



National Institute of
Environmental Health Sciences



Population-based Rodent Resources for Environmental Health Sciences Meeting

March 18-19, 2015

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Population-Based Rodent Resources for Environmental Health Sciences

AGENDA

Day One – March 18, 2015

8:30 a.m.	Welcoming Remarks Linda Birnbaum, <i>National Institute of Environmental Health Sciences</i>
8:40 a.m.	Introduction/Purpose/Background Kim McAllister, <i>National Institute of Environmental Health Sciences</i>
Session One	Overview of Mouse/Rat Resources Chair: David Balshaw, <i>National Institute of Environmental Health Sciences</i>
9:00 a.m.	The Collaborative Cross: What We've Learned From Randomized, Structured Populations David Threadgill, <i>Texas A&M University</i>
9:45 a.m.	Diversity Outbred Gary Churchill, <i>Jackson Laboratory</i>
10:30 a.m.	Hybrid Diversity Panel Brian Parks (<i>Jake Lusis' laboratory</i>), <i>University of California, Los Angeles</i>
11:15 a.m.	Recombinant Inbred Rats: Genetics, Transcriptomes, and Use for Identifying Phenotypic Determinants Boris Tabakoff, <i>University of Colorado School of Medicine</i>
12:00 p.m.	Q&A
12:30 p.m.	Lunch
Session Two	Diverse Applications Chair: Mathew Pletcher, <i>Pfizer</i>
1:30 p.m.	"Fit-For-Purpose," Population Study Designs To Address Specific Hypotheses Ivan Rusyn, <i>Texas A&M University</i>
2:00 p.m.	Mouse Populations Enable Translational Pharmacogenomic Approaches for Understanding and Predicting Adverse Drug Events Alison Harrill, <i>University of Arkansas for Medical Sciences</i>
2:30 p.m.	Identifying G X E Interactions and Thresholds for Toxicity in Diversity Outbred Mice Jef French, <i>National Institute of Environmental Health Sciences</i>
3:00 p.m.	A Diversity Outbred ES Cell Platform for In Vitro Genetics Ted Choi, <i>Predictive Biology, Inc.</i>
3:30 p.m.	Q&A
Session Three	Poster Session
4:00 p.m.	Poster Session
6:00 p.m.	Adjourn for the Day



Population-Based Rodent Resources for Environmental Health Sciences

AGENDA

Day Two – March 19, 2015

Session Four Computational Tools and Analysis Approaches

Chair: Daniel Pomp, *University of North Carolina, Chapel Hill*

8:30 a.m. Advancing Risk Assessment with Population-based Experimental Resources

Weihshueh Chiu, *Texas A&M University*

9:00 a.m. Mixed Model and Meta-analysis Methods for G X E Analysis in Mouse Studies

Eleazar Eskin, *University of California, Los Angeles*

9:30 a.m. Computational Mapping Tools

Dan Gatti, *Jackson Laboratory*

10:00 a.m. Q&A

Session Five Disease Applications

Chair: Cheryl Marks, *National Cancer Institute*

10:30 a.m. Genetic Regulatory Variation and Environmental Response

David Aylor, *North Carolina State University*

11:00 a.m. Harnessing Diversity in the CC and DO Populations for the Study of Behavior

Elissa Chesler, *Jackson Laboratory*

11:30 a.m. Genetic Diversity in Ebola Response

Martin Ferris, *University of North Carolina, Chapel Hill*

12:00 p.m. Q&A

12:30 p.m. Lunch

Session Six Breakout Groups Highlighting Experimental Designs/Test Cases: Challenges and Opportunities for Utilizing These Population-based Rodent Resources

1:30 p.m. Initial Charge

Nigel Walker

1:45 p.m. Breakouts

(Note: Selected assignments below are attempting to distribute expertise among some of the invited speakers, chairs, and other confirmed researchers, but all other participants are invited to join in and contribute as well!)

Breakout Group One:

Co-chairs: Warren Casey, Terry Kavanagh

Heather Patisaul

Igor Pogribny

William Valdar

Mathew Pletcher

David Threadgill

Ivan Rusyn

Eleazar Eskin

David Aylor

Notetaker/Scribe: Rick Paules/Leroy Worth



1:45 p.m.

Breakouts *(continued)*

Breakout Group Two:

Co-chairs: Fernando Pardo Manuel de Villena, Paul Foster

Samir Kelada

Laura Saba

John Bucher

Gary Churchill

Cheryl Marks

Dan Gatti

Notetaker/Scribe: June Dunnick/Sri Nadadur

Breakout Group Three:

Co-chairs: Tim Wiltshire, Mike Devito

Jessica Mayeux

Brian Bennett

Arun Pandiri

Daniel Pomp

Brian Parks

Elissa Chesler

Jef French

Notetaker/Scribe: Dan Shaughnessy/Fred Tyson

Breakout Group Four:

Co-chairs: Jonathan Pollock, David Dix

Greg Crawford

Amelie Baud

Alison Harrill

Weihsueh Chiu

Byron Jones

Martin Ferris

Ted Choi

Boris Tabakoff

Notetaker/Scribe: Keith Shockley/Jonathan Hollander

2:45 p.m.

Prepare Report-back

3:00 p.m.

Report-backs by Co-chairs of Each Breakout Group (Approx. 10-15 minutes each)

4:00 p.m.

Final Wrap-up/General Recommendations of Next Steps

4:30 p.m.

Adjourn the Meeting

Poster List

1. ***Accounting for population structure in gene-by-environment interactions in genome-wide association studies using mixed models.*** Michael Bilow, UCLA Department of Computer Science
2. ***Baseline brain co-expression networks in the HXB/BXH recombinant inbred rat panel.*** Laura Saba, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus
3. ***Determining the interactive effects of maternal diet and genetic factors on germline epigenetic reprogramming.*** Jing Xue, Nutrition Research Institute, University of North Carolina at Chapel Hill, Kannapolis, North Carolina
4. ***Distinct genetic factors influence different stages of cancer development and progression.*** Kyle Halliwill, University of California, San Francisco
5. ***Diversity outbred mice indicate idiosyncratic drug-induced liver injury potential.*** Lascelles Lyn-Cook Jr., University of Arkansas for Medical Sciences
6. ***Efficient detection of trans-eQTL in a collaborative cross study.*** Wesley Crouse, University of North Carolina at Chapel Hill
7. ***Estimation of heritability from inbred mouse strains.*** Dat Duong, University of California, Los Angeles
8. ***Genetic determinants of cell state in mouse induced pluripotent stem cells.*** Tiffany Garbutt, North Carolina State University
9. ***Genetics basis of social effects – A pilot study on indirect genetic effects in laboratory mice.*** Amelie Baud, EMBL – European Bioinformatics Institute
10. ***Heterogeneity in quantum dot induced lung inflammation and toxicity in recombinant inbred mouse strains of the collaborative cross.*** David Scoville, University of Washington
11. ***Host genetic determinants of diversity in viral-induced disease pathology.*** Candice Brinkmeyer-Langford, Texas A&M University
12. ***Identification of causal genes for complex traits.*** Farhad Hormozdiari, University of California, Los Angeles
13. ***Identification of genetic regulators of the atherosclerosis-associated metabolite trimethylamine-n-oxide in the diversity outbred mice population.*** Brian Bennett, University of North Carolina at Chapel Hill
14. ***Susceptibility to multi-walled carbon nanotube-induced acute lung pathology varies with mouse strain.*** Megan Cartwright, University of Washington
15. ***Systems genetics approach uncovers Dusp7 as a novel phosphatase regulating skeletal muscle insulin signaling.*** Marcus Seldin, University of California, Los Angeles
16. ***Systems genetics of microbial abundance, host transcriptome, and disease in the collaborative cross.*** Jason Bubier, The Jackson Laboratory
17. ***The collaborative cross as a source of new models for human disease.*** Andrew Morgan, University of North Carolina at Chapel Hill
18. ***The effects of a high fat diet on male diversity outbred mice.*** Michael DeVito, National Institute of Environmental Health Sciences (Division of National Toxicology Program, National Toxicology Program Laboratory)
19. ***The Oncology Models Forum: A translational research collaborator.*** Cheryl Marks, National Cancer Institute
20. ***Using variation in micronucleus response to benzene exposure in diversity outbred (J:DO) mice to identify population-based exposure thresholds and genetic factors influencing genotoxicity.*** Kristine Witt, National Institute of Environmental Health Sciences/National Toxicology Program



Poster Abstracts

1. Accounting for population structure in gene-by-environment interactions in genome-wide association studies using mixed models

Presenting Author: Michael Bilow, University of California, Los Angeles (UCLA),
Department of Computer Science

Contributing Authors: Sul, J, Broad Institute
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He, D, UCLA
Eskin, E, UCLA

Abstract:

Although genome-wide association studies (GWASs) have discovered numerous novel genetic variants associated with many complex traits and diseases, those genetic variants typically explain only a small fraction of phenotypic variance. Factors that account for phenotypic variance include environmental factors and gene-by-environment interactions (GEIs). Recently, several studies have conducted genome-wide gene-by-environment association analyses and demonstrated important roles of GEIs in complex traits. One of the main challenges in these association studies is to control effects of population structure that may cause spurious associations. Many studies have analyzed how population structure influences statistics of genetic variants and developed several statistical approaches to correct for population structure. However, the impact of population structure on GEI statistics in GWASs has not been extensively studied and nor have there been methods designed to correct for population structure on GEI statistics. In this paper, we show both analytically and empirically that population structure may cause spurious GEIs and use both simulation and two GWAS datasets to support our finding. We propose a statistical approach based on mixed models to account for population structure on GEI statistics. We find that our approach effectively controls population structure on statistics for GEIs as well as for genetic variants.

2. Baseline brain co-expression networks in the HXB/BXH recombinant inbred rat panel

Presenting Author: Laura Saba, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus

Contributing Authors: Saba, L, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado
Hoffman, P, School of Medicine, University of Colorado
Tabakoff, B, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado

Abstract:

The brain is one of the most heterogeneous organs of the body. Although it is made up of many different cell types and brain regions, the complex communication and interactions between cells and regions in brain are responsible for the intricate response of this organ to environmental factors. Altered gene expression in one cell type or region is likely to cause a cascade of biological events that alter gene expression not only within that cell type or brain region, but across both cell types and brain regions. To capture the magnitude and the detail of these complex interactions, we have surveyed the brain transcriptome of 32 strains from the HXB/BXH recombinant inbred (RI) rat panel using high throughput RNA sequencing and identified co-expression networks that include both protein-coding and non-coding transcripts. This co-expression network serves as a 'basal', i.e., unchallenged, level of expression and connectivity in the brain. This network can be used to find 'predisposing factors' to a multitude of behavioral and physiological phenotypes by associating module expression with a quantitative phenotype. It can also be used to identify relationships among genes/transcripts that are altered after environmental exposure or as a result of genetic manipulation. To begin building this brain co-expression network, we quantified the expression of all ensembl transcripts in our RNA-Seq samples derived from ribosomal RNA-depleted total RNA. Using weighted gene co-expression analysis, we identified several hundred co-expression modules. In addition to characterizing modules based on standard network measures, we also examined their association with genetic variants in this RI panel to hypothesize about genetic controls of expression variation including microRNAs and transcription factors and their association with each other. These data and several other large RNA expression data sets from rodent RI panels are publically available at <http://phenogen.ucdenver.edu>. The data described here are part of a National Institutes of Health (NIH) resource grant that will continue to grow by including the addition of: 1) small RNA (e.g., microRNA, snoRNA), 2) biological replicates within strains (to generate accurate estimates of heritability of transcript expression), 3) eight common inbred rat strains, 4) liver RNA expression estimates from all strains, and 5) information on sex differences in brain expression. Supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (AA013162 and pilot grant from INIA-West Consortium).

3. Determining the interactive effects of maternal diet and genetic factors on germline epigenetic reprogramming

Presenting Author: Jing Xue, Nutrition Research Institute, University of North Carolina at Chapel Hill, Kannapolis, North Carolina

Contributing Authors: Ideraabdullah, F, Nutrition Research Institute, University of North Carolina at Chapel Hill, Kannapolis, North Carolina and Department of Genetics, Department of Nutrition, University of North Carolina at Chapel Hill.

Abstract:

In utero nutrition imposes a prominent effect on fetal development and contributes to risk of diseases in offspring throughout their life and potentially the life of the next generation. This is in part due to the fact that duration of maternal diet overlaps with somatic and germ cell development in the developing fetus, which requires major reprogramming of epigenetic landscapes. We propose that maternal nutrition perturbation alters germ cell epigenome during fetus development and that the vulnerability is determined by genetic factors. Collaborative cross (CC) inbred mouse lines were used for the purpose of characterizing the genetic and dietary components in determining individuals' epigenetic response to maternal nutrition. CC lines were chosen because they displayed increased genetic and phenotypic diversity, outperforming traditional inbred lines in mimicking human population. Reciprocal mating pairs from 20 CC lines were assigned to four diets (control, low protein, low vitamin D, and methyl donors supplemented) five weeks before mating, and F1 male progenies were switched to regular chow diet at weaning. Physical (body weight and fat mass) and reproductive (total sperm count, and testis weight, and histology) parameters were measured at age of eight weeks in F1 males. Data collected to date indicate a significant role of genetic and dietary factors on male reproductive function and germline development. Initial locus specific pyrosequencing on F1 sperm cells showed epigenetic changes on imprinted regions, and is followed by targeted next generation sequencing to look at global methylation changes in sperm cells. Heritability of affected traits and epigenetically perturbed loci will be investigated in F2 progenies. Oxidative stress markers (malonaldehyde and reactive oxygen species) in testis, plasma hormones (luteinizing hormone and testosterone), and fecundity rate for producing F2 progenies will be quantified to further characterize the fertility of F1 males. Genetic factors that contribute to differences in responsiveness to in utero nutrition will be characterized by functional single nucleotide polymorphism (SNP) present in key metabolism genes. The ultimate aim of the study is to elucidate genetic mechanisms that determine how maternal nutrition influences the male germline epigenome.

4. Distinct genetic factors influence different stages of cancer development and progression

Presenting Author: Kyle Halliwill, University of California, San Francisco

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Abstract:

Cancer is a constellation of diseases with multiple distinct phases. Typically, these phases include tumor initiation, promotion, progression, and metastasis. Each phase involves specific genetic and environmental alterations. Of these phases, metastasis is currently the least well understood, owing to ethical considerations in human patients as well as technical limitations. In order to gain insight on the genetic factors influencing each phase of tumor development, we have generated a genetically heterogeneous cohort of over 800 interspecific (Mus Spret x FVB/N) backcross mice and induced tumor development in the skin using the DMBA/TPA model. Using this cohort we have monitored benign tumor emergence, the progression of these lesions into malignancy, and finally the development of metastases. By comparing the underlying genetics of this cohort to the observed tumor susceptibilities we have been able to identify distinct genetic loci associated with tumor promotion, progression, and metastasis, showing that these phases are under separate genetic control. Further, using a systems biology approach we have been able to nominate candidate genes and gene expression networks associated with these phenotypes. The results from this experiment will improve our understanding of the genetics driving cancer development and progression. Further, these results have the potential to shed valuable insight into the process of metastasis, a critical and poorly understood phase of tumor development.

5. Diversity outbred mice indicate idiosyncratic drug-induced liver injury potential

Presenting Author: Lascelles Lyn-Cook Jr., University of Arkansas for Medical Sciences

Contributing Authors: Lyn-Cook Jr, L, University of Arkansas for Medical Sciences
Gatti, D, The Jackson Laboratory, Bar Harbor, Maine
Luo, S, University of Arkansas for Medical Sciences
Churchill, G, The Jackson Laboratory, Bar Harbor, Maine

Abstract:

Hepatotoxicity is a major cause of attrition during pharmaceutical development. While newer models have offered improvements in predicting incidence of common (high frequency) hepatotoxic events, the ability to detect idiosyncratic (low frequency) drug-induced liver injury (DILI) has remained elusive. While rodent models involving external or internal manipulation have enabled mechanistic study of certain drugs, there remains a need for an animal model that can detect rare (“idiosyncratic”) liver liabilities where the mode of action is unknown. A critical issue is that conventional models lack genetic diversity, which in several instances has been shown to play a role in adverse drug reactions. The Diversity Outbred (DO) mice comprise a genetically diverse population with variability that surpasses that of the human population, but in which the minor allele frequency is greater in the DO (12.5% on average). We hypothesized that the DO could provide a model for idiosyncratic DILI that occurs in patient populations. In this study, female DO mice (N=50/group) were administered orally one of three drugs associated with rare liver toxicity that are still used clinically (diclofenac, zileuton, isoniazid) or 0.5% methylcellulose vehicle. Mice were dosed (i.g.) daily up to 14 days and blood samples were taken before dosing and at necropsy. As a group, diclofenac and zileuton both caused significant elevations in alanine aminotransferase (ALT) from the pre-dose (baseline) values at necropsy ($P < 0.05$). ALT was not elevated by 0.5% methylcellulose ($P > 0.05$). Fold elevations in ALT ranged from 0.2-8.3 fold for diclofenac and from 0.2-13.6 fold for zileuton, and group mean-SEM for diclofenac and zileuton post-dosing were 82.8-7.3 U/L and 123.8-10.0 U/L, respectively, compared to 32.39-5.4 U/L in the vehicle group. MicroRNA-122 is by far the most abundant microRNA in the liver, and release into the blood along with ALT improves confidence of liver origin. As a group, zileuton and isoniazid both caused significant elevations in miR-122 fm quantification, in comparison to 0.5% methylcellulose ($P = 0.001$, $P = 0.025$) but not in diclofenac. Group mean \pm SEM for zileuton and isoniazid were 45.62 \pm 9.187 fm and 26.78 \pm 6.049 fm, respectively compared to 10.81 \pm 2.157 fm in the vehicle group. These data provide an important first step to qualifying the DO mouse population as a tool for improved prediction and understanding of rare drug safety liabilities.

6. Efficient detection of trans-eQTL in a collaborative cross study

Presenting Author: Wesley Crouse, University of North Carolina at Chapel Hill

Contributing Authors: Crouse, W, University of North Carolina at Chapel Hill
Valdar, W, University of North Carolina at Chapel Hill
Kelada, S, University of North Carolina at Chapel Hill

Abstract:

Genome-wide linkage (GWL) in a genetic reference population such as the collaborative cross (CC) or diversity outbred (DO) can be a useful method to detect quantitative trait loci (QTL), including QTL associated with responses to environmental exposures. QTL have a causal relationship with the phenotype of interest and provide insight into the genetic basis of phenotypic variation. When gene expression is used as the phenotype, GWL identifies expression QTL (eQTL) that can be proximal (cis-eQTL) or distal (trans-eQTL) to the gene. Trans-eQTL are thought to be more abundant in the context of an environmental perturbation and can provide information about biological pathways that mediate response to the exposure. Detecting trans-eQTL is difficult because their effects are generally weak, but accounting for the effects of cis-eQTL in a conditional framework may improve their detection. However, conditional analyses in multiparental crosses such as the CC or DO reduce statistical power because genetic effects are estimated for each founder haplotype rather than for a biallelic variant. This reduction in power makes it particularly challenging to model relationships that depend on more than one locus. This study presents a method for collapsing founder haplotypes into functional haplotypes at a QTL, reducing the number of model parameters that must be included in conditional analyses. The method identifies parsimonious groupings of the founder strains by estimating models using all possible subgroups of the founder haplotypes and selecting the model that minimizes the Bayesian Information Criterion. The resulting functional haplotype subgroups are then used as covariates in conditional analyses to detect trans-eQTL. This method is applied to microarray data from a model of environmentally-induced airway disease using the CC. We evaluate the utility of this approach and highlight biologically relevant examples.

7. Estimation of heritability from inbred mouse strains

Presenting Author: Dat Duong, University of California, Los Angeles

Contributing Authors: Duong, D, University of California, Los Angeles
Gai, L, University of California, Los Angeles
Eskin, E, University of California, Los Angeles

Abstract:

Over the past several years, in human studies, data from large genome wide association studies have been utilized to estimate the heritability of traits. These methods, utilizing mixed models, have been developed to estimate the heritability of traits from unrelated individuals. Direct application of these methods to inbred mouse studies entail several challenges. Typically, inbred mouse studies are a combination of genetically identical animals distributed among strains that have between themselves a complex genetic structure. In addition, inbred mouse datasets are typically smaller than human GWAS datasets. First, we test the robustness of a traditional mixed model for heritability on data from multiple inbred strains. We then extend the mixed model by accounting for SNP-SNP interactions, taking into account the complex genetic structure of inbred strains. We also explore methods to account for differences in variance between strains.

8. Genetic determinants of cell state in mouse induced pluripotent stem cells

Presenting Author: Tiffany Garbutt, North Carolina State University

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Department of Biological Sciences, College of Sciences

Aylor, A, North Carolina State University, Program in Genetics,
Department of Biological Sciences, College of Sciences

Threadgill, T, Texas A&M University, Department of Molecular and Cellular Medicine,
College of Medicine

Abstract:

Induced pluripotent stem cells (iPSCs) are derived by somatic reprogramming and have become a likely alternative to embryonic stem cells (ESCs) because of their potential for patient specific medicine and the insights they can provide on pluripotency regulation and cell fate determination. We generated iPSCs from the eight parental strains of the collaborative cross (CC) mouse genetic reference population, a genetically defined model system for investigating complex traits. Six of eight strains yielded ESC-like iPSCs. The NOD/ShLtJ (NOD) strain, a common model for human Type I diabetes, and the WSB/EiJ (WSB) strain were found to be non-permissive. Non-permissive mouse strains cannot form ESCs or iPSCs under standard conditions and instead form developmentally primed epiblast stem cell (EpiSC)-like colonies with limited differentiation potential. We generated fibroblast-derived ESC-like iPSCs from an F1 cross between NOD and the permissive 129S1/SvImJ strain, indicating that the EpiSC-like state is recessive to the ESC-like state. A complementation test revealed that the NOD and WSB EpiSC-like phenotypes do not complement. Using a glycogen synthase kinase 3 β inhibitor, a mitogen-activated protein kinase inhibitor, and varying treatment length, we derived ESC-like iPSCs from both the NOD and WSB strains. Immunofluorescence staining for the ESC marker PECAM1 and the EpiSC marker CD40 reveal that EpiSC-like iPSC colonies contain both ESC-like cells and EpiSC-like cells. Studies are underway using single cell analysis and RNA sequencing to characterize genomic differences between strains, cell states, and treatments to provide better insight into pluripotency and cell state regulation.

9. Genetics basis of social effects – A pilot study on indirect genetic effects in laboratory mice

Presenting Author: Amelie Baud, EMBL – European Bioinformatics Institute

Contributing Authors: Baud, A, EMBL – European Bioinformatics Institute
Mulligan, M, EMBL – European Bioinformatics Institute
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Abstract:

We explored the possibility that phenotypes of laboratory mice may be affected by the genotypes of the mice they interact with (their cage-mates). Such indirect genetic effects have been reported to affect growth in pigs¹ and plumage condition in hens² for example. We show that anxiety, growth, and wound healing but not general locomotor activity or helplessness of DBA/2J and C57BL/6J mice depend on the genotypes (strain) of their cage-mates. We also identify genes whose expression in the prefrontal cortex is affected by the genotypes of the cage-mates. We further investigate the mechanisms underlying indirect genetic effects on prodynorphin expression, which is most significantly affected by the genotypes of the cage-mates (p -value = $4.10 \cdot 10^{-6}$): prodynorphin has been associated with social fear and social conflict, yet none of the 20 measures collected to assess social status and aggression in our experiment explains variation in prodynorphin expression as well as the genotypes of the cage-mates do. This result suggests that identifying the genes and pathways underlying these indirect genetic effects could improve our understanding of how cage-mates affect each other. Our results bring to light an understudied component of phenotypic variation and introduce a promising approach to investigate effects of the social environment on phenotypes of biomedical interest and intermediate molecular traits.

10. Heterogeneity in quantum dot induced lung inflammation and toxicity in recombinant inbred mouse strains of the collaborative cross

Presenting Author: David Scoville, University of Washington

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Kelada, S, University of Washington
Kavanagh, T, University of Washington
Kosyk, O, University of North Carolina
Rusyn, I, University of North Carolina

Abstract:

Quantum dots (QDs) are engineered nanoparticles commonly composed of a CdSe/ZnS core/shell and outer coatings specific to their potential use in electronics, research, and medicine. However, their small size and heavy metal composition has generated concerns regarding their toxicity. Nanoparticle toxicity is composition and coating dependent, and it would be impractical to do comprehensive mechanistic studies on all nanoparticle formulations. Thus we propose that systems genetics could be useful for efficiently identifying genes and pathways associated with nanoparticle toxicity, and prioritizing them for further mechanistic interrogation. The collaborative cross (CC) is an excellent resource for carrying out such systems genetics-based studies. In prior work, we found that the eight inbred founder strains of the CC varied widely in their susceptibility to QD-induced lung inflammation and toxicity. Since the RI strains are unique combinations of the founder genomes and because of the polygenic nature of the inflammatory response, we hypothesized that the RI strains would also vary in their susceptibility, and that we might observe phenotypes that were outside the range of those present in the eight founder strains. We observed significant heterogeneity among 12 RI strains of the CC in biomarkers of QD-induced lung inflammation eight hours after oropharyngeal aspiration. These included the percentage of neutrophils, the levels of total protein, and levels of lactate dehydrogenase (LDH) in bronchoalveolar lavage fluid (BALF). Lung tissue heme oxygenase (HMOX1) levels also varied by strain and were weakly but significantly correlated with lung tissue glutathione (GSH) levels. For some of the RI strains, BALF protein levels and percent neutrophils were outside the range of the founder strains. Interestingly, lung tissue GSH levels varied less among the RI strains, than among the eight CC founder strains. Our findings support future systems genetics studies using genotype, phenotype, and gene expression data, in which we will hopefully identify candidate susceptibility genes. Measuring the transcriptome of the RI strains using RNA-Seq is currently in progress. This study will provide insights into mechanisms of QD related toxicity, help to identify biomarkers of susceptibility, and ultimately provide information for the design of safer engineered nanomaterials. Supported by NIEHS grants U19ES019545, P30ES007033, and T32ES007032.

11. Host genetic determinants of diversity in viral-induced disease pathology

Presenting Author: Candice Brinkmeyer-Langford, Texas A&M University

Contributing Authors: Brinkmeyer-Langford, C, Department of Veterinary Integrative Biosciences, Texas A&M University

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Welsh, C, Department of Veterinary Integrative Biosciences, Texas A&M University

Abstract:

Infection by a specific virus can cause diverse outcomes and disease pathologies, influenced by the genetic background of the host. In mice, Theiler's murine encephalomyelitis virus (TMEV) infection leads to heterogeneous neurological conditions, depending on the mouse strain infected. Because of the relevance of TMEV infection as a tool for studying virally-influenced neurological conditions in humans, there is a critical need to determine genetic variants and their mechanisms that link TMEV infection to disease outcome. Our objective is to determine how genetic background influences disease diversity following TMEV infection. Our central hypothesis is that genetic background, as modeled by a new population-based mouse resource called the collaborative cross (CC), will differentially modify susceptibility to TMEV-induced diseases based upon genetic polymorphisms. We have performed a pilot study to demonstrate phenotypic variation in different CC strains in response to TMEV infection. For this, we infected six female and three male four-week-old mice from three different CC lines with 5.0×10^4 plaque-forming units (PFU) of the moderately virulent BeAn strain of TMEV in 20 μ l of PBS, via intracerebral injection. Daily or weekly measurements of TMEV-induced sickness included weight, seizure activity, hind limb impairment, foot print analysis, and rotarod. Age- and gender-matched uninfected mice from the same CC strain were used as controls. For all measures, we observed marked phenotypic variation among CC lines. Within three days post-infection, all infected CC013 and CC016 mice experienced seizures. CC041 mice did not develop seizures, but all infected CC041 mice presented with hind limb impairment at 10 days post-infection (p.i.) similar to poliomyelitis or ALS. By 10 days p.i. seizures had ceased in CC013 and CC016 mice but all infected CC013 mice displayed decreased grip strength in the front paws while all infected CC016 mice exhibited tremors. We noted encephalitis as well as sickness behaviors, including piloerection and hunched posture, in infected CC041 and CC013 mice. The condition of the CC041 mice stabilized to the extent that we were able to observe periods of improvement followed by periods of deterioration in health status and hind limb impairment. Our future plans include performing RNA sequencing and QTL analyses to test the hypothesis that genomic diversity within CC mice influences variable disease phenotypes. The results of these experiments will increase our understanding of the genetic determinants responsible for phenotypic diversity following TMEV infection using the CC population of mice. These findings are expected to constitute an early step in a continuum of research that will ultimately lead to the development of predictive models for the prevention or treatment of virally-influenced complex conditions in humans.

12. Identification of causal genes for complex traits

Presenting Author: Farhad Hormozdiari, University of California, Los Angeles

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Abstract:

Although genome-wide association studies (GWAS) have identified thousands of variants associated with common diseases and complex traits, only a handful of these variants are validated to be causal. We consider “causal variant(s)” as variant(s) which are responsible for the association signal at a locus. As opposed to association studies that benefit from linkage disequilibrium (LD), the main challenge in identifying causal variants at associated loci lies in distinguishing among the many closely correlated variants due to LD. This is particularly important for model organisms such as inbred mice, where LD extends much further than in human populations, resulting in large stretches of the genome with significantly associated variants. Furthermore, these model organisms are highly structured, and require correction for population structure to remove potential spurious associations. In this work, we propose CAVIAR-Gene, a novel method that is able to operate across large LD regions of the genome while also correcting for population structure. A key feature of our approach is that it provides as output a minimally sized set of genes that captures the true causal gene with probability p . Through extensive simulations we demonstrate that our method not only speeds up computation, but also outperforms commonly used approaches by an average of 10 percent. We validate our method using a real mouse high density lipoprotein data (HDL) and show that CAVIAR-Gene is able to identify *Apoa2* (a known causal gene for HDL), while reducing the number of genes that need to be tested for functionality by a factor of two.

13. Identification of genetic regulators of the atherosclerosis-associated metabolite trimethylamine-n-oxide in the diversity outbred mice population

Presenting Author: Brian Bennett, University of North Carolina at Chapel Hill

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Abstract:

Dietary choline and its derivatives have been associated with various aspects of lipid metabolism. Recently, the choline metabolite trimethylamine-N-oxide (TMAO) has been associated with atherosclerosis in both mice and humans. Traditional studies of atherosclerosis in mice use genetic or dietary manipulation to induce atherosclerosis in inbred mouse strains. However, traditional quantitative trait locus (QTL) mapping studies using inbred strains often identify large genomic regions, containing many genes, due to limited recombination and/or sample size which hamper candidate gene identification and translation of these results into possible risk factors and therapeutic targets. As an alternative approach, here we use the multi-parental diversity outbred (DO) mouse panel for genetic mapping in order to aid in the identification of causal genes and variants associated with TMAO and its precursor choline. We fed DO mice either a high-fat, cholesterol-containing (HFCA) diet or a low-fat, high-protein diet for 18 weeks and measured circulating metabolites at baseline and after diet. Among our highly significant loci, we detected a 4.6 Mb QTL interval on chromosome 12 (LOD = 10.0, $p < 0.05$) associated with plasma concentrations of the metabolite trimethylamine-N-oxide at baseline, containing 116 genes; the same QTL was also identified after dietary treatment (LOD= 6.7, $p < 0.1$). By using a database of mouse gene expression and measuring gene expression in the eight progenitor strains by RNA-sequencing, we identified three potential candidate genes, including the positional candidate gene *numb*, which encodes a clathrin adapter with a role in endocytosis that was recently shown to modulate intestinal cholesterol absorption. We show that TMAO and *numb* exhibit inverse strain variation across the DO founder strains and that the novel chromosome 12 TMAO locus co-localizes with a highly significant cis-expression QTL for *numb*, indicating a potential functional relationship.

14. Susceptibility to multi-walled carbon nanotube-induced acute lung pathology varies with mouse strain

Presenting Author: Megan Cartwright, University of Washington

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Abstract:

Multi-walled carbon nanotubes (MWCNTs) are concentric cylinders of graphene which possess useful industrial properties as well as potential human respiratory toxicities. To model how human genetic variation may alter susceptibility to these potential respiratory toxicities, we have examined variations in susceptibility to MWCNTs across six genetically-diverse inbred mouse strains selected from the collaborative cross: A/J; C57BL/6J; NOD/ShiLtJ; NZO/HiLtJ; 129SvImJ; and WSB/EiJ. Eight-week-old male mice from each strain were exposed via oropharyngeal aspiration to vehicle or 25 µg/mouse of a non-functionalized, unpurified MWCNT, and sacrificed after 24 hours. We observed significant neutrophil influx in A/J and WSB/EiJ; a trend of increased influx in the C57BL/6J and NZO/ShiLtJ; and non-significant influx in NOD/ShiLtJ and 129SvImJ. We also observed strain-dependent up-regulation of cell and oxidative stress proteins heme oxygenase-1 and glutamate cysteine ligase subunits in lung tissue. At this dose, we did not observe signs of severe lung toxicity, as would be indicated by an elevation of total protein and acellular lactate dehydrogenase in bronchoalveolar lavage fluid (BALF), nor were there indications of severe oxidative stress, as indicated by altered levels of total glutathione in lung tissue or BALF. Our data show (1) that susceptibility to MWCNT-induced acute lung pathology varies with mouse strain, indicating that genetic variation in humans may similarly alter susceptibility; and (2) that the common use of the C57BL/6 strain may underestimate the pathological effects of MWCNT respiratory exposure. Supported by NIH Grants U19ES019545, P30ES007033, U19ES019544; and NSF grants CBET-0932885 and DGE-0718124.

15. Systems genetics approach uncovers Dusp7 as a novel phosphatase regulating skeletal muscle insulin signaling

Presenting Author: Marcus Seldin, University of California, Los Angeles

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Abstract:

As the largest organ inside the human body, skeletal muscle exists as a crucial regulator of many physiologic processes. Among many other roles, it accounts for a majority of nutrient breakdown for energy production and thus, maintenance of whole-body metabolism. To further study the physiologic and metabolic contribution of this vital organ, we subjected 109 strains of mice within the hybrid mouse diversity panel (HMDP) to a high fat/high sucrose diet and observed significant variation in circulating glucose, insulin and HOMA-IR. These important physiologic parameters were then compared to global skeletal muscle gene expression using microarrays in the same cohort of HMDP mice. This approach uncovered Dusp7 muscle expression as showing the strongest correlation with HOMA-IR ($r=0.399$, $p=2.21 \times 10^{-5}$). The Dusp7 gene encodes a dual specificity phosphatase to which very little functional implications have been tied. Follow up studies demonstrate Dusp7 mRNA in skeletal muscle can be significantly induced by glucose, independent of insulin both in vitro and in vivo. Using siRNA-mediated knock-down in C2C12 mouse myotubes, we show a ~50 percent reduction of Dusp7 expression markedly enhances the capacity of insulin to activate its intracellular signaling cascade. More specifically, knock-down cells treated with insulin for 1-4 hours showed prolonged phosphorylation of key activating residues on insulin receptor substrate 1 (IRS1), phosphoinositide-dependent kinase 1 (PDK1) and protein kinase B (Akt). We then test the capacity of insulin treatment to engage expression of downstream target genes in control and knock-down cells. In control cells, insulin treatment enhanced expression of central regulators of muscle metabolism carbohydrate-responsive element binding protein (ChREBP), glucose transporter 4 (GLUT4), glycogen synthase (GS) and insulin receptor (IR) to a significant but modest degree. Comparably, in Dusp7 knock-down cells, insulin elicited a striking capacity (10-100 fold) to induce the same genes. Our data demonstrates how the HMDP was used to identify Dusp7 as a key phosphatase regulating signaling and downstream consequences of insulin action in skeletal muscle.

16. Systems genetics of microbial abundance, host transcriptome, and disease in the collaborative cross

Presenting Author: Jason Bubier, The Jackson Laboratory

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Abstract:

The collaborative cross mouse genetic reference population presents a novel system in which naturally occurring host polymorphisms, transcriptional variation, naturally occurring microflora and phenotypic diversity can be dissected to understand the role of microflora in health and disease. We employed a systems genetics approach to harness genetic variation to discover relations among diverse phenotypes, microbiomes, and the host intestinal microenvironment. Using mice from generation G2:F5-G2:F8 of the CC breeding population at ORNL, we collected cecal luminal contents, cecal tissue, and phenotypic information for physiological, anatomical, and behavioral measures on approximately 200 mice from 100 strains. 16S sequencing of the cecal contents enabled us to identify and characterize the microbiome, and correlate these values with transcriptomic measures from the host tissue in direct contact with the cecal contents. These data provide several paths to investigate the role of microflora in health and disease, starting from host genetic variation, disease associated transcriptional variation, disease associated microflora, or phenotypic assays of disease related traits. We mapped 18 statistically significant microbial abundance QTL and expression QTLs, including some previously implicated in human disease. The overlap of expression QTL and microbial QTL identify transcripts associated with the role of microflora in disease, potentially providing insight into the host mechanisms of action of the microbe. Microbial abundance and transcripts were clustered using combinatorial algorithms to identify co-abundant microbes and transcripts, which can be used across species to identify candidate microflora for the study of intestinal disease. The correlation of phenotypes and microbe abundance, identified disease associated microbes. Simultaneous systems genetic analysis of host and microbe provides diverse insights into the interplay of gut microflora with host genetic variants, genomic mechanisms, and disease traits.

17. The collaborative cross as a source of new models for human disease

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Abstract:

The collaborative cross (CC) was originally conceived as a platform for genetic analysis which would maximize both genetic and phenotypic diversity across a set of recombinant inbred lines. When extreme phenotypes overlap with a disease state, CC lines also constitute new, reproducible disease models. Over the past two years, CC lines have been identified which are susceptible to inflammatory bowel disease (CC011/Unc and OR559), bronchiectasis (CC017/Unc) and Ebola haemorrhagic fever (CC001/Unc x CC017/Unc). These extreme phenotypes are overwhelmingly associated with trans-subspecies epistasis: the fixation of alleles from different subspecies at two loci within the genome of a single CC line. The vast majority of these combinations are completely novel; they have not been observed in 100 classical inbred strains and are extremely unlikely to occur in the wild. Trans-subspecies epistasis cannot be observed – or, importantly, replicated – in any mouse resource other than the CC. Within the CC it is pervasive and likely underlies both the widespread extinction during the inbreeding process and the prevalence of extreme phenotypes in this population.

18. The effects of a high fat diet on male diversity outbred mice

Presenting Author: Michael DeVito, National Institute of Environmental Health Sciences (NIEHS), Division of National Toxicology Program (DNTP), National Toxicology Program Laboratory (NTPL)

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Abstract:

The effects of a high fat diet on male diversity outbred mice were evaluated after 14 weeks on the diet. Mice were fed ad libitum, except during designated fasting periods, either a control diet (10 kcal percent fat; D12450J) or a high fat diet (60 kcal percent; D12492) (Research Diets, New Brunswick, New Jersey) at the start of the study. Serum insulin and leptin were determined one week prior to the start of the study and at week 14 at terminal sacrifice. Blood glucose was measured one week prior to the start of the study and during weeks five, nine, and 14 using a blood glucose monitoring system meter (AlphaTRAK 2). At termination, body, liver, brain, kidney, testes, and epididymis were weighed. Epididymal sperm motility and concentration parameters were measured by computer-assisted sperm analysis (CASA, Hamilton-Thorne, Beverly, MA) per National Toxicology Program (NTP) specifications. Upon arrival, mice weighed approximately 23.6 ± 2.9 g. The range of body weights is consistent with the NTP specifications for body weights at the start of a study. After 14 weeks, mice on the high fat diet weighed approximately 30 percent more than animals on the control diet (43.8 g vs 33.2 g, respectively). Mice on the high fat diet gained more than twice as much weight as the controls (20.2 g vs 9.7g, respectively). Approximately one-fourth of the mice on the high fat diet had blood glucose levels equivalent to the controls and approximately one-fourth of the mice had blood glucose levels twice the controls. Serum insulin and leptin concentrations increased over the course of the study, with greater increases observed in animals on the high fat diet. The distribution of insulin concentrations were skewed at the high end with approximately 10 percent of the animals showing high insulin concentrations at the end of the study. This phenomenon was less pronounced with serum leptin. The most striking observation in the present study was the 70 fold range in sperm counts in the diversity outbred mice. In comparison, at the NTP, sperm count varies no more than two-fold within a study in the B6C3F1 mice. Of note is that approximately one-fourth of the mice on the high fat diet did not respond with changes in body weight or clinical chemistry different from the controls and approximately 10 percent of the control animals did not differ from the mice that responded to the high fat diet. This study demonstrated that for some endpoints the DO mice vary greatly, while other endpoints the variance is similar to the B6C3F1 mouse used by the NTP.

19. The Oncology Models Forum: A translational research collaboratory

Presenting Author: Cheryl Marks, National Cancer Institute

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Abstract:

From 1999 to 2014, the National Cancer Institute (NCI) supported a research consortium to generate mouse disease models. From it, the NCI found that community-wide expertise is required to meet the needs of the translational research community for well-validated, credentialed animal models. The NCI considered effective ways to work with the oncology research and clinical communities to debate, test, refine, and disseminate solutions for issues that confound translational animal model use. One tactic useful to various communities of science is a collaboratory environment. A collaboratory is defined as “a research center without walls,” an Internet communication locus for cross-pollination of ideas, collaborative research, data and tool sharing, community building, and open global debate. All oncology stakeholder communities favor the NCI’s decision to form an open, Internet-accessible, animal models forum for cancer research; successful translational research support for precision medicine requires cross-cutting expertise that may not reside in a single institution, or even in the U.S., and is a dynamic process of matching expertise to evolving clinical challenges. The NCI established NCIP Hub using HUBzero® open source informatics as the collaboratory environment. HUBzero,® hosted at Purdue University, sustains many cross-cutting activities within the U.S. and internationally. The Oncology Models Forum collaboratory will enable community-building centered on reliable ways to make and use animal models, consensus about a wide range of necessary resources, community-based evolution of best practices, standards, educational materials, and informatics, and, connections among individuals, teams, and institutions engaged in cancer research. The NCI envisions that the forum will evolve to a dynamic knowledge base to sustain the international oncology research community’s need for up-to-date information that informs selection and use of appropriate, reliable animal models for all facets of oncology research. Of equal importance is the capacity of the forum site to enable real-time global collaborations, and to capture in significant detail the workflow of collaborative or individual projects. Forum users can publish all research project details as digital object identifiers (DOIs) to share through the forum site and include as references in print and on-line journal articles. The detailed DOIs may be an important tool to improve research reproducibility.

20. Using variation in micronucleus response to benzene exposure in diversity outbred (J:DO) mice to identify population-based exposure thresholds and genetic factors influencing genotoxicity

Presenting Author: Kristine Witt, National Institute of Environmental Health Sciences (NIEHS), Division of National Toxicology Program (DNTP)

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Abstract:

Exposure-related toxicity and associated disease prevalence may be influenced by variations in complex exposures and by genetic variation within a population. To better understand the impact of inter-individual genetic variation, we evaluated the diversity outbred (DO) mice as a tool for exposure threshold assessment and identification of genetic factors that determine susceptibility to chemical-induced genotoxicity. Benzene – a ubiquitous carcinogen that is hematotoxic, genotoxic, and tumorigenic to humans and rodents – was selected as the stressor. We exposed male DO mice to benzene (0, 1, 10, or 100 ppm; 75 mice/exposure group) via inhalation for 28 days (6 hr/day, 5 days/week) and repeated the study using two independent cohorts of 300 mice. To assess genotoxicity, we measured the frequency of micronucleated reticulocytes in peripheral blood before and after 28 days of exposure, and in bone marrow at the end of the exposure period, and applied benchmark concentration modeling to estimate a population level point of departure. Micronuclei are biomarkers of chromosome damage arising through breakage or whole chromosome loss during mitosis. We observed a dose-dependent increase in benzene-induced chromosomal damage and estimated a benchmark concentration limit of 0.205 ppm benzene for DO mice. In isogenic B6C3F1 mice, the BMCL estimate is ~18X greater (3.66 ppm benzene). We performed linkage analysis and identified a locus on Chr 10 (31.87 Mb) encompassing two sulfotransferase genes. Over-expression of these genes was correlated with suppression of benzene-induced genotoxicity in the 100 ppm exposure group. In this study, DO mice displayed wide inter-individual variation in response to benzene-induced genotoxicity, more accurately reflecting the range of response observed in human populations. Importantly, replication of the study using two independent cohorts demonstrated a highly reproducible response to benzene exposure across the DO mouse population.



Presentation Abstracts

David Aylor

North Carolina State University

“Genetic Regulatory Variation and Environmental Response”

Gene expression differences between individuals explain a substantial portion of trait and diseases differences, and genetic variants that regulate gene expression are therefore very important for complex traits and environmental response. We identified open chromatin regions in embryonic fibroblasts (MEFs) from eight inbred mouse strains using DNaseI hypersensitivity. A substantial portion of these DNaseI peaks varied between inbred strains, and we related these putative gene regulatory regions to previous eQTL results from the collaborative cross (CC). In addition, we will present new gene expression results from our study on differential susceptibility to diethylstilbestrol (DES) exposure.

Elissa Chesler

Jackson Laboratory

“Harnessing Diversity in the Collaborative Cross and Diversity Outbred Populations for the Study of Behavior”

The collaborative cross (CC) and diversity outbred (DO) populations present new opportunities for genetic analysis of brain and behavior. Conventional populations of laboratory mice have been bred and collected over many centuries, under substantial human intervention. It has long been acknowledged that the commonly used laboratory population had various selection pressures for behavioral and skin phenotypes which share ontogeny with behavioral and neurological systems. The result has been lower phenotypic and genetic diversity leading to restriction of behavioral variation and trait co-variation. Early results in this population show increased behavioral variation, increased co-variation, increased precision for genetic mapping of behavior and increased resolution of molecular networks. These properties will enable the use of the CC and DO populations to precisely identify traits with common biological substrates and to reconstruct those networks from allelic variation through molecular and behavioral mechanisms. The high-precision and high-diversity populations enable improved applications in behavioral disorders, behavioral toxicology, age related neurological decline, substance abuse, and alcohol related traits. Supported by DA037927, GM076468.

Weihshueh Chiu

Texas A&M University

“Advancing Risk Assessment with Population-based Experimental Resources”

The advent of population-based experimental models, such as the rodent resources discussed at this meeting, offers an opportunity to advance human health risk assessment in three key areas: (1) The identification of potential toxic hazards and susceptible populations, (2) the evaluation of mechanisms of toxicity, and (3) the characterization of dose-response relationships. For instance, by testing a broader range of genetic backgrounds, toxicity evaluated in a population-based model can potentially reduce both false positive and false negative signals due to idiosyncrasies of individual inbred strains. Furthermore, the availability of genetic mapping allows for the identification of key biological pathways that may be involved in toxicity and/or susceptibility, potentially increasing confidence in how rodent data are extrapolated to humans. Finally, probabilistic statistical approaches can be applied to population-based toxicity data to quantitatively estimate the degree of toxicokinetic/toxicodynamic variability that may be expected in humans, potentially replacing the generic 10-fold human variability factor with chemical-specific factors for different quantiles of the population.

Ted Choi

Predictive Biology, Inc.

"A Diversity Outbred ES Cell Platform for In Vitro Genetics"

To address the cost and scale limitations of complex trait mapping in animals, we are building an in vitro genetics platform using a panel of 1000 embryonic stem cell lines established from diversity outbred mice. Genetic mapping of toxicant response with DO ES cells presents unique opportunities as well as challenges, and progress toward in vitro screens for cytotoxicity, cardiotoxicity, and neurotoxicity will be presented.

Gary Chruchill

Jackson Laboratory

"Diversity Outbred"

The diversity outbred (DO) population is a heterogeneous stock of mice derived from eight genetically diverse founder strains. DO mice display a broad range of phenotypes; they also present new analytical challenges. We will discuss study design and analytical techniques for DO mice. There are many parallels with human association mapping but also considerable new features that are unique to this model system. The availability of the collaborative cross – inbred strains derived from the same eight founders – provides a resource for independent validation of findings from the DO and presents new opportunities to advance our understanding of human health using the mouse as a model system.

Eleazar Eskin

University of California, Los Angeles

"Mixed Model and Meta-analysis Methods for G X E Analysis in Mouse Studies"

Neither genetics nor environment are solely responsible for producing individual variation, and virtually all traits show gene-environment interactions, the phenotypic effect of interactions between genes and the environment. Methods for detecting gene-by-environment (GxE) interactions in genome-wide association studies (GWASs) datasets are now becoming of major interest in the genetic community. In this talk, I will describe two classes of methods for discovery of GxE interactions. The class of methods are mixed-model methods extending our previous work on mixed models such as the EMMA algorithm. The second class of methods are meta-analysis methods which exploit the relationship between heterogeneity of effect sizes which can be discovered with random-effects meta-analysis and GxE interactions.

Martin Ferris

University of North Carolina at Chapel Hill

"Genetic Diversity in Ebola Response and Immune System Profiles"

Despite ongoing concerns with the emergence and severity of Ebola virus disease, current small animal models fail to recapitulate many aspects of this disease. We investigated the role of host genetic variation on Ebola virus disease by utilizing F1 animals generated from the collaborative cross panel. These animals showed a wide range of Ebola virus disease phenotypes, including resistance, hemorrhage, and hepatic involvement, unlike classical small animal models. Furthermore, study of these F1 crosses across a range of pathogens and immune assays shows a widespread role of host genetic variation on driving immune and viral-disease induced responses.

John French

National Institute of Environmental Health Sciences

"Identifying G X E Interactions and Thresholds for Toxicity in Diversity Outbred Mice"

Research models based upon intrinsic (e.g., genetic variation) and extrinsic (e.g., toxic exposures) factors are critical to identifying and characterizing presumptive risk of chemical exposures to humans. Using diversity outbred (DO) mice, we were able to derive population-based benchmark concentration level (BMCL) estimates and haplotypes associated with a significant range of susceptibility or resistance to benzene genotoxicity. Specifically, we identified a dominant quantitative-trait locus containing two phenol sulfotransferases associated with high levels of expression and resistance to benzene genotoxicity. These results indicate that DO mice have the potential to improve hazard identification and characterization, provide population-based estimates for BMCL exposure thresholds for toxicity, and identify quantitative-trait loci that can guide research to establish mechanisms of action to improve across species extrapolation in risk assessment.

Dan Gatti

Jackson Laboratory

"Computational Mapping Tools"

The use of complex crosses involves several computational challenges, including haplotype reconstruction and genetic mapping methods. Gatti will present an overview of the pipelines that we use for haplotype reconstruction in the mouse as well as a variety of mapping tools that have become available in the past several years.

Alison Harrill

University of Arkansas for Medical Sciences

"Mouse Populations Enable Translational Pharmacogenomic Approaches for Understanding and Predicting Adverse Drug Events"

Accurate prediction of adverse drug reactions continues to pose a risk toward patients and contributes to increasing development costs of new pharmaceuticals. Genetics plays an important, yet underappreciated role in adverse drug responses and current models largely fail to accurately model genetic variation that is present in human populations. Data will be presented demonstrating that mouse population based models, such as the diversity outbred mice, may provide a more accurate predictive tool for detecting adverse drug reactions. Also presented will be data subsequently collected using systems biology (omics) approaches following detection of sensitive and resistant individuals that enable mechanistic insight into toxicity susceptibility. Such approaches may improve estimates of risk toward patient populations, as well as enabling development of co-diagnostic pharmacogenetic tests that inform personalized prescribing.

Brian Parks

University of California, Los Angeles

"The Hybrid Mouse Diversity Panel"

The Hybrid Mouse Diversity Panel (HMDP) is a renewable mouse population ideal for systems genetics and dissection of complex biological traits. The HMDP has been successfully used to identify novel genes influencing disease and dissect biological pathways. This presentation will highlight the diverse applications of the HMDP and overview our efforts in systems genetics.

Ivan Rusyn

Texas A&M University

"Fit-For-Purpose," Population Study Designs to Address Specific Hypotheses

Estimation of the degree of inter-individual variability in the population is a required step in assessment of human health hazards from environmental chemicals. Several genetically-diverse experimental model systems are now available to address this need. Mouse populations, such as collaborative cross, provide an excellent testing system for evaluation of the complexities in toxicokinetics and toxicodynamics. The availability of the genetically-diverse, genetically-defined, renewable source of human cells enables in vitro toxicity testing at the population scale. While the diversity of the population-based models creates opportunities to characterize susceptibility and variability with real data, the researchers and regulators need to pay special attention to problem formulation step in both study design and decision-making to make sure that the data fits the purpose of a particular human health-related evaluation.

Boris Tabakoff

Texas A&M University

"Recombinant Inbred Rats: Genetics, Transcriptomes, and Use for Identifying Phenotypic Determinants"

The rat has been a favorite animal for pre-clinical studies of biochemical, physiologic, pharmacologic, and toxicologic phenomena. A gap in knowledge existed regarding the rat genome in comparison to mouse and man, but this gap has been rapidly disappearing. We, and others, have produced genomic information for a large number of inbred and recombinant inbred rat strains. Using this information, we quantitated the transcriptome of rat brain, heart, and liver using exon arrays. More recently we completed total brain RNA sequencing of 30 strains of the HXB/BXH recombinant inbred (RI) rats, we have reconstructed the transcriptomes, and have utilized the quantitative information for Weighted Gene Coexpression Network Analysis (WGCNA) to develop a topography of brain transcript networks. Our aim is, to create from this data, and data we are collecting from an additional 30 inbred strains of rats, the steady state transcriptional "connectome" within the organs listed above. Using the data we have already collected and analyzed, we will demonstrate how the calculated brain networks can be used for exploring toxicologic processes, starting with a toxin such as lead and one of its targets, and generating information on how perturbation of this target for lead may be transmitted to a network of transcripts coding proteins important for neural development, synaptogenesis (particularly for GABA neurons), and retinal cell development. This network is a logical candidate for the pathologies seen in adults and possibly children exposed to lead. We will also show how, starting with a quantitative behavioral phenotype of alcohol consumption, one can use QTL analysis of phenotype and module eigengene values, together with correlation analysis, to extract information on transcriptional networks predisposing low or high ethanol preference. All data and data analysis tools for this presentation and much additional data on the rat transcriptomes is available on <http://Phenogen.ucdenver.edu>. Supported by NIAAA 5R24 AA13162.

David Threadgill

University of Colorado School of Medicine

"The Collaborative Cross Genetic Reference Population: Past, Present and Future"

The collaborative cross was originally designed to support quantitative genetics but has evolved to be the systems genetics platform of choice. The structure of the population is ideally suited to support integrative analysis across labs and over time. Examples of how the population has and can be used to support integrative genetic analyses will be presented.



Biographies

David Aylor
North Carolina State University

David Aylor is assistant professor of biological sciences at North Carolina State University. The Aylor Lab's core goal is to identify genetic variants that influence complex traits, genome function, and environmental response. Aylor's scientific work has been focused on developing new systems genetics approaches to accomplish that goal. Systems genetics integrates modern high-throughput molecular biology with classical complex trait analysis by considering molecular profiles (such as mRNA abundance) alongside clinical and developmental traits. This approach relies on experimental populations that maximize diversity and statistical power – such as the mouse collaborative cross (CC). Aylor was a key member of the team that executed the initial genotyping and genetic analysis in the CC lines. Current projects in the Aylor Lab focus on genetic and environmental control of reproduction in the CC and other inbred mouse strains. The lab uses cell-based systems to dissect how genetic variants affect gene regulation and expression. These projects have the potential to reveal the genetic causes and the molecular mechanisms of gene regulation, reproductive trait variation, and disease.

Linda Birnbaum
National Institute of Environmental Health Sciences

Linda Birnbaum, Ph.D., D.A.B.T., A.T.S., is the director of the National Institute of Environmental Health Sciences, National Institutes of Health, and the National Toxicology Program.

A board certified toxicologist, Birnbaum has served as a federal scientist for over 34 years. Birnbaum has received many awards and recognitions, including the Women in Toxicology Elsevier Mentoring Award, the Society of Toxicology Public Communications Award, Environmental Protection Agency's (EPA) Health Science Achievement Award and Diversity Leadership Award, the National Center for Women's 2012 Health Policy Hero Award, Breast Cancer Fund Heroes Award, and 14 Science and Technology Achievement Awards, which reflect the recommendations of EPA's external Science Advisory Board, for specific publications. Birnbaum was also elected to the Institute of Medicine of the National Academies, and received an honorary degree from Ben-Gurion University in Israel.

Birnbaum is a former president of the Society of Toxicology, the largest professional organization of toxicologists in the world; former chair of the Division of Toxicology at the American Society of Pharmacology and Therapeutics; and former vice president of the American Aging Association. She is the author of more than 700 peer-reviewed publications, book chapters, and reports. She is also an adjunct professor at several universities, including the University of North Carolina at Chapel Hill and Duke University.

A native of New Jersey, Birnbaum received her master's degree and doctorate in microbiology from the University of Illinois at Urbana-Champaign.

Elissa Chesler
Jackson Laboratory

Elissa Chesler has been working in complex trait analysis since her graduate studies. Her research emphasizes the development and application of methodological approaches in genetics, genomics, and informatics to the unique challenges presented by behavioral science, including trait heterogeneity, laboratory environmental influences, sex differences, and the challenge of classification of behavioral traits and psychiatric disorders. Her early contributions to systems genetics include the first genetic analysis of mammalian brain gene expression, gene-phenotype network analysis, and the design of many features of the widely used systems genetics platform, GeneNetwork.org. She is the former leader of the Systems Genetics Group at the Oak Ridge National Laboratory, where she was the principal investigator of the Department of Energy project to breed and characterize the large U.S. cohort of the collaborative cross. She is now an associate professor at The Jackson Laboratory, where her group leads the development of the cross-species data integration platform, GeneWeaver.org, the integrative genetics resource, Mouse Phenome Database spearheaded by Molly Bogue, and research on systems genetics analysis of brain and behavior in the diversity outbred population.

Weihshueh Chiu
Texas A&M University

Weihshueh Chiu is a professor in the Department of Veterinary Integrative Biosciences in the College of Veterinary Medicine and Biomedical Sciences at Texas A&M University. Prior to joining Texas A&M University, Chiu worked at the EPA for over 14 years, most recently as chief of the Toxicity Pathways Branch in the Integrated Risk Information System (IRIS) Division of the National Center for Environmental Assessment. His research has focused on human health risk assessment, particularly with respect to toxicokinetics, mechanisms of toxicity, physiologically-based pharmacokinetic modeling, dose-response assessment, and characterizing uncertainty and variability. He led the development of the EPA's 2011 IRIS assessment of trichloroethylene, which pioneered the use of probabilistic methods for characterizing uncertainty and variability in toxicokinetics and dose-response. He was a member of a WHO/IPCS workgroup on uncertainty and variability, and is a lead author of the 2014 WHO/IPCS Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization. At WHO/IARC, he participated in monograph 106 and chaired the Mechanistic and Other Relevant Evidence sub-group for monographs 110 and 113. He is also currently serving on the U.S. National Academies of Sciences/National Research Council Committee on Predictive Toxicology Approaches for Military Assessment of Acute Exposures. Chiu received a bachelor's degree in physics from Harvard University and a doctorate in physics from Princeton University, and holds a certificate in science, technology, and environmental policy from the Woodrow Wilson School for Public and International Affairs.

Ted Choi
Predictive Biology, Inc.

Ted Choi is the president and chief scientific officer, a company focused on developing stem cell genetics approaches to understanding variability of drug response and toxicant exposure. Prior to founding Predictive Biology, he was the director of molecular genetics at Deltagen, overseeing target validation, drug metabolism, and transgenics technology development programs. Choi has led teams developing mouse models of human genetic disorders at Parke-Davis Pharmaceuticals, AxyS Pharmaceuticals, and GenPharm International. He received a doctorate in biology from Massachusetts Institute of Technology in 1990.

Gary Churchill
Jackson Laboratory

Churchill is a statistical geneticist at The Jackson Laboratory (<http://churchill.jax.org>), where he has made major contributions to understanding the genetics of health and disease using the mouse as a model system. Churchill contributed to the conception and implementation of the collaborative cross and diversity outcross, new mouse populations for systems genetics. The Churchill Lab has generated a wealth of resources for mouse genetics including the first high-density genotyping platform for the mouse; the quantitative trait locus (QTL) archive, a repository of genetic mapping data; the mouse SNP database; R/maanova software for the analysis of gene expression microarray data; and Java/Quantitative Trait Locus (J/qtl) software for QTL analysis. As director of the Center for Genome Dynamics (<http://cgd.jax.org>), a National Center for Excellence in Systems Biology, Churchill leads a consortium of investigators with a shared interest in systems genetics.

Eleazar Eskin
University of California, Los Angeles

Eleazar Eskin is a professor in the Departments of Human Genetics and Computer Science at University of California, Los Angeles (UCLA). When he was a doctorate student at Columbia University studying machine learning methods, the first draft of the human genome was completed and Eleazar changed his research area to develop and apply computational techniques to analyze biological data. After his doctoral studies, he was a postdoctoral researcher at the Hebrew University in Jerusalem, Israel. At UCLA, his research focuses on developing strategies to identify genetic variation involved in disease by analyzing both human and mouse data.

Martin Ferris

University of North Carolina at Chapel Hill

Martin Ferris is a research assistant professor in the Department of Genetics at the University of North Carolina at Chapel Hill. He received a Bachelor of Science in ecology and evolutionary biology from the University of Rochester in 2002. Following this, he obtained a doctorate in evolutionary biology from the University of North Carolina at Chapel Hill, studying viral evolution and host range expansion. In his postdoctoral research, he transitioned to studying the role of host genetic variation on viral disease.

He has carried these systems genetics approaches into his current research program. Specifically, Ferris is interested in using complex genetic systems to disentangle the identity and role of host genetic polymorphisms driving responses to immune responses and virus-induced pathogenesis. By integrating genetic, transcriptional, and phenotypic responses, Ferris hopes to disentangle and identify the causal networks underlying the complex processes driving resistance, susceptibility, and virus-induced pathogenic responses.

John French

National Institute of Environmental Health Sciences

John French, Ph.D., received his doctorate from North Carolina State University in Raleigh in comparative biochemistry and molecular toxicology under Ernest Hodgson and John Roberts in 1975. He was a postdoctoral trainee in radiation biology at the NIH-National Naval Medical Center (NNMC) in Bethesda, Maryland (1975-78) where he investigated ionizing radiation toxicity and suppression of immune and xenobiotic metabolism systems in multiple model organisms. Tenured at the NIH-FDA as a supervisory research physiologist in 1979, he led a research group and served as a scientific reviewer for New Drug Applications using biological therapeutics. In 1982 he joined the NIEHS-NTP program in Research Triangle Park, North Carolina, where he served as study scientist and project officer for toxicology and carcinogenesis studies and studied the effects of caloric restriction and antioxidants on growth hormone and IGF1 axis mechanisms on suppression of cancer. He received an NIH-USPHS fellowship to research loss of heterozygosity and cancer susceptibility genes in lung cancers related to asbestos and smoking exposures under the Nordic Ministries Cancer Research Initiative at the Finnish Institute of Occupational Health in Helsinki, Finland and the Swedish Institute of Occupational Health in Stockholm (1989-91), returning to the NIEHS in 1990. French led the Transgenic Carcinogenesis Group (Laboratory of Environmental Carcinogenesis and Mutagenesis and Laboratory of Molecular Toxicology, NIEHS) and used genetically altered mouse models (Trp53, Hras, etc.) to investigate chemical and ionizing radiation mutagenesis and carcinogenesis until 2007. Between 2007 and 2013, French led the Host Susceptibility initiative for the NTP/NIEHS. Research was focused on the development and use of population-based animal models to investigate chemical and ionizing radiation toxicity and cancer phenotypes. Currently, he is a NIH special volunteer and serves as adjunct professor in the Center for Pharmacogenetics and Individualized Therapy in the Eshelman School of Pharmacy and the Department of Nutrition (biochemical) in the Gillings School of Global Public Health at the University of North Carolina at Chapel Hill. He has co-authored more than 140 peer-reviewed research papers and published technical reports.

Dan Gatti

Jackson Laboratory

Dan Gatti's interests lie in using mouse models to improve human health. He has broad experience in the entire range of mouse research including mouse handling, bench work, bioinformatics, and publication. While at the University of North Carolina, Gatti received extensive training in mouse genetics, the statistical analysis of microarray data, and quantitative trait locus mapping. He provides statistical advice on experimental design to several investigators. He curates data sets and ensures a high level of data quality. Gatti performs quantitative trait locus mapping using a variety of tools. He also develops methods for modeling multi-strain data, performing quantitative trait locus mapping and genotyping complex crosses.

Alison Harrill

University of Arkansas for Medical Sciences

Alison Harrill is an assistant professor in the Department of Environmental and Occupational Health's Regulatory Sciences Program at the University of Arkansas for Medical Sciences. She is the founding and former principal investigator of the Translational Pharmacogenetics Laboratory at the Hamner Institutes for Health Sciences and a graduate of the Toxicology Program at the University of North Carolina at Chapel Hill (2009). Harrill's research has focused on the intersection between genetic variation and adverse drug responses. Specifically, she has utilized mouse population-based models, including the mouse diversity panel and diversity outbred mice, to predict and understand inter-individual variation in drug toxicity outcomes, with particular emphasis on hepatotoxicity. For her work, she has received numerous awards, including the Best Paper Advancing the Science of Risk Assessment (2009) and the Molecular and Systems Biology Best Paper of the Year (2014) from the Society of Toxicology. The Burroughs Wellcome Fund recently recognized her work with an Innovation in Regulatory Science Award (2013-2018).

Harrill serves in leadership roles in both consortia and professional society endeavors. These roles include: secretary/treasurer of the Toxicology Division in the American Society for Pharmacology and Experimental Therapeutics, appointed member of the Contemporary Concepts in Toxicology Committee and junior counselor of the Molecular and Systems Biology Specialty Section within the Society of Toxicology, and steering team member of the Application of Genomics to Risk Assessment Technical Committee within the Health and Environmental Sciences Institute.

Kim McAllister

National Institute of Environmental Health Sciences

Kim McAllister received her doctorate in human genetics from the University of Michigan with a doctoral dissertation identifying the initial gene responsible for hereditary hemorrhagic telangiectasia. She did her postdoctoral training at NIEHS where she developed several new mouse models for breast cancer and Fanconi Anemia. She is currently a program administrator at NIEHS with a portfolio related to genetic epidemiology, gene-environment interactions, comparative biology, and animal models of human diseases.

Brian Parks

University of California, Los Angeles

Brian Parks, Ph.D., is a postdoctoral fellow in the laboratory of Aldons "Jake" Lusis at the University of California, Los Angeles. He received his doctorate at the University of Alabama at Birmingham, where he studied heart disease and lipid mediators. His current work focuses on understanding how genes and environmental factors interact to contribute to metabolic diseases such as obesity and diabetes.

Ivan Rusyn
Texas A&M University

Ivan Rusyn is a professor in the Department of Veterinary Integrative Biosciences in the College of Veterinary Medicine and Biomedical Sciences at Texas A&M University. Prior to joining Texas A&M University, Rusyn was professor of environmental sciences and engineering at the University of North Carolina at Chapel Hill. Rusyn's laboratory has an active research portfolio with a focus on the mechanisms of chemical toxicity, the genetic determinants of the susceptibility to toxicant-induced disease, and computational toxicology. His studies on health effects of chemical agents resulted in over 150 peer-reviewed publications. He has served on several U.S. National Academies of Sciences/National Research Council committees and is currently a member of the Committee on Emerging Science for Environmental Health Decisions, Committee on Toxicology, and Committee on Incorporating 21st Century Science in Risk-based Evaluations. He participated in WHO/IARC monographs 96, 100, 101, and 106, and chaired the overall monograph 110, as well as chaired the Mechanistic and Other Relevant Evidence sub-group for monographs 101, 106, and 112. He is also serving on the Science Advisory Board for the North Carolina Department of Environment and Natural Resources. Rusyn received a Doctor of Medicine from Ukrainian State Medical University in Kiev and a doctorate in toxicology from the University of North Carolina at Chapel Hill.

Boris Tabakoff
Texas A&M University

Tabakoff received his doctorate in pharmacology and behavioral genetics from the University of Colorado and rose to the rank of professor of physiology and biophysics at the University of Illinois School of Medicine. He served as scientific director for the National Institute on Alcohol Abuse and Alcoholism for a seven-year period, and then returned to Colorado as chairman of the Department of Pharmacology at the University of Colorado School of Medicine. His research has had a continuous focus on the effects of addictive drugs, particularly ethanol, and the genetics of susceptibility to organ pathology and neural maladaptation produced by the addictive compounds.

David Threadgill
University of Colorado School of Medicine

David Threadgill is the director of the Texas A&M Institute for Genome Sciences and Society at Texas A&M University. He is a professor with a joint appointment in the Department of Veterinary Pathobiology in the College of Veterinary Medicine and Biomedical Sciences and the Department of Molecular and Cellular Medicine in the College of Medicine, where he also holds the Tom and Jean McMullin Chair of Genetics.

Threadgill's research program uses the mouse as an experimental genetic model to investigate genetic and environmental factors that contribute to inter-individual differences in health and susceptibility to disease. His research program is primarily focused on the role of host genetics in modulating response to environmental exposures including natural and man-made toxicants. He was one of the originators of the concept for re-designing the laboratory mouse into a population resource that gave rise to the collaborative cross.

Session Chairs

David Balshaw

National Institute of Environmental Health Sciences

David Balshaw, Ph.D., is a program director in the Center for Risk and Integrated Sciences at the National Institute of Environmental Health Sciences (NIEHS). Balshaw is responsible for the planning and administration of NIEHS-funded research programs in bioengineering, integrated systems, and computational methods to understand complex systems; development of sensor technologies for environmental exposure assessment; discovery and validation of emerging biomarkers; and application of innovative “omics” research for reducing the risk of exposure and disease including development of databases.

Balshaw received training in pharmacology and biophysics from the University of Cincinnati and University of North Carolina at Chapel Hill. His interdisciplinary training has enabled him to effectively bridge between disparate communities including engineering, mechanistic toxicology, and both clinical and public health application. These successes have led to recognition of his leadership as an expert translational scientist at the NIH and leadership roles in the NIH Common Fund, the NIEHS DISCOVER Program, and the NIH Genes, Environment, and Health Initiative Exposure Biology Program.

Cheryl Marks

National Cancer Institute

Cheryl Marks, whose doctorate is from The George Washington University, is associate director of the National Cancer Institute's (NCI) Division of Cancer Biology. Previously, she performed research at the National Institute of Neurological Disorders and Stroke. In 1999, she initiated the interdisciplinary NCI Mouse Models of Human Cancers Consortium. Its recent phase-out, and widespread translational adoption of animal models, justifies a new NCI program, the Oncology Models Forum. This international research resource supports the cancer research community's needs for validated, credentialed animal models, best practices for their translational use, and novel models and tool strains. The forum also fosters debate about the appropriate, reproducible, and judicious use of pre-clinical animal models.

Mathew Pletcher

Pfizer

Mathew Pletcher received a Bachelor of Science in biology from Duquesne University and a doctorate in human genetics from the Johns Hopkins School of Medicine. As a postdoctoral fellow at the Genomics Institute of the Novartis Research Foundation (GNF), he provided genetics support to a large mouse mutagenesis screen, aiding in the identification of genes underlying immunological, metabolic, and behavioral phenotypes. At GNF, Pletcher published the first haplotype map of mouse inbred strains. From there, Pletcher accepted a position at The Scripps Research Institute as an assistant professor in the Molecular Therapeutics Department and the director of the Genetics and Genomics Core Facility. The work in Pletcher's laboratory focused on the use of mouse inbred strains to understand the genetic underpinnings of variable antidepressant efficacy. Pletcher next joined Pfizer Global Research and Development, where he founded the Non-clinical Pharmacogenomics Laboratory with the goal of establishing a mouse model of the human population as a means to better predict adverse drug responses. Currently, Pletcher holds the position of director of medical genetics in the Rare Diseases Research Unit where he leads drug development efforts in areas such as sickle cell disease, progeria, mucopolysaccharidosis, and amyotrophic lateral sclerosis.

Daniel Pomp

University of North Carolina at Chapel Hill

Daniel Pomp is a professor in the Departments of Genetics (School of Medicine) and Nutrition (School of Public Health) at the University of North Carolina at Chapel Hill. He is a member of UNC's Carolina Center for Genome Science, Nutrition Obesity Research Center, Lineberger Comprehensive Cancer Center, and Center for Environmental Health and Susceptibility. He holds a Bachelor of Science (1983) in agricultural sciences from the Hebrew University of Jerusalem, a master's degree (1986) in quantitative genetics from the University of Wisconsin–Madison, a doctorate (1989) in animal genetics and biotechnology from North Carolina State University, and received postdoctoral research and teaching experience at the University of California, Davis. Pomp specializes in the genetic and genomic analyses of complex traits related to energy balance, a universal core driver of both biomedically important human diseases and economically relevant agricultural traits.

Breakout Group Chairs

Warren Casey

National Institute of Environmental Health Sciences

Warren Casey, Ph.D., is director of the U.S. National Toxicology Program's Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), NIEHS. He received his undergraduate degree in biochemistry and his doctorate in microbiology from North Carolina State University. Casey also serves as an adjunct associate professor in the Department of Microbiology at NCSU and is Diplomate of the American Board of Toxicology (D.A.B.T.). Prior to joining NICEATM, Casey was the manager of pharmaceutical microbiology at Glaxo Inc. from 1994 to 1999; head, biomarker development, at GlaxoWellcome, Inc., from 1999 to 2002; and a senior scientist for discovery and investigative toxicology, at GlaxoSmithKline, Inc., from 2002 to 2009.

Fernando Pardo Manuel de Villena

University of North Carolina at Chapel Hill

Fernando Pardo-Manuel de Villena is a professor and associate chair for Research of the Department of Genetics. He is also the director of the Program of Systems Genetics at UNC and supervises the UNC Systems Genetics Core Facility that is in charge of the development and distribution of the collaborative cross. De Villena obtained his bachelor's degree in biology from the University of Leon (Spain) in 1989 and graduated summa cum laude in genetics at the University Complutense of Madrid (Spain) in 1994. He was a postdoctoral fellow at the Fels Institute for Cancer Research and Molecular Biology at Temple University School of Medicine in Philadelphia from 1994 to 2001.

His research is focused on the mechanisms of inheritance beyond the role of single genes in mendelian traits with an emphasis in three areas: chromosome segregation, epigenetics, and complex traits always using the house mouse as a model. Recent examples of the work from his laboratory is the identification, cloning, and characterization the first mammalian meiotic drive system in which a DNA sequence in the middle of chromosome is able to direct its own segregation during meiosis. This exciting work was recently published in PLoS Genetics and a companion perspective article stated "this works represents a tour de force in characterizing a complex multilocus TRD system in a genetically tractable mammalian model system." His lab is now investigating whether this system can be made portable and thus can be applied to a broad range of both biomedical and biotechnology questions. Fernando Pardo-Manuel de Villena has established a strong network of collaborations with researchers both here at UNC and worldwide, anchored on use of the collaborative cross and the diversity outbred to gain new insights on the genetics of human diseases (Recent publications on Ebola virus hemorrhagic fever and inflammatory bowel disease are just two examples of this quickly expanding line of work).

Mike Devito

National Institute of Environmental Health Sciences

Michael DeVito, Ph.D., is serving as the acting chief of the NTP Laboratory. DeVito was most recently in the NTP Toxicology Branch leading the Experimental Toxicology Group, where his group was characterizing the toxicologic and/or carcinogenic potential of chemicals and agents nominated to the NTP. He also served as the discipline leader for NTP pharmacokinetic modeling efforts. Prior to coming to NIEHS/NTP in 2009, DeVito was a principal investigator in the Pharmacokinetics Branch of the National Health and Environmental Effects Research Laboratory at the U.S. EPA. From 2002-2009, DeVito was chief of the Pharmacokinetic Branch. DeVito served as one of the lead health effects researchers on EPA's Dioxin Reassessment from 1991-2009.

David Dix

U.S. Environmental Protection Agency

David Dix is acting director of the U.S. EPA's National Center for Computational Toxicology (NCCT), at Research Triangle Park, North Carolina, where he is leading the development of high throughput decision support tools for screening and assessing chemical exposure, hazard, and risk. Prior to acting director, Dix was the NCCT deputy director and a research biologist conducting research in reproductive, genomic, and computational toxicology at EPA. Dix is an adjunct associate professor in the Department of Environmental Sciences and Engineering at the University of North Carolina at Chapel Hill. He earned his undergraduate degree in biological sciences from the University of Illinois at Chicago, a doctorate in physiology from Rush University in Chicago, and completed postdoctoral training at NIEHS. He has published over 100 articles, reviews, reports, and book chapters, serves on several editorial boards, and has given numerous national and international presentations on EPA research.

Paul Foster

National Institute of Environmental Health Sciences

Paul Foster received his doctorate from Brunel University, Uxbridge, England in 1977 and is currently the chief of the Toxicology Branch of the Division of the NTP at NIEHS in Research Triangle Park, North Carolina. The Toxicology Branch is responsible for the scientific leadership of the NTP's cancer and non-cancer testing program. Prior to joining NIEHS in 2002, he was the director of the research program in endocrine, reproductive and developmental toxicology at the CIIT Centers for Health Research (CIIT). He joined CIIT in December 1995 after a 13-year career at Zeneca's (formerly Imperial Chemical Industries) Central Toxicology Laboratory in Cheshire, England, where he was head of Reproductive and Developmental Toxicology, responsible for all aspects of the company's activities in this field, in both the research and regulatory arenas. Foster's research interests span from understanding the potential human health effects of environmental endocrine disruptors (particularly antiandrogens); mechanisms of testicular toxicity; the study of early testicular leydig cell dysfunction induced by chemicals as a prelude to hyperplasia and tumors, and the toxicokinetic and dynamic parameters affecting the induction of reproductive and developmental toxicity. He also has a broad interest in risk assessment issues in these areas and currently serves as NTP's senior discipline leader in Reproductive, Developmental and Endocrine Toxicology.

Terry Kavanagh
University of Washington

Terrance Kavanagh is a professor of Environmental and Occupational Health Sciences, and adjunct professor of Pulmonary and Critical Care Medicine at the University of Washington. He received a Master of Science in physiology and doctorate in environmental toxicology and genetics from Michigan State University. He is a former president of the Mechanisms Specialty Section of the Society of Toxicology and of the Pacific Northwest Association of Toxicologists. Kavanagh currently serves as director of the UW Center for Ecogenetics and Environmental Health, and director of the UW Nanotoxicology Center. He is a Diplomate of the American Board of Toxicology, with expertise in in vitro and in vivo toxicology, transgenic mouse models, analytical cytology methods, and gene-environment interactions. His areas of research interest include glutathione metabolism, free radical biology, oxidative stress biomarkers, toxicogenomics, systems genetics, and nanotoxicology.

Jonathan Pollock
National Institute on Drug Abuse

Jonathan Pollock received his doctorate in physiology at Columbia University under the mentorship of Eric Kandel, M.D., in 1985. His doctoral thesis is on serotonin modulation of the S postassium channel pleural sensory neurons that modulate the tail withdrawal reflex of *Aplysia Californica*. He subsequently did postdoctoral work at Caltech in the laboratory of Mark Tanouye and in the laboratory of Mario Capecchi. He then became a research associate in pediatrics and assistant scientist in physiology at Indiana University School of Medicine, where he made a mouse model for chronic granulomatous disease and knockouts for the mu opioid receptor and the small GTP binding protein Rac2. Pollock is currently the branch chief for Genetics and Molecular Neurobiology Research Branch in the Division of Basic Neuroscience and Behavioral Research at the National Institute on Drug Abuse (NIDA) and chairs the NIDA Genetics Workgroup. The focus of the branch's effort is on the genetics and epigenetics of drug abuse and addiction. Pollock played a major role in initiating the first phase of the Knockout Mouse Project, now known as KOMP1. He is currently interested in using natural variants in mouse and rodent strains to identify gene variants that influence drug abuse and addiction. The Genetics and Molecular Neurobiology Research Branch supported the discovery of variants on 15q25 for *chrna5-chrnb3-chrna3* associated with nicotine dependence. This has led to important insights into the role that the habenula plays in mediating the aversive component of nicotine.

Tim Wiltshire
University of North Carolina at Chapel Hill

Tim Wiltshire's lab research focuses mainly on pharmacogenetics and broad aspects of drug toxicity. They have used the mouse as an extremely useful model for this work. One of the confounding factors in the response of an organism to a drug or compound is the genetic variance on which the drug is tested. Standard models of drug testing have routinely used only one strain of mouse or rat, but this approach does not take into account the complexity of response that is apparent because of genetic variation. They have used a wide selection of inbred mouse strains, and more recently the collaborative cross mice, to screen for variable phenotypic responses to drug. They have focused largely on toxicity responses in in vivo mouse models, but also have championed the use of in vitro "cellular genetics" approaches to identify variable drug response. The key to understanding the variable drug response is to be able to provide associated genetic analysis and identify the genetic variation responsible. Using these mouse models, they have been able to identify genes that impact specific drug response pathways.

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