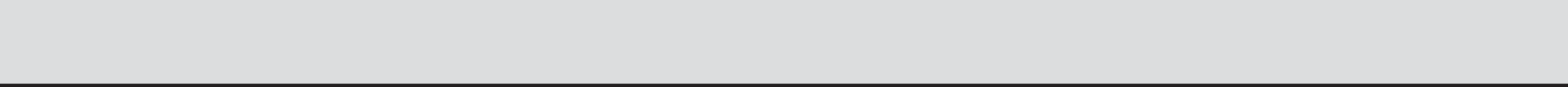


Wednesday October 31
Oral Presenters Abstracts



**IMMUNITY/INFECTION
ORAL PRESENTATION****Wednesday October, 31****9.00 – 9.15am****O7-1****IMMUNOLOGICAL PROFILING OF LABORATORY INBRED AND WILD-DERIVED MOUSE STRAINS DEVELOPED IN JAPAN**

Yasuyuki Kitaura¹, Kazuyuki Mekada¹, Hatsumi Nakata¹, Yoshibumi Matsushima², Jan Mei-Ling^{1,3}, Toshihiko Shiroishi⁴, Kazuo Moriwaki¹, Yuichi Obata¹, Atsushi Yoshiki¹

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A number of mouse inbred strains has been established and greatly contributed to immunology and cancer biology. Since most standard inbred strains originated from the small genetic pool, genetic variants of distinct origins must be valuable for the study of gene functions. RIKEN BioResource Center has been established as a global not-for-profit biological resource center to collect, preserve and distribute high-quality mouse resources developed mainly in Japan. In this study we carried out immunological profiling by FACS of inbred and wild-derived strains developed in Japan such as NOD, KK, NC, SL/Kh, SL/Ni, DDY, DDD, II-TES, JF1, MSM, KOR1, KOR5, KOR7, AIZ and STM1. C57BL/6J mice were used as normal control. We measured the percentage of T cells, B cells, granulocytes and monocytes in spleens at 8 weeks of age by using anti-TCRbeta, -B220, -Gr1 and -Mac1 antibodies, respectively. T cells were subdivided further into CD4T cells and CD8T cells using anti-CD4 and -CD8 antibodies, respectively. We found characteristic flow cytometric phenotypes among these strains: increased B cells in SL/Kh, increased T cell ratio in NOD and SM/J, increased CD8T cells in SM/J, decreased CD8T cells in KOR5 and DDY. Interestingly, a Japanese wild-derived strain, KOR5 was found to be severely deficient in CD8T cells. Thus, immunological profiling by FACS using antibodies for lineage-specific markers may provide important information on immunology, allergy, inflammation and cancer, and can add values on the unique inbred strains.

**IMMUNITY/INFECTION
ORAL PRESENTATION****Wednesday October, 31****9.15 – 9.30am****O7-2****EXTENDING THE HOST RANGE OF LISTERIA MONOCYTOGENES TO INCLUDE THE MOUSE**

Thomas Wollert¹, Bastian Pasche², Maïke Rochon³, Stefanie Deppenmeier⁴, Joop van den Heuvel³, Achim D. Gruber⁴, Dirk W. Heinz³, Wolf-Dieter Schubert¹ and [Andreas Lengeling](#)^{2,5}

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Most pathogens specialize on and are hence restricted to a limited number of hosts. Occasionally, however, they switch their host spectrum abruptly, causing dramatic outbreaks in the naive host population. We have reproduced such a switch in host tropism by extending the host range of the human pathogen *Listeria monocytogenes* to include the mouse. Two point mutations in the invasin Internalin (InIA), chosen on the basis of the complex between InIA and human E-cadherin and verified biophysically, induce recognition of formerly foreign murine E-cadherin. Re-engineered bacteria carrying these point mutations breach the intestinal barrier of gastrically challenged mice and cause systemic infection with 1000-fold greater bacterial numbers in liver and spleen. Thus, seemingly insignificant atomic-level changes impact dramatically on an entire biological system. Our re-engineered bacterial strain allows human Listeriosis to be investigated in a generally applicable murine infection model allowing immunological responses to intracellular pathogens and the role of virulence factors involved in host colonization to be analyzed *in vivo*.

**IMMUNITY/INFECTION
ORAL PRESENTATION****Wednesday October, 31****9.45 – 10.00am****O7-3****EPISTATIC INTERACTIONS IN WILD-DERIVED MICE IDENTIFY IRAK-1 BINDING PROTEIN AS AN IMPORTANT REGULATOR OF INFLAMMATION**James Conner^{1,2}, Irina Smirnova¹, Alexander Poltorak¹¹Department of Pathology, Tufts University School of Medicine, ²Program in Immunology, Sackler School of Biomedical Sciences

Recognition of pathogens by the innate immune system activates TLR-mediated pathways, resulting in the production of inflammatory cytokines. While signalling events leading to the pro-inflammatory response are well characterized, the mechanisms that define specific cytokine profiles, as well as ways to prevent the detrimental release of excessive amounts of these molecules, are less clearly understood. The acute phase cytokine interleukin-6 (IL-6) exemplifies the need for specific and efficient regulation, based on its deleterious potential in inflammatory and autoimmune disorders. Here, we use positional cloning in wild derived mouse strains to implicate the IRAK-1 binding protein (IRAK1BP, also known as SIMPL) as a negative regulator of TLR mediated IL-6 production. Human PBMC and primary macrophages from wild derived mouse strains, but not from C57BL/6J mice, upregulated IRAK1BP mRNA by 4 h after stimulation with agonists of various TLRs. The suppressive role of IRAK1BP in IL-6 secretion emerged in a forward genetic analysis, showing an epistatic interaction between the IRAK1BP containing locus and another locus with a positive contribution to IL-6 production. When overexpressed in RAW 264.7, a murine macrophage cell line, IRAK1BP potently inhibited transcription of IL-6. Conversely, shRNA knockdown of IRAK1BP in these cells enhanced IL-6 expression 100 fold. Our results reveal that IRAK1BP is a critical factor preventing dangerous overproduction of IL-6 by the innate immune system. Furthermore, these results show that the genetic diversity of wild derived mouse strains make them a unique model for elucidating important human gene functions that have been lost in laboratory inbred strains.

**IMMUNITY/INFECTION
ORAL PRESENTATION****Wednesday October, 31****10.00 – 10.15am****O7-4****UNRAVELLING THE HOST RESPONSE TO STREPTOCOCCUS PNEUMONIAE USING ENU
MUTAGENESIS**

Vera Ripoll-Nunez¹, Andrew R Haynes¹, Sian Polley³, Vitor Fernandes², Ayo A Toyé², Aras Kadioglu², Peter W Andrew² and Paul Denny¹

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Lung infections, according to a measure combining morbidity and mortality used by the World Health Organisation, have perhaps the most significant impact on public health of all categories of disease (1). *Streptococcus pneumoniae*, the pneumococcus, is one of the most common causes of community acquired pneumonia and also bacterial meningitis, otitis media and sepsis. Effective vaccines and antibiotics have improved therapy, but they are an incomplete solution because of the serotype variability, genomic plasticity and ever-increasing frequency of resistant strains of the pneumococcus. Several single-gene association studies have demonstrated the importance of genetics in susceptibility to pneumococcal infection, but whole-genome linkage or association studies have been impractical due to insufficient well-characterised clinical cases. One way of complementing human studies, to circumvent these limitations, is by exploring the genetics of pneumococcal disease susceptibility in the mouse. We have shown that BALB/c mice are resistant to acute pneumococcal disease and associated morbidity (2, 3). This natural resistance is now being exploited in dominant and recessive screens for N-ethyl-N-nitrosourea (ENU)-induced genetic variants associated with infection susceptibility, on a purebred BALB/c genetic background. Mutant mice from this screen will undergo a variety of in vitro assays related to innate immunity and the inflammatory response, including measurement of inflammatory mediators e.g. TNF-alpha and other cytokines, flow cytometry of blood leukocytes and histological assessment of inflammatory lesions in the lung. The first phenodeviant mice have been identified and we will report progress in the phenotype screen. 1. Mizgerd, J. P. (2006). *PLoS Medicine* 3(2): e76. 2. Gingles, N. et al. (2001) *Infect Immun* 69(1): 426-34. 3. Denny, P., E. Hopes, et al. (2003) *Mamm Genome* 14(7): 448-53.