

Monday November, 13
4.30pm – 6.30pm
Poster Session 2
Immunity and Infection
Posters P50 – P53

**S7/
P50 CHEMICAL MUTAGENESIS OF THE MOUSE GENOME TO UNVEIL HOST
RESISTANCE GENES**

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P51 GENETIC ANALYSIS OF HOST RESISTANCE TO PROGRESSIVE CRYPTOCOCCAL PNEUMONIA

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**P52 CONGENIC MICE FOR THE IDENTIFICATION OF GENES RESPONDING TO INFECTION WITH
TRYPANOSOMA CONGOLENSE**

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P53 MICROBE-RELATED PHENOTYPES, GOOD AND BAD, ITS GOOD TO BE AWARE

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Cryptococcus neoformans is a unicellular fungus with global distribution that has been recognized as an emerging pathogen. The clinical manifestations of human *C. neoformans* infection include pneumonia, meningitis, and disseminated disease. In the absence of highly active antiretroviral therapy (HAART), *C. neoformans* is a leading cause of pneumonia in HIV patients and has been associated with a 42% mortality rate.

To investigate the hypothesis that the outcome of cryptococcal pneumonia is genetically regulated, a clinically relevant mouse model was chosen to study the influence of host defense factors on progressive disease. Ten well-characterized inbred mouse strains were screened for relative susceptibility towards cryptococcal pneumonia following direct intratracheal challenge with 10⁴ cfu/ml of encapsulated *C. neoformans* 24067 (serotype D). Phenotypic susceptibility or resistance was defined as a quantitative trait by determining the number of colony forming units (CFU) in the lungs four weeks after infection. Notably, the lung fungal burden among these inbred strains varied by over 1000-fold. C57BL/6J was the most susceptible strain (mean log CFU/lung of 6.94 ± 0.16 SEM) in comparison to the two most resistant strains, CBA/J (mean log CFU/lung of 4.27 ± 0.27 SEM) and SJL/J (mean log CFU/lung of 3.25 ± 0.20 SEM). A completely dominant mode of inherited phenotypic resistance was observed in [CBA/J x C57BL/6J] F1 hybrids. Gender specific differences in the distribution of host resistance were observed in 93 segregating [CBA/JxC57BL/6] F2 animals with a larger proportion of male mice exhibiting a relatively resistant phenotype. Genome-wide linkage analysis is currently underway to identify quantitative trait loci that mediate gender specific host resistance to progressive *C. neoformans* pneumonia.

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AJ, Balb/c and C57BL/6 mice differ in response to infection with *Trypanosoma congolense* with mean survival times of 15, 60 and 120 days after infection. Five QTL on chromosomes 17, 5, and 1 have been identified that are involved in the control of this phenotype. We have constructed three congenic mouse lines with the most resistant C57BL/6 alleles introgressed into the most susceptible AJ background. The congenic mice have been phenotyped and for each line the difference in survival time between congenic mice and litter mate controls is not significantly different from the difference in survival attributed to the corresponding QTL.

The mice have been genotyped with 800 informative SNP from the Illumina murine SNP mapping set to identify residual regions of C57BL/6 DNA that have not been eliminated by backcrossing. The expression of all liver genes has been determined on Affymetrix and compared with the expression of genes from inbred parental AJ mice.

A number of genes outside the introgressed regions (and shown to be of AJ origin) were found to be differentially expressed relative to AJ inbred controls suggesting that these genes are trans regulated by genes in the QTL.

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MICROBE-RELATED PHENOTYPES, GOOD AND BAD, ITS GOOD TO BE AWARE

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Infectious or infesting agents may be introduced intentionally into genetically engineered mice (GEM) for the purpose of eliciting phenotypes that elucidate gene function, but often are examples of environmental (nurture) factors that can impact a wide variety of phenotypes. Induced pathology, disease or phenotypes frequently are strain dependent, and vary with other factors including sex and age of the host, strain and dose of the agent, route of infection, copathogens, spontaneous mutations and genetic manipulations. Infectious agents are more common in laboratory mouse colonies than many of us realize. The most prevalent agents do not cause overt clinical disease in most of the mice we use. They are neither obvious nor uncommon in colonies that are termed 'SPF' or 'barriers'. Worldwide the most prevalent agents include Mouse Hepatitis Virus (MHV, a Coronavirus), mouse parvoviruses, Theilers mouse encephalitis virus (TMEV or GDVII, a Picornavirus), mouse Rotavirus (EDIM), helicobacters, *Pasteurella pneumotropica*, pinworms and mites. While these agents may not cause significant morbidity or mortality, they should be expected to immunomodulate and to cause or impact a variety of other phenotypes, including but not limited to CNS and neurobehavioral phenotypes, enterohepatic and metabolic phenotypes, fecundity, growth, physiology, cancer susceptibility and progression. Infections are not all bad, and their phenotypic effects may improve our understanding of gene functions. However, we should be aware of the agents in our colonies, and of their potential impacts on phenotypes. Phenotypes related to some of the most common agents in our colonies will be discussed briefly.