

**Tuesday November, 14**  
**10.30am – 12.30pm**  
**Poster Session 3**  
**Development/Aging**  
**Posters P54 – P66**

- S13/ P54** **THE GENETIC ARCHITECTURE OF THE DDK SYNDROME**  
FY Ideraabdullah, K Kim, F Pardo-Manuel de Villena  
University of North Carolina at Chapel Hill, Chapel Hill, NC, United States
- P55** **CHARACTERIZATION OF POLYCYSTIC KIDNEY DISEASE PROTEIN-PROTEIN INTERACTIONS**  
EE Stagner, DJ Bouvrette, EC Bryda  
University of Missouri, Columbia, MO, United States
- S9/ P56** **MAMMALIAN NURF IS AN ESSENTIAL COMPONENT OF TGF $\beta$  SIGNALING IN THE PRE-GASTRULATING EMBRYO**  
J Landry, H Xiao, E Southton, L Tessarollo, Y Zhang, T Yamaguchi, C Wu  
National Institutes of Health, Bethesda, MD, United States
- S2/ P57** **NELL1-DEFICIENT MICE HAVE REDUCED EXPRESSION OF EXTRACELLULAR MATRIX PROTEINS CAUSING CRANIAL AND VERTEBRAL DEFECTS**  
JB Desai<sup>1</sup>, ME Shannon<sup>2</sup>, MD Johnson<sup>3</sup>, DW Ruff<sup>2</sup>, LA Hughes<sup>4</sup>, MK Kerley<sup>4</sup>, DA Carpenter<sup>4</sup>, DK Johnson<sup>4</sup>, EM Rinchick<sup>4</sup>, CT Culiati<sup>4</sup>  
<sup>1</sup>Graduate School for Genome Science and Technology, University of Tennessee-Oak Ridge National Laboratory, Oak Ridge, TN, United States, <sup>2</sup>Applied Biosystems, Foster City, CA, United States, <sup>3</sup>The University of Tennessee Graduate School of Medicine, Knoxville, TN, United States, <sup>4</sup>Life Sciences Division, Oak Ridge National Laboratory, Oak Ridge, United States
- S5/ P58** **FILAMIN B REPRESSES RUNX2 THROUGH THE TGF- $\beta$ /SMAD3 PATHWAY TO REGULATE CHONDROCYTE HYPERTROPHY**  
L Zheng, HJ Baek, MJ Justice  
Baylor College of Medicine, Houston, TX, United States
- S10/ P59** **FUNCTIONAL CHARACTERIZATION OF A NOVEL MINICHROMOSOME MAINTENANCE PROTEIN, MCM9**  
SA Hartford, JC Schimenti  
Cornell University, Ithaca, NY, United States
- P60** **ASH1L, A HOMOLOG OF A DROSOPHILA HOMEOTIC SELECTOR GENE, IS NECESSARY FOR NORMAL HEAD DEVELOPMENT**  
NM Solomon<sup>1</sup>, KM Owens<sup>1</sup>, ML Brinkmeier<sup>1</sup>, RH Lyons<sup>1</sup>, P Carninci<sup>2</sup>, Y Hayashizaki<sup>2</sup>, SA Camper<sup>1</sup>  
<sup>1</sup>University of Michigan Medical School, Ann Arbor, MI, United States, <sup>2</sup>RIKEN Genomic Sciences Center, Yokohama, Kanagawa, Japan
- S12/ P61** **TRANSCRIPTIONAL PROFILING OF MOUSE EMBRYONIC STEM CELL DERIVED CARDIOMYOCYTES TO IDENTIFY NOVEL CARDIAC GENES**  
RA Miller, AS McCallion, JD Gearhart  
Johns Hopkins School of Medicine, Baltimore, MD, United States
- P62** **CHARACTERIZATION OF SMAD4 MUTATIONS IN MOUSE**  
L Williams, Y Chen, T Magnuson  
University of North Carolina, Chapel Hill, Chapel Hill, NC, United States
- S3/ P63** **AN ENU MUTANT MOUSE MODEL OF OCULODENTODIGITAL DYSPLASIA IS EXPLOITED TO UNDERSTAND THE ROLE OF CONNEXIN 43 IN BLOOD AND BONE DEVELOPMENT**  
NM Anderson<sup>1</sup>, R Zirngibi<sup>1</sup>, C Owen<sup>2</sup>, F Chen<sup>1</sup>, L Moreno<sup>1</sup>, M Grympas<sup>1</sup>, J Henderson<sup>3</sup>, J Aubin<sup>1</sup>, W Stanford<sup>1</sup>  
<sup>1</sup>University of Toronto, Toronto ON, Canada, <sup>2</sup>Mount Sinai Hospital, Toronto ON, Canada, <sup>3</sup>McGill University, Montreal, Quebec, Canada

**P64 NOTCH/RBP-J SIGNALING CONTROLS MELANOCYTE LINEAGE DEVELOPMENT**

G Aubin-Houzelstein<sup>1</sup>, F Bernex<sup>1</sup>, J Djian<sup>1</sup>, V Delmas<sup>2</sup>, I Yajima<sup>2</sup>, JJ Panthier<sup>3</sup>

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**P65 CHARACTERISATION OF THE ENU-INDUCED BATFACE MUTATION**

NS Powles-Glover, A Hardy, V Tucci, A Parker, S Polley, R Kendell, R Arkell, P Nolan  
MRC Harwell, Oxfordshire, United Kingdom

**P66 RETROVIRAL GENE DELIVERY AND PCG CONTROL IN MOUSE HEMATOPOIETIC STEM CELLS**

LV Bystrykh, A Gerrits, J Kaplon, V van den Boom, E Weersing, B Dontje, G de Haan  
RUG UMCG, Groningen, Netherlands

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## **P55**

### **CHARACTERIZATION OF POLYCYSTIC KIDNEY DISEASE PROTEIN-PROTEIN INTERACTIONS**

EE Stagner, DJ Bouvrette, EC Bryda  
University of Missouri, Columbia, MO, United States

Rodent models, including the Han:SPRD-Cy rat and the *jcpk* mouse, have been useful for identifying and characterizing genes that cause Polycystic Kidney Disease (PKD). The Han:SPRD-Cy model is the result of a spontaneous mutation that affects the Sterile Alpha Motif (SAM) domain of the *Cy* gene product (SamCystin). Similarly, the disease-causing mutation in the *jcpk* mouse results in the loss of a SAM domain within the Bicaudal C protein (Bicc1). In several other proteins that contain sterile alpha motifs, the SAM domains participate in protein-protein interactions and these interactions can involve association specifically between the SAM domains. Our hypothesis is that Bicc1 and SamCystin act in a common molecular pathway to cause PKD. Preliminary studies involving co-immunoprecipitation demonstrate that the Bicc1 and SamCystin proteins physically interact. Deletion constructs that remove the SAM domain have been generated to determine if the absence of the SAM domain in the Bicc1 protein will cause the loss of the SamCystin-Bicc1 protein interaction. These studies will provide critical information about the relationship of these two proteins, which can be used to further understand the pathogenesis of PKD.

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## **P60**

### **ASH1L, A HOMOLOG OF A DROSOPHILA HOMEOTIC SELECTOR GENE, IS NECESSARY FOR NORMAL HEAD DEVELOPMENT**

NM Solomon<sup>1</sup>, KM Owens<sup>1</sup>, ML Brinkmeier<sup>1</sup>, RH Lyons<sup>1</sup>, P Carninci<sup>2</sup>, Y Hayashizaki<sup>2</sup>, SA Camper<sup>1</sup>  
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Pituitary gland development involves differentiation of five hormone producing cell types. At least seven different homeobox genes are necessary for normal pituitary development and the earliest acting genes also influence craniofacial development. Humans and mice with inactivating mutations in *Prop1* exhibit pituitary hypoplasia and failed differentiation of hormone producing cells. To understand the molecular basis of this process we prepared cDNA libraries from pituitary primordia of normal and *Prop1* mutant mouse embryos at critical embryonic times (E12.5; E14.5), sequenced over 30,000 clones, and established a searchable database with gene ontology terms.

We chose *Ash1l* for functional studies. It is orthologous to the *Drosophila ash1* gene, absent, small, homeotic discs-1, a critical regulator of homeotic selector genes. Given the importance of *ash1* as a chief controller of correct imaginal disc formation in the fly, we considered it might also regulate expression of some homeobox genes with known roles in pituitary development. *Ash1l* is prominently expressed in embryonic pituitary, brain, lens and heart. *Ash1l* expression persists in these tissues through adulthood, including skeletal muscle.

Mice heterozygous for an *Ash1l* gene trap in intron 1 are normal. Homozygotes are born viable, but display severe growth insufficiency and abnormalities of the eye, eyelid and craniofacial structures. *Ash1l* mutants also exhibit balance problems and fragile skeletal structure. Preliminary analysis of *Ash1l* mutant pituitaries suggests anterior pituitary hypoplasia. We are in the process of establishing the mechanism of *Ash1l* function in head development and placing it within the genetic hierarchy of known transcriptional regulators.

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## P62 CHARACTERIZATION OF SMAD4 MUTATIONS IN MOUSE

L Williams, Y Chen, T Magnuson  
University of North Carolina, Chapel Hill, Chapel Hill, NC, United States

*Smad4* is a central mediator of the TGF-beta-related signaling and is implicated in numerous biological and disease processes including control of cellular growth, differentiation, migration, and extracellular matrix production; these processes are all essential for normal development. Targeted disruption of *Smad4* results in peri-gastrulation lethality and implicates a role for *Smad4* in epiblast proliferation, mesoderm formation, and extraembryonic tissue-mediated early embryo patterning events. However, the precise molecular deficits underlying these phenotypes are unknown. An allelic series of mutations in *Smad4* was obtained by screening a cryopreserved mouse embryonic stem cell library mutagenized with ENU using the DHPLC mutation detection technology. The identified mutations were distributed throughout the coding region of the *Smad4* gene. The functional consequence of the mutations is assessed through germ line transmission. The phenotypes ranged from embryonic lethality to adult viability. Depletion of SMAD4 from the oocyte resulted in a preimplantation lethality indicating the importance of the oocyte-derived SMAD4 protein for normal preimplantation development. The genetic and biochemical characterization of this phenotype provides insights into the *in vivo* function of SMAD4 during early development.

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## P64 NOTCH/RBP-J SIGNALING CONTROLS MELANOCYTE LINEAGE DEVELOPMENT

G Aubin-Houzelstein<sup>1</sup>, F Bernex<sup>1</sup>, J Djian<sup>1</sup>, V Delmas<sup>2</sup>, I Yajima<sup>2</sup>, JJ Panthier<sup>3</sup>  
<sup>1</sup>UMR955 Institut National de la Recherche Agronomique-Ecole Nationale Vétérinaire d'Alfort, Maisons-Alfort, France, <sup>2</sup>Developmental Genetics of Melanocytes, UMR146 CNRS-Institut Curie, Orsay, France, <sup>3</sup>Mouse functional Genetics Unit, Institut Pasteur, 25 rue du Docteur Roux, Paris, France

Notch signaling is an evolutionarily conserved mechanism that regulates numerous cell fate decisions. Upon ligand binding, the intracellular domain of Notch receptor is translocated to the nucleus where it interacts with the recombination signal binding protein-J (RBP-J) within a multiproteic complex which activates various target genes. We first thought that Notch signaling may be important for mouse melanocytes when we found that overexpression of *Strawberry notch* (*mSno*) gene in either patchwork (*pwk*) mutant mice or in transgenic mice led to lack of differentiated melanocytes in the hair matrix of newborn. We examined the effect of inhibition and activation of Notch signaling in melanocytes using a melanocyte-specific gene targeting approach. Inhibition of the Notch pathway had several effects. In the embryo, it resulted in a reduced number of melanoblasts migrating through the epidermis. Postnatally, it induced precocious melanocyte differentiation in the bulge region and ectopic pigmentation in the hair follicle. It further led to progressive loss of differentiated melanocytes within the hair matrix and to premature hair whitening. Activation of Notch led to altered expansion of melanoblasts in the embryonic skin, variable body spotting in newborn. However activation of Notch signaling did not lead to accelerated hair greying. Thus, Notch signaling is involved in the expansion of migrating melanoblasts in the embryo and in the maintenance of melanocyte stem cells in the adult hair follicle. These data are consistent with the contention that Notch maintains the progenitor state and inhibits differentiation.

**P65****CHARACTERISATION OF THE ENU-INDUCED BATFACE MUTATION**

NS Powles-Glover, A Hardy, V Tucci, A Parker, S Polley, R Kendell, R Arkell, P Nolan  
MRC Harwell, Oxfordshire, United Kingdom

A dysmorphology screen for dominant mutations in progeny of N-ethyl-N-nitrosourea (ENU) mutagenised mice identified a mouse mutant, called batface (*Bfc*), with craniofacial anomalies and a broad range of behavioural deficits. The penetrance and expressivity of the mutation varies with background. The heterozygous phenotype is fully suppressed in crosses with *Mus m castaneus* whereas in crosses with C57BL/6J additional phenotypes including cleft palate, anophthalmia and tail kink are found. Our studies show that the mutation is semi-dominant, with homozygous mutants dying during embryogenesis. Developmental anomalies in both heterozygotes and homozygotes include a reduced forebrain, exencephaly and oro-facial clefting. An initial genome scan localised the *Bfc* mutation to distal chromosome 9 and fine mapping and sequencing revealed a mis-sense mutation in Beta-Catenin. The *Bfc* allele therefore reveals a previously unrecognized neurological role of Beta-Catenin and highlights the ability of ENU mutagenesis to uncover novel attributes of well characterised genes. Embryonic phenotyping, behavioural testing and analysis of the mutant protein is being used to determine how this mutation affects the function of Beta-Catenin, either within the canonical Wnt-signalling pathway or through its interaction with membrane-bound cadherins.

**P66****RETROVIRAL GENE DELIVERY AND PCG CONTROL IN MOUSE HEMATOPOIETIC STEM CELLS**

LV Bystrykh, A Gerrits, J Kaplon, V van den Boom, E Weersing, B Dontje, G de Haan  
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The present concept of differentiation of embryonic stem and hematopoietic stem cells (HSC) claims a key role of Polycomb Group (PcG) genes to suppress differentiation pathways and thereby keep stem cells proliferating with minimal loss of repopulating capacity.

In general, activity of PcG complexes is expected to drop upon differentiation, and it is almost completely absent in terminally differentiated and senescent cells. We found that *Ezh2* expression in BXD mice is largely controlled by a locus on chr. 18, which likely controls more genes involved in epigenetic control of gene expression in mice. Possible candidates are identified and are currently under investigation. Our previous studies demonstrated that retroviral overexpression of *Ezh2* considerably prolonged viability of HS cells in mice upon serial transplantations, which agrees with the present concept. In a longer term, however, mice transplanted with *Ezh2*-transgenic stem cells developed a myeloproliferative syndrome. Therefore, it is an important question how overexpression of *Ezh2* postpones aging of the recombinant HSC and influences differentiation of blood cells. One of the key features of ageing is surveillance of genomic endogenous retroelements by CpG methylation of DNA and chromatin condensation.

Expression of endogenous retroelements such as *MusD*, *IAP* and *MuERV* was easily detectable in serially transplanted bone marrow cells with or without *Ezh2* overexpression, which suggests loss of retroviral surveillance in old recombinant mice.

We propose that both *Ezh2* overexpression and derepression of endogenous retroelements contribute to the myeloproliferation event.