SUNDAY NOVEMBER 2

STUDENT SATELLITE SYMPOSIUM SESSIONS

Student Satellite Symposium Session 1 – Sunday November, 2 1.00pm – 1.15pm

S1/P107

IDENTIFICATION AND CHARACTERIZATION OF TWO MOUSE MUTANTS WITH DEVELOPMENTAL DEFECTS

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Congenital abnormalities can be modeled in the mouse using genetic approaches such as phenotype driven mutagenesis screens. Mouse ENU mutagenesis screens create point mutations throughout the genome and can be employed to elucidate the function of genes that are conserved between the mouse and human. Region-specific mutagenesis screens can determine the functional content of a defined chromosomal region based on the mutant phenotypes isolated. A region-specific mutagenesis screen directed at mouse chromosome 11 allowed the isolation of the *l11Jus27* and embryonic hydrocephalus (*EHC*) mouse mutants. The *l11Jus27* mutant has defective cardiovascular development causing lethality at mid-gestation. Morphological analysis revealed that pericardial effusion and reversal of left/right asymmetry are prevalent in mutants. Whole mount *in-situ* hybridization indicates that mutant cardiac muscle development is impaired. A combination of meiotic mapping and deletion mapping has refined the *l11Jus27* candidate interval to 5Mb. To date no mutation that displays a similar cardiac phenotype has been mapped to this region of chromosome 11. The *EHC* mutant exhibits non-communicating hydrocephalus and cardiac defects leading to lethality at late gestation. Histological analysis revealed that *EHC* mutants have enlarged cardiomyocytes that fail to undergo proper cytokinesis, ventricular septal defects, and an abnormal epicardium. Mapping data and western blot analysis indicates that the EHC phenotype is due to a mutation in the non-muscle Myosin IIB gene. Further study of developmental mutants such as *l11Jus27* and *EHC* can identify genes that may contribute to congenital birth defects in humans.

Student Satellite Symposium Session 1 – Sunday November, 2 1.15pm – 1.30pm

S2/P106

A NOVEL REGULATOR IN TERMINAL MEGAKARYOCYTE DIFFERENTIATION IDENTIFIED BY ENU MUTAGENESIS

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Platelets play a critical role in thrombosis, a mechanism that protects and treats vascular leakage. Alterations in platelet numbers occur in numerous hematopoietic diseases and can contribute to cardiovascular disease. Yet, the molecular mechanisms controlling megakaryocytic/platelet lineage development and function are poorly understood. To identify novel regulars of thrombopoiesis, we are performing dominant and sensitized screens assayed by peripheral blood counts. In the dominant screen, we identified a thrombocytopenic (low platelet) mutant (strain *7238*). *7238/+* mice present with a 56 percent reduction in peripheral blood platelet counts (PBPC), and homozygous *7238/7238* mice present with a 75% reduction in PBPC. There are no significant differences in megakaryocytic progenitor (CFU-Mk) frequency or total numbers between wild type and mutant (heterozygous or homozygous) mice. However, preliminary flow cytometric and histological analyses in heterozygous *7238/+* mice demonstrated megakaryocyte hypolobulation. Bone marrow-derived megakaryocytes demonstrated dramatically reduced ploidy in culture, all suggesting a block in megakaryocytic differentiation leading to reduced platelet production. Other hematological analyses including peripheral blood counts, flow cytometry and clonogenic assays suggest the only hematopoietic lineage affected is the megakaryocyte/platelet lineage and pathological analyses suggest that the phenotype is restricted to the platelets. The interval encoding the *7238* mutation has been narrowed to a 600kb region on Ch. 15, encoding 30 protein-coding genes. To identify the mutated gene, we have undertaken massive parallel sequencing of the 600kb interval enriched by hybridization of the genomic DNA to a high-density tiling array covering the interval. The results of this cloning strategy will be discussed.

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S3/P108

A SENSITIZED ENU MUTAGENESIS SCREEN FOR DOMINANT GENETIC MODIFIERS OF THROMBOSIS IN THE FACTOR V LEIDEN MOUSE

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Venous thrombosis results in ~300,000 hospitalizations per year in the USA. A gain-of-function mutation in the factor V gene, Factor V Leiden, (FVL) is the most common known inherited risk factor for venous thrombosis. However, penetrance is incomplete, with only ~10% of FVL carriers experiencing clinically significant blood clotting. Previously, we demonstrated synthetic lethality between FVL and genetic deficiency of a key coagulation component, tissue factor pathway inhibitor (TFPI) in mice. Complete TFPI deficiency is embryonic lethal, whereas TFPI heterozygotes (*Tfpi+/-*) survive normally. However, when *Tfpi+/-* is co-inherited with homozygosity for FVL (*FvQ/Q*), the result is uniform neonatal lethality due to blood clotting. This synthetic lethal genetic interaction was utilized as a phenotyping tool for a sensitized ENU mutagenesis screen. Male *FvQ/Q* mice were ENU mutagenized and bred to *FvQ/+ Tfpi+/-* double heterozygous females. Surviving G1 offspring were analyzed to identify rescued mice with the *FvQ/Q Tfpi+/-* genotype. Our screen will uncover novel dominant mutations that restore hemostatic balance as measured by restoration of *FvQ/Q Tfpi+/-* mouse survival. Analysis of 6300 (~2X genome coverage) G1offspring from our screen has identified 82 mice that survived to weaning. Of the 18 mutants progeny tested to date, 7 are heritable. Extensive pedigrees have been produced for genetic mapping of these mutant lines. In addition, we have validated our experimental design by using a candidate gene approach. We restored survival to *FvQ/Q Tfpi+/-* by breeding heterozygous deficiency of the tissue factor gene onto this background. Thus, tissue factor is one of the genes that should emerge from our screen. Our preliminary findings demonstrate the feasibility of our sensitized approach in the identification of dominant suppressors of the *FvQ/Q Tfpi+/-* lethal phenotype and suggest that there are 10 to 20 blood clotting modifier loci for the *FvQ/Q Tfpi+/-* phenotype. Genetic loci identified in these studies will become candidate modifier genes for contributing to the penetrance of blood clotting in FVL positive humans.

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S4/P46

A LOCUS ON CHROMOSOME 7 DETERMINES INFARCT VOLUME IN THE FOCAL CEREBRAL ISCHEMIA MOUSE MODEL OF STROKE

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Ischemic stroke is a complex phenotype caused by a combination of genetic and environmental factors. Although epidemiological studies have provided substantial evidence for genetic influences in the development of stroke, genetic determinants of the extent of ischemic tissue damage remain unknown. Through the use of a surgically-induced mouse model of focal cerebral ischemia we and others have shown large, reproducible differences in infarct volume among different inbred mouse strains. BALB/c mice show approximately 5-fold larger cortical infarcts than C57BL/6J (B6) mice. A genome-wide linkage scan was performed in 103 F2 intercross animals which identified a locus on chromosome 7 (LOD 11.4) that accounts for 54% of the phenotypic variance in infarct volume. Measurement of infarct volume in chromosome substitution strains validates that the B6 chromosome 7 is required for the protective effect. Measurement of infarct volume in 16 inbred strains allowed a SNP haplotype-based approach to fine-mapping the chromosome 7 locus, reducing the possible candidate genes to only three. None of these three genes shows strain-specific expression differences in cortical tissue. However, BAG3, a modulator of a cellular anti-apoptotic pathway, harbors a non-synonymous coding SNP (I81M) between the strains. *In vitro* and *in vivo* studies are currently underway to investigate the role of this gene in modulating tissue damage after ischemia. The results of this study may uncover novel genes that modulate the severity of human ischemic stroke, as well as provide new targets for therapeutic intervention.

Student Satellite Symposium Session 1 – Sunday November, 2 2.00pm – 2.15pm

S5/P45

INVESTIGATION OF MYOTILIN AS A MODIFIER GENE IN A MOUSE MODEL OF CARDIOMYOPATHY

Pei-Lun Chu[1], Tracy Handnott[2], Monica Moza[3], Olli Carpen[3], Douglas Marchuk[2]
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The Calsequestrin (CSQ) transgenic mouse model of cardiomyopathy exhibits wide variation in phenotypic progression dependent on genetic background. Using this model, we have previously identified seven loci (*hrtfm* or heart failure modifier) which modify disease progression and outcome. *Hrtfm4*, (chromosome 18) is linked to differential survival (12% of the strain variance) as well as heart function. We now report the investigation of a strong candidate gene for this locus. Myotilin is a structural protein of the sacromere in striated skeletal and cardiac muscle. It is located at the Z-disc and binds α-actinin, γ-filamin, and binds and bundles F-actin. Strains used in mapping the locus show a non-synonymous coding SNP, rs30173993, causing an N443I amino acid substitution. The asparagine at residue 443 is highly conserved across species from Xenopus to human, and the 443I isoform is predicted to be pathologic by several web-based programs (PolyPhen, PMut and Panther). This substitution is located within the region of the protein required for actin binding/bundling. Currently, we are attempting to compare the actin-binding capacity of the N- and I-forms of myotilin using a quantitative yeast-two-hybrid assay, and using *in vitro* myotilin – actin binding and bundling assays. In parallel, we are crossing a myotilin knockout to the CSQ transgene to determine the effects of loss of function of myotilin on the CSQ-induced cardiomyopathy.

Student Satellite Symposium Session 1 – Sunday November, 2 2.15pm – 2.30pm

S6/P93

GENETICS AND BIOLOGY OF THE GERM CELL TUMOR SUSCEPTIBILITY LOCUS, *TER*.

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Our lab discovered that inactivation of the mouse *Dead-end* (*Dnd1*) gene causes the *Ter* phenotypes of sterility and testicular germ cell tumor development. DND1, a RNA-binding protein, is expressed in and is essential for primordial germ cell viability. Our laboratory is studying the genetics and molecular function of *Ter* (*Dnd1*). Genetic studies indicate that interaction of the *Ter* locus with loci on Chr X modulates testicular tumor incidence.
There are two DND1 protein isoforms in the mouse, DND1-α and DND1-β. To study the function of these two isoforms in germ cells, we are creating a conditional null allele of DND1-α. DND1 functions by binding the 3' UTR of mRNA targets to prevent miRNA-mediated repression. We found that DND1 interacts with the Apolipoprotein B Editing Complex 3 (APOBEC3) protein, which is also expressed in germ cells. However, in genetic crosses between *Ter* and *APOBEC3* null mice, no rescue of the *Ter* phenotypes was found. Therefore, APOBEC3 does not function antagonistically with DND1, but may act synergistically with it. Recent studies show that APOBEC3 interacts with cellular RNA-binding proteins and mRNAs to inhibit miRNA-mediated repression of mRNA. We are using luciferase assays to determine if interaction between DND1 and APOBEC3 inhibits repression of DND1 mRNA targets. These studies will help elucidate the functional role of DND1 in germ cells and in germ cell tumorigenesis.

Student Satellite Symposium Session 1 – Sunday November, 2 2.30pm – 2.45pm

S7/P91

LINKING GENE EXPRESSION CHANGES TO PROTEIN SPATIAL LOCATION IN MUSCLE

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To gain further insight into mammalian muscle development, we have implemented an interactive 3D virtual muscle (VMus3D) representative of the core structural protein arrangements of striated muscle as an internet-orientated browser for integrating sets of databases and visualisation methods. The objective of this approach is to avoid restricting gene expression results to genes preferentially expressed or differentially expressed within muscle, which cannot provide an integrated model for understanding the overall function of muscle structural proteins. This is especially true for understanding the transition of widely expressed and mobile protein complexes into constrained arrangements present in striated muscle. To test the utility of the VMus3D, we have used it to enhance the information contained in a number of publicly available gene expression datasets (Waardenberg *et al. submitted*). Using the VMus3D, intracellular spatial patterns and certain characteristic expression profiles that are unique to myogenesis have been recognised and a model of muscle development has been constructed. Of particular interest, components of the costamere lacked the expression change and muscle tissue specificity that other muscle structural arrangements within the same or other complexes clearly demonstrated. This indicated that these components are expressed prior to early muscle development presumably performing other roles before being constrained into their muscle specific protein arrangements present in developed muscle. We are now working on integrating various types of datasets, including but not limited to gene expression, regulatory site and protein interaction data, permitting interactome layering within the spatial context of VMus3D. It is anticipated that the continued development of VMus3D will enable us to gain further understanding of the programs defining muscle development.

Student Satellite Symposium Session 1 – Sunday November, 2 2.45pm – 3.00pm

S8/P48

IN THE MP MOUSE, MUTANT *FIBRILLIN-2* ACCUMULATION IN THE ER OF DEVELOPING CILIARY-BODY CELLS ELICITS THE UNFOLDED PROTEIN RESPONSE AND CAUSES PAN-OCULAR MALFORMATIONS

Joe Rainger, David FitzPatrick, Ian Jackson
MRC Human Genetics Unit, Edinburgh, United Kingdom

The *Mp* mouse has a phenotype of microphthalmia and hind-limb syndactyly. Using a positional cloning approach we mapped *Mp* to a locus on chromosome 18 and identified a balanced inversion of 660 kb, which creates two aberrant reciprocal fusion transcripts: *Fbn2* exons 1-63 are fused to *Isoc1* exon 5; and *Isoc1* exons 1-4 are fused to *Fbn2* exons 64-65. *Isoc1* expression is not detected during development and the fusion results in a premature stop codon that is predicted to result in nonsense-mediated decay. The developmental expression of *Fbn2* in both the eye and limb is unperturbed in *Mp*. Loss of function *Fbn2* mutations cause isolated hind-limb syndactyly, however the *Mp* mouse displays additional severe pan-ocular malformations. We ascribe the ocular pathology to the production of a truncated $Fbn2^{Mp}$ protein, which accumulates in the ER where it forms large microfibre-like aggregates. In wild-type animals, *Fbn2* is expressed in cells of the developing ciliary body and in *Mp*, accumulation of mutant protein in these cells triggers the unfolded protein response. These events are coincident with a disruption of ocular development from 15.5 dpc, leading to abnormal retinal patterning and subsequent ocular degeneration. This mutant reveals an important subgroup of cells that are critical for normal development in the mouse eye but which are vulnerable to ER-stress.

Student Satellite Symposium Session 2 – Sunday November, 2 3.30pm – 3.45pm

S9/P57

THE ROLE OF *SOX4* IN INSULIN SECRETION AND IMPAIRED GLUCOSE TOLERANCE.

Alison Hough, Michelle Goldsworthy, Roger Cox
Medical Research Council, Harwell, Oxfordshire, United Kingdom

Two ENU mouse models of impaired glucose tolerance and insulin secretion have different mis-sense mutations in the highly conserved DNA binding domain, the HMG box, of *Sox4.* Complementation studies between both alleles and the chromosome deletion, del36H, confirmed both *Sox4* mutations affect the function of the protein.
Sox4 is a transcription factor that alters DNA conformation and depends on partner proteins to regulate transcription of target genes. It is required for pancreatic islet development but its role in the adult pancreas is unknown.
RNAi using an insulin-secreting cell line confirmed a reduction in glucose stimulated insulin secretion. *Sox4* knockout cells also had reduced insulin secretion in response to tolbutamide (stimulates insulin secretion by closing K_{ATP} channels). K_{ATP} channel closure results in calcium influx, as calcium influx is normal in *Sox4* knockout cells we postulate that *Sox4* acts downstream of the Ca^{2+} channel. Electron microscopy analysis of islets, show no abnormalities in secretory vesicles. Insulin content is normal and no differences are seen in islet area, so the reduction in insulin secretion is not due to a lack of β-cell mass.
Sinner *et al* (2007) presented a novel mechanism by which Sox proteins regulate the canonical Wnt signaling pathway in gut epithelium. They reported that *Sox4* interacts with either β-catenin or TCF7L2. We are determining whether these interactions are found in the β-cell given the implication of TCF7L2, a known Type II Diabetes susceptibility gene, in insulin secretion. A 33% reduction in β-catenin RNA expression is seen in *Sox4* knockout cells.

Student Satellite Symposium Session 2 – Sunday November, 2 3.45pm – 4.00pm

S10/P67

MOUSE MODELS FOR FUNCTIONAL ANALYSIS OF FTO

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Human gene variants of the fat mass- and obesity-associated (FTO) gene have been strongly associated with body mass index (BMI) and type two diabetes. We are testing the role of FTO in obesity, glucose and insulin sensitivity, and body weight regulation using mouse models. These models include mice with an N-ethyl-N-nitrosourea (ENU) derived mutant allele, a knockout, and overexpressing allele of FTO.

A mouse carrying an ENU missense mutation in FTO has been identified (FTO I367F). These mice exhibit a reduction in body and fat mass ($P < 0.01$). In addition FTOI367F heterozygous mice have an increased metabolic rate ($P < 0.05$) with no increase in food intake.

We are examining the association between FTO genotypes on BMI and metabolic traits including, blood plasma glucose, insulin, triglycerides, hormones and urine biochemistry. Furthermore energy intake is being investigated using metabolic cages and energy expenditure is assessed by indirect calorimetry. Body composition is being determined by dual energy X-ray absorptiometry.

Targeted mouse embryonic stem (ES) cells have been achieved by homologous recombination and utilise the Cre-loxP system for tissue specific interruption of the FTO transcript and overexpression of FTO cDNA. A pronuclear random transgenic overexpression of FTO has also been generated.

The development of mouse models for FTO expression and function may elucidate the molecular mechanism for FTO in obesity and type two diabetes.

Student Satellite Symposium Session 2 – Sunday November, 2 4.00pm – 4.15pm

S11/P17

MAPPING OF OBESITY AND FAT DEPOT-SPECIFIC QTLS USING HAPLOTYPE ASSOCIATION AND OTHER RECENTLY DEVELOPED BIOINFORMATICS METHODS

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Obesity presents a growing health problem and an unwanted component of growth in domestic animals. Monogenic forms of obesity are rare and hence the attention has turned to investigating genetics of the more common polygenic form of obesity by quantitative trait locus (QTL) mapping. One objective of this study was to find candidate genes and narrow down the genetic intervals of previously mapped Chr 15 obesity QTL in our polygenic mouse model using interval-specific haplotype analysis and comparative genomics. The second objective was to identify regional adiposity (fat depot-specific) QTLs throughout the mouse genome by genome-wide haplotype association mapping. We phenotyped a large number of different inbred mouse strains and used high density SNPs to identify associations between haplotypes and various traits, in particular different fat pad weights. Our results identify positional candidate genes on Chr15 in our polygenic model as well as reveal genomic regions involved in the control of different fat depot growth. As certain fat depots (e.g., mesenteric fat) have a more pronounced role in obesity-associated diseases (e.g., metabolic syndrome), knowledge of fat depot-specific genes can lead to a more targeted diagnostic and treatment development in humans.

Student Satellite Symposium Session 2 – Sunday November, 2 4.15pm – 4.30pm

S12/P117

MAPPING QTLS FOR MOUSE ANXIETY-RELATED BEHAVIOR USING CONSOMICS

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Anxiety and other psychiatric disorders are one of the most common diseases in humans. About 29% of the U.S. population are affected by an anxiety disorder sometime during their life. Anxiety is a multidimensional phenomenon presumed to have a complex inheritance, involving (the interaction of) multiple genes in combination with epigenetic and environmental factors. Family, linkage and twin studies have consistently indicated that genes indeed play a role in the etiology of anxiety disorders. Unfortunately, attempts to find these human genes have been largely unsuccessful. Therefore, animal models of anxiety were developed to facilitate the discovery of the genetic and neurobiological substrates of anxiety and test putative anxiolytic drugs. Over the past decade, methods for genome analysis of animal models have been developed to identify and locate QTLs. Chromosome substitution strains (CSS, also called consomic strains) can accelerate the identification and mapping of QTLs. Male mice from a panel of consomic strains - in which a single full-length chromosome from the A/J inbred strain has been transferred onto the genetic background of the C57BL/6J inbred strain - and the parental strains were examined in the modified hole board test. With this test several parameters for anxiety-related behavior towards an unprotected area were measured. We identified one consomic strain (CSS-19) that differed in avoidance behavior from the C57BL/6J, but not in locomotion. QTL analysis of male progeny from an F_2-intercross between C57BL/6J and CSS-19 resulted in significant QTLs, which is a first step in the identification of genes underlying this trait.

Student Satellite Symposium Session 2 – Sunday November, 2 4.30pm – 4.45pm

S13/P19

THE PHENOME INTERDEPENDENCY AND SIMILARITY HIERARCHY: A TOOL FOR GENOME-SCALE PHENOTYPIC ANALYSIS

Jeremy Jay[1], Vivek Philip[4], Yun Zhang[1], Michael A Langston[1], Erich Baker[3], Elissa Chesler[2]
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The Phenome Interdependency and Similarity Hierarchy (PhISH) tool has been designed to construct empirically-derived cross-species phenome ontologies based on user submitted sets of genes. Our approach uses bipartite graphs to employ discrete associations and enhance the multi-domain integration of divergent data types. This bipartite graph is built from genes (and their homologs) connected to the phenotypes they are associated with. Phenotype subsets are defined by common connections to a set of genes, and reside in the root node of an is-a hierarchy for the classification of phenotypes. Child nodes are defined by connections to additional genes, creating supersets, which are associated with the same biological networks as the parent node. This process is repeated incrementally to build a tree describing the genomic relationship between the associated phenotypes. Node splitting rules based on similarity, and stopping rules based on node size, are applied to limit the growth and density of the tree. In this way, relationships between large numbers of phenotypes can be analyzed, unlike the typical pairwise analyses commonly used. This approach is available for use at a free, public Internet resource for the comparative analysis of genomic data sets, the Ontological Discovery Environment (http://ontologicaldiscovery.org). Incorporation into this environment allows comparison with other public data sets uploaded to the site, and integration with other species through homology. Results can be interactively fine-tuned, and further analyzed using other tools already implemented, providing a web-based genome-scale analysis environment.

Student Satellite Symposium Session 2 – Sunday November, 2 4.45pm – 5.00pm

S14/P49

A SYSTEMS GENETICS APPROACH TO IDENTIFY MOLECULAR PATHWAYS THAT MEDIATE GENETIC SUSCEPTIBILITY TO LOW DOSE IONIZING RADIATION

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Systems genetics is both an analysis framework through which to assemble gene-phenotype networks and a means to uncover genetic polymorphisms that cause variation in these networks and lead to variable disease susceptibility. We are using systems genetics to uncover the molecular and biochemical events that underlie the response to low doses of ionizing radiation. A systems genetics approach allows us to address the biological effects of low dose radiation (LDR) by treating it as a complex trait. We use the BXD set of recombinant inbred strains as our reference population. This is a genetically characterized population in which the parental strains (C57BL/6J and DBA/2J) exhibit known differential responses to radiation. Adult mice from 39 BXD strains and the parental strains were irradiated with 10cGy of gamma radiation. Mice were sacrificed 24 or 48 hours after radiation, and various tissues were collected for expression profiling and biochemical assays. Our results show both responses to LDR that are robust to genetic variation (e.g., enhanced neutrophil function) and those from which genetic background significantly impacts the response (e.g., SOD activity). We have also confirmed baseline genetic variation in most traits under study, and we used WebQTL (genenetwork.org) to identify putative QTLs controlling these traits. We also present spleen microarray data from the parental strains that demonstrates that while some gene expression networks are similarly regulated in response to LDR, other networks are differentially expressed between the strains. In addition, preliminary data assessing low dose responsiveness in the collaborative cross will be reported.

Student Satellite Symposium Session 2 – Sunday November, 2 5.00pm – 5.15pm

S15/P3

THE GENETICS OF SUSCEPTIBILITY TO SYSTEMIC PNEUMOCOCCAL INFECTION

Laura Boubbane[1], Aras Kadioglu[2], Pete Underhill[1], Andrew Haynes[1], Ayo Toye[2], Chris Holmes[1], Peter W Andrew[2], Steve Brown[1], Paul Denny[1]
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Streptococcus pneumoniae, is an important human pathogen causing pneumonia, bacteraemia and meningitis and is associated with high morbidity and mortality. Host genetic factors play a significant role in susceptibility to pneumococcal disease, however, genetic linkage analysis is impractical due to the paucity of sibling cases or multiple-case families. As an alternative means of identifying candidate disease genes, we have developed a murine model of genetic susceptibility to pneumococcal infection.

Nine inbred strains of mice were infected with *Streptococcus pneumoniae* D39 and BALB/c and CBA/Ca were found to be resistant and susceptible respectively. A major quantitative trait locus called *S. pneumoniae* infection resistance 1; *Spir1* was mapped to proximal chromosome 7, in an F2 intercross.

The contribution of *Spir1* and other potential loci are being examined in several ways, including genome wide analysis of gene expression. In order to prioritise candidate genes, microarrays are being used to investigate differential gene expression during infection of BALB/c and CBA/Ca mice. Microarray data were analysed using the Limma package in 'R' and genes with expression significantly different between the two mouse strains were investigated further using Ingenuity Pathway Analysis software. Six differentially expressed candidate genes located in the *Spir1* locus are undergoing further analysis by qPCR, Immunohistochemistry and western blot.

The critical region containing the *Spir1* locus is also being refined by congenic mapping on both CBA/Ca and BALB/c backgrounds.

Candidate genes are also being sequenced in parental BALB/c and CBA/Ca DNA and any polymorphisms assessed.