

## **Plenary Speakers**

**Abstracts PL-1 – PL-7**

**PLENARY PRESENTATION – PL1 MONDAY NOVEMBER, 13****8.30AM – 9.00AM****KRAB-ZNF GENES AND THE EVOLUTION OF MAMMALIAN REGULATORY NETWORKS**

A Hamilton, S Huntley, A Yamada, J Fellis, K Nowick, D Baggott, M Tran-Gyamfi, K Segalle, M Wu, S Mabery, and L Stubbs  
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Evolutionary conservation is used extensively as a filter for identifying candidate regulatory sequences in genomic DNA and indeed, many transcription factors, together with their DNA binding sites and the regulatory networks they influence, are deeply conserved in vertebrate species. However, one of the largest families of mammalian transcription factor genes displays a remarkably dynamic evolutionary history. More than 400 KRAB-zinc finger (ZNF) genes are found in the human genome; this single gene family, which encodes potent transcriptional repressors, therefore corresponds to nearly 20% of the predicted human transcription factor repertoire. Similar numbers of genes of this type are found in other mammals, but due to repeated and rounds of lineage-specific gene duplications and gene loss, primates, rodents, and canines contain very different complements of KRAB-ZNF genes. Only 100 human genes are conserved as 1:1 orthologs in mice, and at least 136 genes are specific to primates. The ongoing creation and rapid divergence of these repressor-encoding loci suggest an active selection for change in mammalian regulatory networks. However, since gene targets are known for only a handful of KRAB-ZNF proteins, the functional impact of this dramatic gene-repertoire change remains uncertain.

We have focused on developing robust methods to identify regulatory functions of KRAB-ZNF genes with focus on two specific subclasses. These include the primate specific genes, especially those encoding repressor proteins that are found exclusively in hominids. Also of special interest to our group is a subfamily of embryo-expressed genes including several imprinted loci. Our studies indicate that KRAB-ZNF genes regulate a wide variety of biological pathways, with new duplicates diverging rapidly to acquire novel DNA binding specificities and distinct functional roles. Many KRAB-ZNF genes are active in reproductive, immune, and other rapidly evolving systems, but our data also indicate that lineage-specific regulatory functions are layered onto much more deeply conserved biological pathways. The emerging data suggest a novel mechanism for the expression of individual differences and for the selection of species-specific biological traits.

**VERNE CHAPMAN MEMORIAL LECTURE PL2 MONDAY NOVEMBER, 13 3.30PM – 4.30PM****BARNYARD GENOMICS: CATTLE AND OTHER DOMESTIC ANIMALS**

JE Womack  
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While domestic animals have been intriguing to mammalian geneticists over the years for their vast collection of phenotypes, especially quantitative traits, genetic resources have not been generally available for gene discovery. This has changed dramatically over the last five years. Genomics of domestic animals, including cattle and other livestock species, has followed in the footsteps of the human and mouse genome initiatives, borrowing both their successful strategies and technologies. Whole genome sequencing projects have now been initiated for a number of animal species including dogs, cats, chickens, pigs, horses, and cattle and are in various stages of development. The domestication of animals less than 10,000 years ago and development of breeds over the last 200 years have resulted in extensive phenotypic diversity and unique haplotype structures than can now be exploited by available genetic resources. Using cattle as a principal example, several traits will be discussed as valuable biomedical models, along with successful approaches to the discovery of underlying genes.

**PLENARY PRESENTATION – PL3    TUESDAY NOVEMBER, 14**

**8.30AM – 9.00AM**

**MOLECULAR CONTROL OF THE OOCYTE TO EMBRYO Q TRANSITION**

D Solter, AV Evsikov, AE Peaston, WN de Vries and BB Knowles

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The full-grown mammalian oocyte, arrested in prophase of the first meiotic division, contains all of the molecules that will be utilized to bridge the period of transcriptional silence that begins upon completion of oocyte growth and lasts till the activation of the embryonic genome. Nuclei from differentiated somatic cells can be reprogrammed to totipotency in the oocyte milieu during the oocyte to embryo transition. During this period, approximately two days in the mouse, stores of maternal messages are selectively utilized resulting in the synthesis of known and novel proteins. The Gene Ontology vocabulary was used to annotate the molecular functions of the 2 cell embryo transcriptome and compare it with a composite transcriptome of all other cells and organs in the Mouse Genome Database. The 2 cell embryo is enriched in transcripts encoding translation regulators and RNA binding proteins and is depauperate in those encoding ligands and receptors. Gene expression during the oocyte to embryo transition is controlled by timely translation and homologues of factors described in non-mammalian cells, which bind to specific cis-sequences in the 3'UTR of mRNAs are also found in the mouse oocyte and early embryo. Expression of specific retroviral elements varies in a stage-specific fashion and may change expression of adjacent genes. These mobile elements affect gene evolution and may play a role in epigenetic restructuring of the embryonic genome.

**PLENARY PRESENTATION – PL4 TUESDAY NOVEMBER, 14****1.30PM – 2.00PM****THE MOUSE KNOCKOUT PROJECT**

C Fletcher

NHGRI, on behalf of the KOMP Research Network, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, MD, United States

The National Institutes of Health (NIH) recently awarded a set of cooperative agreements, totaling up to \$52 million over five years, to launch the Knockout Mouse Project (KOMP). The goal of this program is to build a comprehensive and publicly available resource of knockout mutations in the mouse genome. The project includes four major components. The first is a production effort to create at least 8,500 knockout in embryonic stem (ES) cells. The second component is a program to derive, expand, and characterize C57BL/6 ES cells. The third is a data coordination center that will collate and disseminate KOMP related data. The final component is a repository that will distribute the ES cells, mice, and vectors produced by KOMP.

Recipients of the production awards are Regeneron Pharmaceuticals, Inc., in Tarrytown, N.Y., and a collaborative team from Children's Hospital Oakland Research Institute (CHORI) in Oakland, Calif., the School of Veterinary Medicine, University of California, Davis (UC Davis); and the Wellcome Trust Sanger Institute in Hinxton, England. The Jackson Laboratory in Bar Harbor, Maine will be responsible for the establishment of the data coordination center. Finally, NIH awarded cooperative agreements to the University of Pennsylvania in Philadelphia and to the Samuel Lunenfeld Research Institute of Mount Sinai Hospital in Toronto to improve the efficiency of methods for creating B6 ES cells. In addition, Regeneron will receive funds to optimize its existing B6 ES cell line.

The NIH Knockout Mouse Project will work closely with other large-scale efforts to produce knockouts that are underway in Canada, called the North American Conditional Mouse Mutagenesis Project (NorCOMM), and in Europe, called the European Conditional Mouse Mutagenesis Program (EUCOMM). The objective of all these programs is to create a mutation in each of the approximately 20,000 protein-coding genes in the mouse genome. The strategic approaches and current status of KOMP will be described, as well as plans to solicit community input for target selection and prioritization.

**PLENARY PRESENTATION – PL5 WEDNESDAY NOVEMBER, 15**

**8.30AM – 9.00AM**

**EPIGENETIC CONTROL OF GENE ACTIVITY AND REPRESSION AT IMPRINTED DOMAINS IN MOUSE**

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The 1Mb *Dlk1-Dio3* imprinted domain on mouse chromosome 12 contains three developmentally regulated protein-coding genes expressed from the paternally inherited chromosome homologue and a series of non-coding RNAs expressed from the maternally inherited chromosome including over 40 microRNAs, C/D snoRNAs and the large alternatively spliced transcript, *Gtl2*. Imprinting at the *Dlk1-Dio3* domain is regulated by a 4kb intergenic germline-derived differentially methylated region (IG-DMR) located between *Dlk1* and *Gtl2*. Deletion of the unmethylated IG-DMR on the maternal chromosome causes it to undergo an epigenotype switch and behave like the paternal chromosome, resulting in embryonic lethality. In contrast, deletion from the paternally inherited chromosome has no effect. The aims of our lab are to understand the function, regulation and evolution of gene activity and repression at this domain.

Using a range of mouse models, complete sequence of the region in marsupial and monotreme mammals, and a custom genomic tiling array, we are identifying functional and potentially functional genomic features, generating a comprehensive picture of DNA methylation and histone modification across the two parental chromosomes and assessing the role of the protein-coding genes and non-coding RNAs at the locus. These findings are allowing consideration of alternative theories about imprinting evolution and generating a useful model for understanding the epigenetic control of genome function. Recent results will be presented.

PLENARY PRESENTATION – PL6 WEDNESDAY NOVEMBER, 15

1.30PM – 2.00PM

**GENES FOR TYPE 2 DIABETES FROM GENETIC AND GENOMIC STUDIES IN MICE**

AD Attie

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Although most people with type 2 diabetes are obese, most obese people do not develop diabetes. Genetic factors play an important role in determining which obese individuals will go on to become diabetic. We study the obesity/diabetes dichotomy in two mice strains that when made obese, differ in diabetes susceptibility. The C57BL/6 strain, as originally shown by Coleman, is moderately and transiently diabetic when it carries the *leptinob* mutation. In contrast, BTBR mice with the same mutation are severely obese. We mapped several genes controlling insulin and glucose in an F2 intercross derived from these strains. We recently identified the genes underlying one of the QTLs, *SorCS1*. Association studies in two human populations have linked SNPs in *SorCS1* with diabetes-related phenotypes and diabetes itself. This gene encodes a protein that binds to platelet-derived growth factor (PDGF). PDGF plays an important role in pericyte recruitment during the formation of blood vessels. We are now studying vascular phenotypes in mice and in zebrafish associated with variation at the *SorCS1* locus.

From microarray studies, we identified a gene that is highly induced in islets of obese mice, cholecystokinin (CCK). Obese mice lacking the CCK gene have smaller islets and lower insulin levels. We are now studying the mitogenic effects of CCK on islets and suggest that CCK is induced by obesity to mediate compensation for insulin resistance by increased beta cell proliferation.

**PLENARY PRESENTATION – PL7 WEDNESDAY NOVEMBER, 15**

**4.00PM – 4.30PM**

**USING THE MOUSE TO FIND HUMAN DISEASE GENES**

B Paigen

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The remarkable degree of concordance of quantitative trait loci (QTL) between human and mouse for most traits indicates that the genetic and genomic resources of the mouse can be used to find candidate genes that can subsequently be tested in human populations. We review briefly the various bioinformatics steps that can be used to reduce the number of candidate genes in a QTL interval including comparative genomics, combining crosses, haplotype comparisons, and haplotype association mapping. The methods of each bioinformatics step are illustrated with the search for HDL cholesterol QTLs.

For haplotype association mapping, we used the strain survey data to compute the QTLs for red blood cell count (RBC) and HDL cholesterol (HDL). Significant QTL peaks determined by computational methods were then tested by crosses. QTL peaks were confirmed in crosses or found to be in linkage disequilibrium with real QTL peaks.