions across selected strains; synchronized zooming and scrolling; the ability to find genes by disease, phenotype, or other association; and the ability to define and highlight lists of genes. We recently released a preview of version 2 of MGV which offers significantly greater functionality, including the display of gene model structures, ability to zoom to the sequence level, the ability to download selected sequences from across genomes, the ability to download images, and numerous settings to control the display.

*Presenter

P45 : The Gene Expression Database (GXD): What's New in 2019?

Smith Constance (1), Finger Jacqueline (1), Hayamizu Terry (1), Mccright Ingeborg (1), Xu Jingxia (1), Shaw David (1), Baldarelli Richard (1), Smith Cynthia (1), Kadin James (1), Richardson Joel (1), Ringwald Martin* (1)

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The Gene Expression Database (GXD) is an extensive and freely available community resource of mouse gene expression information (www.informatics.jax.org/expression.shtml). Through curation of the published literature and collaborations with large-scale data providers, GXD has integrated data from RNA *in situ* hybridization, immunohistochemistry, *in situ*knock-in reporter, RT-PCR, northern blot, and western blot experiments, with a particular focus on mouse development. GXD now contains more than 348,000 images and over 1.6 million annotated expression results for more than 14,800 genes, including data from over 4,300 mouse mutants. These data are combined with other genetic, functional, phenotypic, and disease-oriented data in MGI, thus making them easily searchable by a wide variety of biologically- and biomedically-relevant parameters. Browsers and interactive matrix views enable the anatomical comparison of expression and phenotype data and foster insights into molecular mechanisms of disease. As part of our efforts to expand GXD to include high throughput expression assays, we have developed a new RNA-seq and Microarray Experiment Search utility that allows users to effectively find specific studies that have examined gene expression in mice. GXD curators use controlled vocabularies for age, anatomical structure, mutant alleles, and sex to annotate samples from experiments stored in EBI's ArrayExpress repository. Integration of these standardized annotations with free text searching of experiment title and description allows for searches that quickly and accurately return experiments of interest. Work to incorporate RNA-seq data itself into GXD is underway and will also be described at the meeting. GXD is supported by NIH/NICHD grant HD062499.

*Presenter

P46 : Genome-wide association studies of personality traits in the European Harvest mouse (Micromys minutus)

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There has been increasing interest in studying behavioral genetics as new technologies and methodologies for sequencing and analyzing the genome become available. While studies in humans and companion animals are at full speed, studies that focus on genetics of behavior in wild species and natural populations are still few and far between due to difficulties in acquiring large datasets. Previous behavioral studies of the European harvest mice (*Micromys minutus*), using established behavioural essays, have shown that personality traits activity, boldness and exploration are consistent and repeatable, pre-requisites for traits that are under genetic effect and therefore ideal starting points to explore their genetics. Genome-wide association studies (GWAS) using SNPs called from RAD-seq harvest mouse data were performed to look for variants associated to the behavioural traits. Further analysis were conducted in order to corroborate the main results. One gene seems particularly promising as associated to trait activity.

*Presenter

P47- TS-18 : Genetic control of hepatic energy metabolism and response to carbohydrate restriction

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The application of genomic approaches to understand unique responses to diet effects has been understudied when compared to genomic characterization of complex disease. In order to advance precision dietetics, we are establishing a predictive measure for responsiveness to carbohydrate consumption. Our laboratory has previously demonstrated the effects of inter-individual response to diet in a study using four inbred mouse strains: C57BL/6J (B6), FVB/NJ (FVB), A/J, and NOD/ShiLtJ (NOD). Increased body fat gain and other negative health effects were observed in B6 mice consuming an American diet (high fat, high carbohydrate) and but not in B6 mice on a ketogenic diet (high fat, no carbohydrate). The negative health effects observed in FVB mice exposed to the American diet persist in FVB mice exposed to the ketogenic diet. This suggested that the individual response to a high fat diet is more dependent upon the presence or absence of carbohydrates than exposure to the high fat diet alone for B6 mice, whereas FVB mice showed no differential responsive when carbohydrates were restricted. Consequently, B6 mice are predicted to respond to a dietary intervention restricting carbohydrate consumption while FVB should be non-responsive. Analysis of the liver transcriptomes suggests that hepatic energy metabolism is a major determinant of response or non-response to carbohydrate restriction. An intercross (F2) population was generated to further investigate the divergence observed in hepatic energy metabolism.Half of the F2 mice were placed on American diet and half on ketogenic diet for three months before characterizing changes to body composition and weight gain. Genetic analysis in each of the F2 populations revealed quantitative trait loci (QTL) on Chr 7 (American) and 5 (ketogenic). We are systematically investigating the effects of the ketogenic diet on glucose metabolism and liver health as it relates to hepatic energy metabolism in these mice.

*Presenter

P48 : Generation of mutated mice combining CRISPR/Cas9 and electroporation

Lorentz Romain* (1) (2), Schaeffer Laurence (1) (2), Erbs Valérie (1) (2), André Philippe (1) (2), Kujath Christelle (1) (2), Fougerolle Jean-Victor (1) (2), Legeay Sandrine (1) (2), Prevost Géraldine (1) (2), Ayadi Abdel (1) (2), Herault Yann (1) (2), Pavlovic Guillaume (1) (2), Birling Marie-Christine (1) (2),

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The CRISPR/Cas9 system has been employed to efficiently edit the genomes of diverse model organisms. CRISPR-mediated mouse genome editing is typically accomplished by microinjection of Cas9 RNA and single guideRNA (sgRNA) into zygotes to generate modified animals in one step. However, microinjection is a technically demanding, labor-intensive, and costly procedure with poor embryo viability. In our lab, we performed electroporation to deliver Cas9/crRNA-tracRNA ribonucleoproteins or Cas9/sgRNA into mouse zygotes. Using this technique, we generated mutant models with required deletions, point mutations, and small insertions. We also compared homemade sgRNA with commercial crRNA-tracRNA. Results showed an increase of HDR efficiency with home-made sgRNA.
In comparison to microinjection, electroporation is a simple, high throughput, and highly efficient technique. CRISPR/Cas9 electroporation considerably reduces (3Rs rule) the number of animals required per experiment.

*Presenter

P49 : Generation of genomic structural variants and chromosomal manipulation by CRISPR/Cas9 genome editing in rodents

Schaeffer Laurence* (1) (2), Lorentz Romain (1) (2), André Philippe (1) (2), Lindner Loic (1) (2), Maréchal Damien (2), Ayadi Abdel (1) (2), Sorg Tania (1) (2), Pavlovic Guillaume (1) (2), Birling Marie-Christine (1) (2), Herault Yann (1) (2)

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The human genome contains many large number of gene clusters. Up to now, very few have been tested experimentally. Indeed, generating duplication and deletion of genomic regions was labor intensive and time consuming. With the advent of CRISPRCas9, it is now possible to generate at much lower expenses and in a record time both duplication and deletion. We have implemented droplet digital PCR (ddPCR) and PCR junction sequencing to validate our animals. We have obtained established lines with deletions, duplications and inversions of genomic regions as large as 24.4 Mb, reproducing in rat a Down syndrome model similar to a previously generated mouse model (*Birling et al*., 2017).
Using the same approach we have engineered the Ts(17^{16})65Dn mini-chromosome by specifically removing a 6.2 Mb region corresponding to the chr 17. Ts(17^{16})65Dn mice are recognized as one of the best models for Down syndrome. The new line will allow us to better understand the role of the genes localized on the different regions of the mini-chromosome. We have shown that the CRISPR approach allows the scientific community to manipulate the rodent genome in a fast and efficient manner that was not possible before and this opens new fields in research.

*Presenter

P50 : Standardization of the health status of CC strains at the Systems Genetics Core Facility at UNC and update of the CC genomes

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The Systems Genetics Core Facility (SGCF) was established in 2012 to distribute Collaborative Cross (CC) mice to the research community. At that time, the CC strains were in an advanced state of inbreeding, but were still segregating founder haplotypes for up to 10% of the genome. The SGCF provided a description of the genomes of each CC strain based on the genetic information of obligate ancestors of mice distributed from the SGCF. CC strains have been maintained in two health statuses, SPF (negative for IDEXX comprehensive) and barrier (also excluding MNV and helicobacter). UNC has 25 CC strains in the barrier facility with the remaining 35 in the SPF facility.

In early 2019 the SGCF decided to 1) standardize all of the CC strains by rederivation into the cleaner barrier facility and 2) create new genetic information based on current obligate ancestors of each strain. By September 2019 the SGCF will have 48 strains in the barrier facility (25 previous and 23 rederived), leaving only 12 strains to rederive.

CC genomes will be updated by WGS of all obligate ancestors of any CC mouse that will be distributed from the colony going forward. Sequencing will be performed by pooling equimolar quantities of DNA of ~15-20 obligate ancestors and sequencing that pool at a depth sufficient to identify all segregating alleles with a MAF of >10%.

The SGCF is undertaking this effort with the expectation that this will: 1) ease the import of CC strains to other facilities; 2) reduce an unintended source of phenotypic variability; 3) update the CC genomes to reflect the significantly more inbred status of the current colony; and 4) facilitate genetic analysis in line with other inbred strains with the added advantage of population-wide genetic information versus a single representative animal.

*Presenter

P51 : Deep genome sequencing and variation analysis of 45 inbred mouse strains

Shivalikanjli Anu* (1), Lilue Jingtao (1), Wong Kim (2), Adams David (2), Keane Thomas (2)(1)

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The Mouse Genomes Project has sequenced the most medically relevant laboratory mouse strains and produced comprehensive maps of all forms of genetic and transcriptional variation in mouse. Thousands of novel haplotypes across the strains and effects on genetic variations on the phenotypes have been catalogued. The latest variation release contains sequence and structural variants annotations for 45 inbred strains with five recent additions (B10.RIII-H2r H2-T18b/(71NS)SnJ also known as B10.RIII, C57BL/10SnJ, SJL/J, QSi3, and QSi5). The new strains are models for arthritis, demyelinating diseases, and sarcomas. B10.RIII is highly susceptible to both chronic and acute arthritis. Non MHC loci strongly associated with arthritis have been identified in B10.RIII besides the classically implicated MHC alleles in other strains. This strain is used to study the link between epidemiologically associated rheumatoid arthritis and periodontal disease. We have identified private missense variants located in these non-MHC QTLs associated with CIA, CII and CAIA autoimmunity. C57BL/10SnJ has MHC class 1 haplotypes b, d or k and is able to clear Theiler's virus infection compared to mice of identical backgrounds with other haplotypes. C57BL/10SnJ develops more pronounced schistosome infection than C57BL/6J due to significantly underexpressed *Ym1* loci on chromosome 4. While variants in SJL/J render it highly susceptible to reticulum cell sarcomas, it is most resistant to pneumonia. Among the new, B10.RIII and C57BL/10SnJ display lower variation with approximately 0.95M and 0.55M variants respectively.

*Presenter

P52 : A New Mouse Model for Adult-Onset Seizures

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Epilepsy is a chronic and debilitating disorder characterized by recurrent seizures. Epilepsy affects 65 million people worldwide and up to one-third of these individuals do not achieve adequate benefit from currently available medications. Although more than 40 different types of epilepsy have been identified in the human population, the etiology of epilepsy in most patients remains unknown. The Collaborative Cross (CC) was developed as an advanced resource for mapping multigenic traits. The CC is a multiparent panel of new recombinant inbred mouse strains derived from 8 genetically-diverse progenitor inbred strains. While working with one CC colony, a single male was observed to spontaneously express recurrent seizures starting at 7 months of age. Further breeding revealed that a subset of his offspring also exhibited adult-onset generalized seizures. Male offspring were first detected with seizures between 5-10 months of age, whereas female offspring were first detected with seizures between 12-18 months of age. Our research is designed to further characterize the seizure phenotype and the inheritance pattern, and to identify high priority candidate genes for *in vitro* and *in vivo* analyses. Towards these goals, we established genetic crosses to determine the chromosomal location of the locus (or loci) causing seizures. Analysis of the CC pedigree and preliminary results from outcrosses of seizure mutants suggest that the seizure phenotype is inherited as a multigenic trait. Our long-term goal is to elucidate the molecular mechanisms of seizure causation in this new mouse model and pave the path for innovative therapies to prevent and/or treat epilepsy.

*Presenter

P53 : Comparative Disease Model Data at Mouse Genome Informatics and the Alliance of Genome Resources

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Exome sequence data from patients with diseases with unknown etiology have provided several hundred new candidate genes for many diseases, and targeted re-sequencing technologies have provided gene variation information on dozens of these candidate genes in tens of thousands of individuals with high specificity and sensitivity. Comparison of gene, phenotype and genetic model disease data provided by animal models aids in the refinement of human disease candidate genes and selection of potential therapeutic targets.
Mouse Genome Informatics (MGI; www.informatics.jax.org) together with the Alliance of Genome Resources (www.alliancegenome.org) provide several mechanisms to explore and compare human, mouse and other model organism phenotypes and their associations with known human diseases and supporting references. Searches can be initiated based on human or model organism data using one or more parameters, including genes, genomic locations, or phenotypes or disease terms. Integration of these data using controlled vocabularies and ontologies across multiple species ensures accurate and robust retrieval of curated information. Alliance disease reports include annotations from human data and from the participating model organisms and show the affected genes, alleles or genomic models, association type, evidence codes and references. New ribbon summary displays of disease information on Alliance gene pages includes annotations from orthologous genes in other model organisms and in humans, aligned in a side by side view for easy comparison.

*Presenter

P54 : GUDMAP an online data base for the GenitoUrinary Development Molecular Anatomy Project

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The GenitoUrinary Development Molecular Anatomy Project (GUDMAP) is an open access online resource developed by a consortium of laboratories (the PIs listed here) working to provide the scientific and medical community with gene and protein expression data, transgenic mice, high-resolution 2D and 3D morphological and molecular data accompanied by tools to facilitate research and teaching in genitourinary (GU) development. The goal is to stimulate further research into genitourinary development by identifying novel cell types and gene expression domains in the kidneys, ureters, bladder, prostate, urethra, external genitalia, and associated reproductive structures and accompanying innervation. The GUDMAP database includes mouse gene expression and histological data in the form of annotated images of *in situ* hybridization, immunofluorescence, 3-D Optical Projection Tomography (OPT) images, nanoscale computed tomography (nanoCT), microarray, RNA-Seq and ChIP-seq gene expression data from pools as well as single cells that is complemented by high-resolution histology. Expression data are annotated using a high-resolution ontology specific to the developing murine GU system. The database is searchable based on gene name, function, or anatomical structure. Database queries can be refined based on stage, organ, or expression. Recent efforts have integrated complementary gene expression and morphological data on human GU and reproductive tract development into GUDMAP to facilitate comparative studies. Online tutorials are provided that detail the complex anatomical changes that occur during GU development. Detailed protocols for methods used to generate the data are also available on the site and are similarly searchable. GUDMAP data are curated and freely accessible at www.gudmap.org. GUDMAP is supported by the NIDDK.

*Presenter

P55 : Prediction of pioneer transcription factors from DNA methylation profiles

Noguchi Shuhei (1), Miyajima Yurina (1), Suzuki Takahiro (2) (1), Tanaka Yuki (2) (1), Nishimura Hajime (1), Kishima Mami (1), Kasukawa Takeya (1), Suzuki Harukazu* (1)

1 - RIKEN IMS (Japan)
2 - Yokohama City University (Japan)

DNA methylation is widely analyzed as a fundamental epigenetic modification to regulate mammalian gene expression. Each type of cell creates specific methylation pattern during its differentiation. While enzymatic mechanisms of DNA methylation (DNMT3A/3B, DNMT1 and UHRF1) and demethylation (TETs and TDG) are well characterized, little is known about how DNA methylation dynamics are spatiotemporally regulated during cellular differentiation. Recently, a subgroup of transcription factors (TFs) termed pioneer TFs have been shown to carry out DNA demethylation in a binding site-specific manner, although small number of pioneer TFs have been identified yet. We have developed an informatics pipeline to predict pioneer TFs from DNA methylation profiles derived from whole genome bisulfite sequencing (WGBS). The pipeline consists of four steps, preparation of bins, extraction of differentially methylated bins, the TF binding motif enrichment analysis, and filtering of TF gene expression. We applied the pipeline to the International Human Epigenome Consortium (IHEC) WGBS data. In comparison with DNA methylation profiles in ES cells, average number of demethylated bins are 100,000 while methylated bins 20,000 in examined cells/tissues, indicating that DNA demethylation is major event in cellular development. We have predicted more than 100 pioneer TFs including previously identified pioneer TFs such as RUNX1 and SPI1, where distinct sets of pioneer TFs are predicted in cell lineage-specific manner. We also introduce validation of the predicted pioneer TFs by using our developed method that detect DNA demethylation activity of TFs.

*Presenter

P56 : Nested retrotransposition in molossinus mouse genome caused classical nonagouti mutation

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3 - Mouse Genomics Resource Laboratory, National Institute of Genetics, 1111 Yata, Mishima, Shizuoka 411-8540, (Japan)

Black coat color (nonagouti) is one of the widespread classical mutation in laboratory mouse strains. Endogenous retrovirus VL30 inserted in the *nonagouti* (*a*) allele has been considered the cause of the nonagouti phenotype. Here, we revise the previous assumption and reveal the true mutation in the *a* allele. We found that β4, an endogenous retrovirus nested within the VL30, interrupts the *agouti* expression by the abnormal splicing. To demonstrate the normal *agouti* gene expression even with VL30, we used CRISPR/Cas9 to completely delete the β4 element. The β4-deleted mice restored *agouti* gene expression and agouti coat color. In partial deletion of β4 except for the LTR, the mutant allele mimicked the black-and-tan (*a^t*) allele and the coat color. Phylogenetic analyses indicate that the *a* allele and the β4 retrovirus originated from an East Asian mouse linage that is most likely related to Japanese fancy mice, JF1. Structural variation in the *agouti* gene among mouse strains reveals that the VL30 insertion is derived from a natural mutation in East Asian wild mice. We propose that the *a* allele was derived from step-by-step insertional mutation events of VL30 followed by β4 retrovirus into an intact *agouti* allele. In conclusion, our findings clarified genetic mechanisms and historic origin of the classical nonagouti mutation.

*Presenter

P57- TS-10 : SAR1A rescues the hypocholesterolemia resulting from hepatic Sar1b deletion in mice

Tang Vi* (1) (2), Xiang Jie (1), Emmer Brian (3) (1), Khoriaty Rami (4) (3), Ginsburg David (5) (6) (7) (3) (1)

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The transport of secretory proteins from the endoplasmic reticulum to the Golgi is mediated by COPII vesicles. SAR1 is a small GTPase that initiates vesicle formation. Mammalian genomes contain two paralogs for SAR1, SAR1A and SAR1B. In humans, mutations in SAR1B result in chylomycron retention disease (CRD), an autosomal recessive disorder characterized by fat malabsorption and plasma hypocholesterolemia. We generated mice with a conditional Sar1b allele (Sar1b-fl) and demonstrated that mice with germline SAR1B deficiency (EIIa-Cre) die perinatally, with gross appearance and histologic analysis indistinguishable from wild-type (WT) litter mate controls. Mice with liver specific Sar1b deletion (Alb-Cre) exhibited low plasma cholesterol compared to WT litter mate controls (20.6±2.6 and 88.4±4.5 mg/dl, respectively, $p < 0.01$). As expected, the hypocholesterolemia was corrected with delivery of an adenovirus (AV) vector that expresses SAR1B compared to a GFP-expressing AV (GFP-AV) (89.1±7.4 versus 15.1±2.2 mg/dl, respectively, $p<0.01$). To test if SAR1A can similarly rescue the hypocholesterolemia resulting from hepatic SAR1B-deficiency, Sar1bfl/fl Alb-Cre(+) mice were injected with a SAR1A-expressing AV (SAR1A-AV) or GFP-AV as control; cholesterol levels were normalized in mice injected with SAR1A-AV (70.2±9.4 and 15.1±2.2 mg/dl, respectively, $p <0.01$). These results demonstrate that SAR1A can rescue the hypocholesterolemia resulting from SAR1B deficiency in mice. To test if SAR1A rescues the lethality of SAR1B deficient mice, we are generating mice with the Sar1a coding sequence inserted into the endogenous Sar1b locus. These mice should be completely deficient in SAR1B, with SAR1A expressed from its native locus as well as under the regulatory control of the Sar1b gene. Rescue of the lethality of SAR1B deficiency in the latter mice would suggest a functional overlap between the two SAR1 paralogs and that strategies aimed at increasing SAR1A expression might be of therapeutic value in patients with CRD.

*Presenter

P58 : Reconstituted H19 ICR sequence with identified cis elements is capable of maintaining genomic imprinting in knock-in mouse

Matsuzaki Hitomi (1), Kuramochi Daichi (2), Hirakawa Katsuhiko (2), Tanimoto Keiji* (1)

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DNA methylation at differentially methylated regions (DMRs) plays an essential role in controlling genomic imprinting and early embryogenesis in mammals. To explore molecular mechanism for how paternal-allele-specific DNA methylation is established and maintained at the *H19* imprinting control region (ICR), a DMR in the *Igf2/H19* locus, we previously generated transgenic mouse (TgM) with a 2.9-kb *H19* ICR fragment and found that it carries an intrinsic methylation imprinting activity. We then dissected the fragment and identified several *cis* elements, some of which are essential for protecting the maternal *H19* ICR from undesired methylation (CTCF and Sox-Oct binding motifs), and the other for inducing its methylation on the paternal allele (5'-portion of the ICR). When the latter sequence was internally deleted from the endogenous *H19* ICR in mouse, the mutant sequence partially lost its methylation even after paternal transmission during post-fertilization period. We then generated a DNA fragment by grafting these elements into a normally non-imprinted bacteriophage lambda DNA sequence to test its ability to instruct imprinted methylation in TgM. While germline methylation of the reconstituted fragment in sperm was not observed, it was capable of acquiring paternal-allele-specific methylation after fertilization, the dynamics of which was comparable to that of the original *H19* ICR in TgM.
In this study, we used the reconstituted fragment to replace the mouse endogenous *H19* ICR. The fragment faithfully recapitulated allele-specific DNA methylation, preferential interaction with CTCF protein upon maternal inheritance, and regulation of imprinted expression of the both *Igf2* and *H19* genes. Importantly, germline methylation of the fragment, as well as normal development of the knock-in mouse was also observed. It is therefore demonstrated that combination of the *cis* elements was required and sufficient to maintain imprinted DNA methylation status at the endogenous *H19* ICR that is established by its unidentified surrounding sequences in the locus.

*Presenter

P59 : Identification of genetic loci associated with susceptibility to lung injury caused by the air pollutant ozone

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Differential susceptibility to air pollution-induced toxicity is observed within both human and mouse populations, suggesting a role for gene-by-environment interactions (GxE). However, there have been relatively few genome-wide searches for quantitative trait loci (QTL) that interact with air pollution exposures. We exploited the Collaborative Cross (CC) mouse genetics reference population to identify GxE QTL with the ubiquitous air pollutant ozone (O3). We exposed 10-12 week-old, female and male mice from 56 CC strains to either filtered-air (n=4/strain) or 2 ppm O3 (n=6/strain) for 3 hours. Mice from each strain were exposed in matched pairs or trios (i.e., one or two O3-exposed mice and one FA-exposed mouse) to enable measurement of response phenotypes, which are defined as change in phenotype (O3-FA) for paired mice. Twenty-one hours after O3 exposure, we collected bronchoalveolar lavage (BAL) fluid to assess two hallmark O3 responses: total protein (a marker of injury) and neutrophil accumulation in the lungs (a marker of inflammation). Distributions of both phenotypes were log-normal, suggesting a polygenic architecture. We calculated broad-sense heritability for total protein and neutrophilic accumulation, which were 0.37 and 0.34, respectively. QTL mapping for the O3-response total protein phenotype yielded two loci that reached genome-wide significance: one locus on chr15 at ~44 Mb that surpassed the 99% permutation-based significance threshold and an additional locus on chr10 at ~45.4 Mb that surpassed the 95% threshold. QTL mapping of related traits (e.g., cytokines) and airway gene expression will be used to help identify candidate susceptibility alleles underlying these QTL. No QTL for airway neutrophil accumulation were identified. In total, our results demonstrate that O3 response phenotypes are under genetic control and we have identified specific regions of the genome that harbor susceptibility alleles for O3-induced lung injury.

*Presenter

P60 : Exploring the Role of Nucleotide Excision Repair in Oxaliplatin Resistance

Vaughn Courtney* (1), Selby Chris (1), Yang Yanyan (1), Hsu Shiaowen (2), Sancar Aziz (1)

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2 - Duke Cancer Institute (United States)

Platinum-based chemotherapies are a mainstay in solid tumor treatment and work by forming guanine-guanine dinucleotide adducts which may ultimately result in cell death. Despite their common use, they are highly toxic and approximately half of patients have tumors that are either intrinsically resistant or will develop resistance to platinum-based drugs. Understanding the mechanisms underlying this resistance is essential for effective patient care. A number of studies claim that enhanced DNA damage repair efficiency is a mechanism of platinum resistance, but the evidence so far is incomplete and inconsistent. We aimed to better define the role of nucleotide excision repair in platinum resistance. Oxaliplatin is a first line treatment for colorectal cancer. Thus for this study, we defined a panel of platinum sensitive and platinum resistant colorectal cancer cell lines based on oxaliplatin IC50. Using this panel we measured DNA damage and repair efficiency following treatment. We measured damage amount and repair rate by slot blot, repair capacity by excision assay, and repair pattern using eXcision Repair-sequencing (XR-seq, a novel method of mapping repair at single nucleotide resolution). While sensitive cell lines have more initial damage than resistant cell lines for the same treatment dose, this difference did not entirely explain resistance. In contrast with the current assumption that repair efficiency is a driver of platinum resistance, we found no significant difference in repair rate, capacity, or pattern indicating that nucleotide excision repair is not essential for platinum resistance in colorectal cancer cell lines. Future studies are needed to determine specific factors that influence initial platinum damage levels and response to this damage.

*Presenter

P61 : Rat Resource and Research Center

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1 - Rat Resource and Research Center, University of Missouri (United States)

The NIH-funded Rat Resource and Research Center (RRRC) serves as a centralized repository for maintaining/distributing rat models and providing rat-related services to the biomedical community. Currently, the RRRC has over 450 rat lines; all are archived by cryopreservation to ensure against future loss. The RRRC distributes live animals, cryopreserved germplasm and rat embryonic stem (ES) cell lines. Quality control measures for all materials include extensive genetic validation and health monitoring. The RRRC has expertise in rat reproductive biology, colony management, health monitoring, genetic analysis, cytogenetic characterization, strain rederivation and cryopreservation, isolation of rat tissues, microbiota analysis and creation/characterization of genetically engineered rats. Our website (www.rrrc.us) allows user-friendly navigation. The University of Missouri is home to the NIH-funded MU Mutant Mouse Resource and Research Center (MMRRC) and the National Swine Resource and Research Center (NSRRC) as well as the MU Animal Modeling Core and MU Metagenomics Center. Together, these highly collaborative groups provide a diversity of animal model-related services across species to facilitate biomedical research. Funding: NIH 5P40 OD01106.

*Presenter

P62- TS-03 : A Statistical Model of Methylation Sequencing Data Identifies Novel Differentially Methylated CpG's and Provides Insights into the Role of Methylation in X-chromosome Inactivation and the Silencing of Transposable Elements

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Mammalian DNA methylation was first documented in the 1940's, and has since been implicated as a major epigenetic modification in a wide range of cellular processes. While it is essential to mammalian development, aberrant methylation is also associated with disease (e.g., cancer). We applied Reduced Representation Bisulfite Sequencing (RRBS) technology to reciprocal F1 females from two genetically divergent mouse inbred strains (129S1/SvImJ and PWK/PhJ) to dissect the strain and parent-of-origin (PoO) effects on differential methylation. We collected whole-brain DNA from four samples and used Illumina HiSeq 2000 to generate 50 bp single end reads. We used a custom RRBS pipeline to align high-quality reads to the pseudogenomes of 129S1/SvImJ and PWK/PhJ. We then fit a novel statistical model to the RRBS data at each CpG site, treating the number of methylated reads as arising from a beta-binomial distribution, which jointly modeled both strain and PoO effects. We accounted for small-sample type-I error inflation by employing the permutation approach of Devlin and Roeder (1999). Despite the small sample size, we identified differentially methylated CpG sites exhibiting PoO effects near 16 genes, 14 of which are known imprinted genes and two of which are novel (*Mir344i* and *2310015A10Rik*). We also identified 7,425 differentially methylated CpG sites that exhibited significant strain effects. We then used the results to investigate the role of DNA methylation in X-chromosome inactivation and the potential silencing of transposable elements (TE). We identified hundreds of CpG's clustered in dozens of regions of the X chromosome with differential methylation patterns that are indicative of X-inactivation status (including skewed X-inactivation). Further, we associated the observed differential CpG methylation with differential insertion of TE's into the 129S1/SvImJ and PWK/PhJ genomes, likely reflecting the role of DNA methylation in their epigenetic silencing.

*Presenter

P63 : Development and characterization of pain-related sodium channel CRISPR/Cas9 mouse model for Scn9aR185H and Scn9aR185X

Xue Yaping* (1), Marie-Christine BIRLING (2); Hamid MEZIANE(2); Claire GAVERIAUX-RUFF(1); Yann HERAULT(1)(2))

1 - Institut de Génétique et de Biologie Moléculaire et Cellulaire (France)
2 - Institut Clinique de la Souris-PHENOMIN (France)

Neuropathic pain is caused by a lesion or disease of the somatosensory system, including peripheral fibers (A-beta, A-delta and C fibers) and central neurons, and affects life quality of 5% of the general population. Nav1.7 channel is a voltage-gated sodium channel and plays a critical role in the generation and conduction of action potentials and is thus important for electrical signaling by most excitable cells. Recent studies show that in primary sensory neurons, the expression and dynamic regulation of several sodium channel subtypes play important roles in neuropathic pain. A number of SCN9A (encoding Nav1.7) gene point mutations are related with human genetic chronic pain syndromes, like SFN (Small fiber neuropathy). For those neuropathic disorders that are inherited, gene editing is an important tool for establishing animal models to investigate the pathogenesis of disease and provide a rapid avenue for functional drug screening. Clustered regularly interspaced short palindromic repeat/CRISPR-associated 9(CRISPR/Cas9) enables targeted genome engineering. The simplicity of this system, its facile engineering, and amenability to multiplex genes make it the system of choice for many applications. In this project, the aim is to establish a pain-related sodium channel mouse model *Scn9aR185H* and *Scn9aR185X* using CRISPR/Cas9 technology and to characterize this mutation.

*Presenter

P64: The National BioResource Project Core Facility of the Mouse in Japan

Atsushi Yoshiki* (1)

1 - RIKEN BioResource Research Center (Japan)

As the core facility of the mouse resource in the National BioResource Project (NBRP) by MEXT/AMED, RIKEN BioResource Research Center (BRC) has collected, preserved, quality-controlled and distributed mouse models for studies to decipher sophisticated biological phenomena and cure human diseases. We have collected 8,850 strains created mainly by Japanese scientists and distributed our mouse resources to 1,400 organizations around the world. The mice are distributed in high-quality by strict microbial and genetic quality control programs which cover mutated alleles generated by various methods. Our users have so far published over 900 outstanding papers and 38 patents. RIKEN BRC has participated in the International Mouse Phenotyping Consortium (IMPC) and contributed to knockout mice production, phenotyping and data integration. Recent genome editing technology enables us to collaborate with external clinical scientists and co-produce knock-in mice of variants or mutations found in patients in addition to the null-knockout mice in the same production platform. We have started to collaborate with clinical scientists of Strategic Research Program for Brain Sciences (SRPBS), Initiative on Rare and Undiagnosed Diseases (IRUD), The Japanese Teratology Society. To disseminate advanced mouse resources and relevant technologies and facilitate collaborations in Asia/Australia, we have founded Asian Mouse Mutagenesis & Resource Association since 2006.

*Presenter

P65: Sensitization of Silent C-Nociceptors after Heat-Capsaicin exposure

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Different pain models have been used in Phase-I human studies to assess experimental allodynia and hyperalgesia, including physical and chemical methods. The study of sensitized skin under these models let the characterization of functional changes of unmyelinated-nociceptors by psychophysical, neurophysiological and structural techniques. In the case of the heat-capsaicin sensitization, no published researches have described yet the behaviour of C-nociceptors by microneurography. The skin innervated by the superficial peroneal nerve of two healthy volunteers, one male and one female, was sensitized by heat and topical capsaicin. Microneurographic recordings were performed in the lateral branch of the superficial peroneal nerve. Mechanical and thermal (cold and heat) stimuli were applied on the skin before and after the sensitization. Preliminary results showed mechanical and/or thermal response of silent C-nociceptors following the application of heat and capsaicin. The behaviour of these 'mechano-heat unresponsive-nociceptors' is similar to what has been reported previously about patients with Painful Small Fibre Neuropathy.

*Presenter

AUTHORS INDEX

TS: Oral Trainee Symposium
O: Oral main meeting
P: Poster

SOCIAL ACTIVITIES

All Activities will take place on Thursday Sept. 26th and Friday Sept. 27th and must have been booked

Introduction to Oenology

Address: 33 rue de Zurich - 67000 Strasbourg

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You will discover during this boat tour Strasbourg, 20 Centuries of History
From the city centre to the European Parliament, via the imperial district of Neustadt, discover Strasbourg by the water, a unique route!

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GALA DINNER

The IMGC 2019 Gala Dinner and Awards Ceremony will take place at the "STORIG" Debus Brewery on Saturday September 28th 2019

Address: 85, route de Bischwiller, SCHILTIGHEIM

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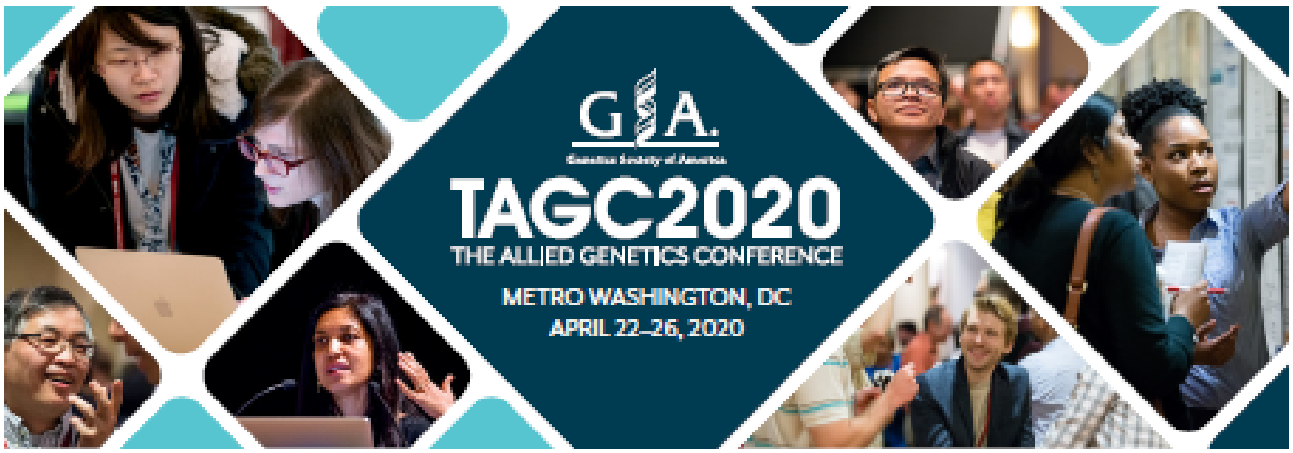

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