Program Supplement Addendum

"Host-Response to Pathogens: Handling the Uninvited Guest"

37th Annual Meeting of the Society for Leukocyte Biology

October 21-23, 2004

The Westin Harbour Castle Hotel, Toronto, Ontario

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Program changes and additions:

Thursday, October 21

8:30-11:30am The AIRIG conference will convene in Harbour Salon C. Posters will be displayed in Pier 4 & 5.

8:00-10:00pm Student/postdoc mixer. The Harbour Sports Grille.

Friday, October 22

8:00-9:00am POSTER WORKSHOP 1:
(Harbour Salon A) Chair: S. Goyert
A continental breakfast will be served.

The order of the presentations in Poster Workshop 1 will be as follows:

5 8:00am **IL-15 and IL-2 oppositely regulate expression of the chemokine receptor CX3CR1 through selective NFAT1- and NFAT2-dependent mechanisms.** J. Barlic, D.H. McDermott, M.N. Merrell, J. Gonzales, L. Via, P.M. Murphy. Molecular Signaling Section, Laboratory of Host Defenses, NIAID, NIH, Bethesda, MD.

46 8:12am **Differential dependence towards lipid rafts of CD4+ and CD8+ T cells in TCR signalling: role in immune senescence.** A.L. Larbi, G.D. Dupuis, N.D. Douziech, A.K. Khalil, T.F. Fulop. Research center on Aging, Qc, Canada.

64 8:24am **Fibronectin Differentially Modulates MMP-9 Production.** N. Lahat, B. Marom, H. Bitterman, M.A. Rahat. Immunology Research Unit, Carmel medical Center and Facylty of Medicine, Technion, Haifa, Israel.

139 8:36am **A Quantitative Proteomic Approach Reveals Functional Protein-protein Interactions in Immune Cells at Real-Time: FLAP-1 and Fliih Modulate the MyD88-dependent Pathway.** TY Wang, S Gu, X Chen, T Ronni. Los Alamos National Lab, Los Alamos, NM.

LB13 8:48am **Protein kinase D (PKC-mu) is involved in inflammatory signalling in response to bacterial flagellin.** Nicholas Graham, Arnawaz Kaleem, Theodore Steiner*. Division of Infectious Diseases, University of British Columbia, Vancouver, BC

Saturday, October 23

8:00-9:00am POSTER WORKSHOP 2:
(Harbour Salon A) Chair: J. Fierer
A continental breakfast will be served.

The order of the presentations in Poster Workshop 2 will be as follows:

89 8:00am **Inhibition of Phagosome Maturation by Legionella Surface Glycoconjugates.** E. Fernandez-Moreira, M.S. Swanson. Dept. of Microbiology and Immunology, Univ. of Michigan Medical School, Ann Arbor, MI.

97 8:12am **Role of TLR4 in *Coxiella burnetti* Infection.** J-L. Mege, D. Raoult, A. Honstettre. Faculty of Medicine, Marseille, France.

112 8:24am **Apoptosis Signal Regulating Kinase 1 (ASK1) and Caspase 8 Play Central Roles in Mycobacteria-Induced Macrophage Cell Death.** A .Bhattacharyya, S. Pathak, C. Basak, M. Kundu, J. Basu. Bose Institute, Calcutta, India.

LB8 8:36am **Inflammatory Macrophages from Mice Fed Ethanol and Infected with *Salmonella enterica* serovar Typhimurium produce higher levels of TNF-a then Macrophages from Infected Control Mice.** Mike P. Burrows, Debbie Vidlak, Jennifer Van Evera, Jennifer Strachota, Thomas R. Jerrells Ph.D. Pathology and Microbiology, University of Nebraska Medical Center, Omaha, Nebraska,

LB15 8:48am **Differential Requirements for NF-κB p65 Translocation, TNF Release and Interferon-β Induction by Human Macrophages Ingesting *Listeria monocytogenes* Point to a Cytosol-Specific Immune Response.** Thornik Reimer*, Thomas W. Jungi. Institute of Veterinary Virology, University of Bern, Switzerland.

Future SLB Meetings:

• April 5, 2005
Guest Society Symposium at the Annual Meeting of the American Society for Investigative Pathology (April 2-6, San Diego, CA)

• September 21-24, 2005
"Phagocytes and Innate Immunity". Oxford, England

• November 9-11, 2006
San Antonio, Texas (Joint meeting with the International Endotoxin Society)

Abstract Changes:

12 **Mycobacterium bovis BCG-Induced Leukocyte Lipid Body Formation in vivo: Cytoplasmic Lipid Domain Involved in Innate Immunity to Intracellular Pathogen.** H D'Ávila[1,2], RCN Melo[2], PE Almeida1,[2], UFTR Silva[1], E Werneck-Barroso[3], HC Castro-Faria-Neto1, PT Bozza[1]. [1]Lab Imunofarmacologia, IOC, FIOCRUZ, RJ, [2]Lab Biologia Celular, UFJF, Juiz de Fora, MG [3]Lab. Farmacocinética, FIOCRUZ, RJ, Brazil

13 Unable to attend meeting.

89 **Inhibition of Phagosome Maturation by Legionella Surface Glycoconjugates.** Esteban Fernández Moreira, *Juergen H. Helbig and Michele S. Swanson Department of Microbiology and Immunology, University of Michigan, Ann Arbor, MI , *Institute of Medical Microbiology and Hygiene, Dresden, Germany.

120 Unable to attend meeting.

151 (revised abstract)

A Critical, Non-redundant Role for CCR5 in West Nile Virus Induced Encephalitis and Mortality. William G. Glass, Rushina Cholera and Philip M. Murphy. National Institutes of Health, NIAID, Bethesda, MD.

We infected C57BL/6 mice sub-cutaneously with 1e4 ffu West Nile Virus (NY1999) and investigated expression of immune modulators in the brain. Virus is detected in the brain as early as 5 days post infection and is cleared by day 18. Previous experiments using μMT and RAG1-/- mice indicate that WNV infection of the CNS is ultimately resolved by the adaptive immune arm. The expression of IFN-g. IL-12, TNF-a and not IL-4 or IL-10 in the CNS indicate the local immune repose is predominantly Th1-shifted. CCR1, CCR5, CXCR3 and CX3CR1 and several ligands of these receptors were up-regulated at either the mRNA, protein level or both. Consistent with this, FACS analysis revealed increased accumulation of CD4 and CD8+ T cells, NK cells, and macrophages in the brain, of which approximately 25% expressed CCR5. WNV infected CCR5-/- mice had diminished CD4+ T cell, NK cell, and macrophage migration to the brain. Further, the number of leukocyte-associated lesions dramatically decreased in CCR5-/- mice as compared to C57BL/6 mice. This reduction in lesions and leukocyte infiltration is likely due solely to the lack of CCR5, as there was no difference in chemokine expression between C57BL/6 and CCR5 -/- mice. In sharp contrast to WNV infected C57BL/6 mice, which have ~35% mortality (n=202), CCR5-/- mice have a ~75% mortality rate (n=66). This increase in mortality was associated with increased viral loads at day 12 compared to C57BL/6 mice. CCR5 appears to have a central role in the development of an adaptive immune response to WNV. Specifically, these data indicate that CCR5 plays a critical, non-redundant role in leukocyte trafficking to the brain and protection from mortality following WNV infection.

Late-Breaking Abstracts

The following late-breaking abstracts will be displayed in the designated Poster Session (PS1 on Thursday, October 21 or PS2 on Friday, October 22) in Pier 4 & 5. Poster session assignment and board numbers are indicated in parentheses.

LB1 (PS1- 65)

Antibacterial cathelicidin peptide CAP11 modulates the LPS-induced suppression of neutrophil apoptosis by blocking the binding of LPS to target cells. Isao Nagaoka*, Shin Yomogida, Hiroshi Tamura and Michimasa Hirata. Department of Host Defense and Biochemical Research, Juntendo University, School of Medicine, Tokyo, Japan; Seikagaku Corporation, Tokyo, Japan; Institute of Ohtaka Enzyme Co., Hokkaido, Japan.

Peptide antibiotics possess potent antimicrobial activities against invading micro-organisms and contribute to the innate host defense. We previously revealed that antibacterial cathelicidin CAP11 (cationic antibacterial polypeptide of 11 kDa) could exert protective actions against murine endotoxin shock model. During Gram-negative bacterial sepsis, LPS activates neutrophils and their apoptosis is suppressed. Prolonged presence of activated neutrophils causes uncontrolled release of toxic metabolites, leading to the systemic tissue injury. In this study, to evaluate a therapeutic potential of CAP11 for Gram-negative sepsis, we investigate the action of CAP11 on LPS-induced suppression of neutrophil apoptosis *in vitro* using human neutrophils.

LPS suppressed neutrophil apoptosis, accompanied with the activation of NF-kB, phosphorylation of extracellular signal-related protein kinase (ERK), expression of Bcl-XL (an anti-apoptotic protein) and inhibition of caspase 3 activity. Interestingly, CAP11 reversed the actions of LPS to trigger these changes, and induced neutrophil apoptosis. Moreover, neutralizing antibodies against Mac-1 (CD11b/CD18) and Toll-like receptor (TLR) 4 completely blocked the LPS-induced suppression of neutrophil apoptosis, suggesting a major role of Mac-1 and TLR4 in the LPS-mediated neutrophil activation. In addition, LPS activated monocytes to produce proinflammatory cytokines (IL-1β, TNF-α and IL-8) and inhibited neutrophil apoptosis. Importantly, CAP11 reduced the cytokine production, thereby inducing neutrophil apoptosis. Finally, CAP11 strongly suppressed the LPS-binding to neutrophils and monocytes.

Together these observations indicate that CAP11 is able to block the LPS-induced survival of neutrophils via the suppression of anti-apoptotic signaling in neutrophils and cytokine production from monocytes by inhibiting the binding of LPS to target cells. Thus, CAP11 is expected to have a therapeutic potential in Gram-negative sepsis to induce neutrophil apoptosis, thereby possibly attenuating tissue injury.

LB2 (PS2 - 63)

***Salmonella* impairs RILP recruitment to Rab7 during maturation of invasion vacuoles.** Rene E. Harrison[1*], John H. Brumell[2], Arian Khandani[1], Cecilia Bucci[3], Cameron C. Scott[4], Xiuju Jiang[2], B. Brett Finlay[5] and Sergio Grinstein[4]. [1]Department of Life Sciences, University of Toronto at Scarborough, 1265 Military Trail, Toronto, Ontario, Canada M1C 1A4, [2] Infection, Immunity and Repair, The Hospital for Sick Children, 555 Univ. Ave., Toronto, Ontario, Canada M5G 1X8. [3] Dipartimento di Scienze e Tecnologie Biologiche ed Ambientali, Universita degli Studi di Lecce, Via Monteroni, Lecce, Italy 73100, [4] Division of Cell Biology, The Hospital for Sick Children, 555 University Ave., Toronto, Ontario, Canada M5G 1X8, [5] Biotechnology Laboratory and Departments of Biochemistry and Molecular Biology, Microbiology and Immunology, University of British Columbia, Vancouver, British Columbia, Canada, V6T 1Z3

Following invasion of epithelial cells, *Salmonella enterica* Typhimurium resides within membrane-bound vacuoles where it survives and replicates. Like endocytic vesicles, the *Salmonella*-containing vacuoles (SCV) undergo a maturation process that involves sequential acquisition of Rab5 and Rab7, and displacement towards the microtubule-organizing center. However, SCV fail to merge with lysosomes and instead develop subsequently into a filamentous network that extends towards the cell periphery. We found that the initial centripetal displacement of the SCV is due to recruitment by Rab7 of RILP (Rab7-Interacting Lysosomal Protein), an effector protein that can simultaneously associate with the dynein motor complex. Unlike the early SCV, the *Salmonella*-induced filaments (Sifs) formed later are devoid of RILP and dynein, despite the presence of active Rab7 on their membranes. Kinesin appears to be involved in the elongation of Sifs. SifA, a secreted effector of *Salmonella*, was found to be at least partly responsible for uncoupling Rab7 from RILP in Sifs and *in vitro* experiments suggest that SifA may exert this effect by interacting with Rab7. We propose that, by disengaging RILP from Rab7, SifA enables the centrifugal extension of tubules from the *Salmonella*-containing vacuoles, thereby providing additional protected space for bacterial replication.

LB3 (PS1 - 66)

Short-term moderate alcohol intoxication impairs hemodynamic and immune response to hemorrhagic shock. *Williams K., Olubadewo J., Zambell K., Vande Stouwe C., Carnal J., Molina PE.

Alcohol intoxication is a factor in 20-37% of all traumatic injury cases seen in emergency rooms. Individuals with a blood alcohol content (BAC) ≥100mg/dL are likely to present with higher injury severity score and develop complications during their hospitalization. The pathophysiology involved is not well understood due to confounding factors such as duration of alcohol consumption, blood alcohol concentrations and injury severity. Studies from our laboratory have previously demonstrated that prolonged (15h) acute alcohol administration (binge drinking) to conscious rodents prior to fixed-pressure hemorrhagic shock (HS) aggravates the hemodynamic and metabolic responses and accentuates early lung pro-inflammatory cytokine expression. The present study aimed to determine whether similar responses were observed following a single dose of alcohol administration prior to HS. Chronically catheterized male Sprague-Dawley rats (250-300g) were randomly selected to receive either an intragastric bolus of ethanol (1.75g/kg) or isocaloric dextrose (1.5mL) 30 minutes prior to a fixed-volume (50% of blood volume) HS followed by fluid resuscitation with Ringer's lactate (20mL). BAC was 144±11 mg/dL at baseline and decreased to 89±11 post-HS. Alcohol produced a 14% decrease in basal mean arterial blood pressure (MABP) a more sustained hypotensive response to 50% blood loss when compared to dextrose-treated animals and a blunted (20%) response to fluid resuscitation. Alcohol administration did not alter basal levels nor did it affect the 3- and 2-fold HS-induced rise in epi and norepinephrine (respectively). HS followed by fluid resuscitation produced upregulation (30-40%) in lung TNF-α, IL-6 and IL-10 expression. Alcohol blunted the hemorrhaged-induced increase in lung TNF-α and IL-10 and completely prevented the rise in IL-6. These results indicate that hemodynamic counterregulatory responses to HS are impaired even following a single dose of alcohol administration, despite a lack of overt alcohol-induced alterations in the sympathetic response to blood loss. Furthermore, in contrast to the pro-inflammatory effects of prolonged (15 h) alcohol administration on HS-induced tissue cytokine expression, a

single dose of alcohol resulted in generalized suppression of lung cytokine responses. These results underscore the differential neuroendocrine and immune effects of acute vs. prolonged alcohol administration on responses to traumatic injury. (Supported by Louisiana Health Excellence Fund, ONRN00014-00-1-0326, AA09803).

LB4 (PS1 - 67)

Anti-apoptotic mechanism and reduced expression of phospholipase D in neutrophil apoptosis. Jong-Young Kwak*, Sun-Young Lee, Min-Jung Lee, Min-Jung Jang, Hae-Young Park, Ja-Woong Kim, Yoe-Sik Bae. Department of Biochemistry, College of Medicine and Medical Research Center for Cancer Molecular Therapy, Dong-A University, Busan 602-714, Korea.
Resistance of neutrophils to apoptosis arises from constitutive or the up-regulated expression of an array of proteins that counteract death signals. Phospholipase D (PLD) catalyzes the hydrolysis of phosphatidylcholine to generate free choline and phosphatidic acid (PA). In neutrophils, phagocytosis, activation of NADPH oxidase, and the degranulation of phagocytes have been related to increased PLD activity. PLD is also secreted by many microorganisms and bacterial PLD may act as a potent virulence factor. However, as compared to research on the functional roles of PLD in neutrophil activation, its role in neutrophil apoptosis has not been investigated and the molecular target of PLD-derived PA has not been identified. Anti-Fas antibody-stimulated increased apoptosis of neutrophils was significantly blocked by the exogenous addition of bacterial PLD from *Streptomyces chromofuscus* (scPLD), and neutrophils cultured for 24 h in the presence of anti-Fas antibody showed lower agonist-stimulated PLD activity compared to untreated cells. The amount of PLD1a protein reduced time-dependently in cultured neutrophils, but was recovered by treating with LPS or GM-CSF. The reduction in PLD1a protein level was blocked by caspase inhibitors. The exogenous addition of scPLD blocked the up-regulation of FADD expression, mitochondrial permeability, and the cleavages of procaspase-8, procaspase-3, and protein kinase C-delta. It was also found that the protein level of apoptosis inducing-factor (AIF) was increased in cultured neutrophils but its expression was reduced by scPLD. However, sulfasalazine-induced apoptosis and change of protein expression were not blocked by scPLD. Taken together, the activity and protein levels of PLD play a role as an anti-apoptotic factor by acting at multiple levels of the apoptotic cascade in neutrophils.

LB5 (PS2 - 64)

Phosphatidylinositol 3-kinase and Cytohesin-1 dependent Cross-Talk between CD14 and CR3 during Phagocytosis of Mycobacteria.

Khalid Sendide[1-2], Jimmy S. I. Lee[1], Sylvain Bourgoin[3], Amina Talal[1] and Zakaria Hmama[1]*. [1]Coastal Health Research Institute, Vancouver, British Columbia, Canada V5Z 3J5. [2]Laboratoire d'Immunologie, Faculté des Sciences Dhar Mahraz, Université Mohamed Ben Abdallah, BP 1796, Atlas, Fès, Morocco. [3]Centre de Recherche en Rhumatologie et Immunologie, Ste-Foy, G1V 4G2, Quebec, Canada

The hypothesis that phagocytosis of mycobacteria involves functional interaction between CD14 and CR3 was investigated using CD14-transfected THP-1 cells (THP-1wt) and cells expressing vector alone (THP-1rsv). Internalization of *Mycobacterium bovis* BCG was limited in THP-1rsv and markedly enhanced in THP-1wt. Phagocytosis was optimal in the presence of normal serum and inhibited with mAbs to either CD14 or CR3. Though suboptimal, phagocytosis under serum free conditions was partially maintained in presence of purified LPS-binding protein. The latter was blocked by anti-CD14, but not anti-CR3 mAb, suggesting dual mechanisms of phagocytosis involving either CD14 alone or a CD14-regulated CR3-dependent pathway. Phagocytosis by THP-1wt cells was attenuated by phosphatidylinositol 3-kinase inhibitors LY294002 and wortmannin. Furthermore, experiments using transfected CHO fibroblasts showed substantial accumulation of phospatidylinositol-3,4,5-P_3 at the BCG attachment site in CHO cells expressing CD14 and Toll like receptor 2 suggesting that bacteria bind to CD14 and utilize Toll like receptor 2 to initiate a phosphatidylinositol 3-kinase signaling pathway. Alternatively, blocking Toll like receptor 2 with specific mAb inhibited phagocytosis by THP-1wt cells. The knock out of cytohesin-1, a phosphatidylinositol 3-kinase-regulated adaptor molecule for β2-integrin activation, specifically abrogated CR3-ingestion of BCG consistent with the observation of physical association between CR3 and cytohesin-1 in cells stimulated with mycobacterial surface components. These findings reveal that mycobacteria promote their uptake through a process of "inside-out" signaling involving CD14, Toll like receptor 2, phosphatidylinositol 3-kinase and cytohesin-1. This converts low avidity CR3 into an active receptor leading to increased bacterial internalization.

LB6 (PS2 - 65)

Augmentation of the bactericidal and LPS-neutralizing activities of guinea pig CAP11-derived antibacterial peptide by amino acid substitutions. Daiju Okuda*, Shin Yomogida, Yuko Tsutsumi-Ishii, Hiroshi Tamura and Isao Nagaoka. Department of Host Defense and Biochemical Research, Juntendo University, School of Medicine, Tokyo, Japan; Seikagaku Corporation, Tokyo, Japan

Mammalian myeloid and epithelial cell express several antibacterial peptides (defensins and cathelicidins) that contribute to the innate host defense by killing invaded microorganisms. CAP11 (cationic antibacterial polypeptide of 11 kDa), which was isolated from guinea pig neutrophils, has been shown to possess the potent bactericidal and LPS-neutralizing activities. Recently, we have characterized the biologically active region of CAP11, and revealed that 18mer peptide of CAP11(1-18) has the most potent activity among various derivatives; however, its bactericidal and LPS-neutralizing activities were much lower than those of native CAP11.

In this study, we tried to enhance the biological activity of CAP11(1-18) by substituting amino acids. Two novel peptides, CAP11(1-18m) and CAP11(1-18m2), whose hydrophobicity and positive charge were modified by the amino acid substitutions, exhibited more potent bactericidal activities against *S. aureus* and *E. coli*, and more strongly inhibited the LPS-binding to CD14+ RAW264.7 cells, compared with CAP11. Notably, the biological activity of CAP11(1-18m2) was about 10-fold greater than that of CAP11. Moreover, CAP11(1-18m2) completely killed both methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) even at 0.1 mg/ml.

Thus, the bactericidal and LPS-neutralizing activities of CAP11-derived antibacterial peptides could be enhanced by the modification of their hydrophobicity and positive charge.

LB7 (PS1 - 68)

Phosphorylation of MRP-14 by p38 MAPK Regulates Association with the Actin Cytoskeleton in Human Neutrophils

G. Lominadze, M.J. Rane, M. Merchant, K.R. McLeish*. Dept. of Medicine and Biochemistry and Molecular Biology, Univ. of Louisville and VAMC, Louisville, KY.

The p38 mitogen-activated protein kinase (p38 MAPK) cascade participates in a number of neutrophil responses, including respiratory burst activity, exocytosis, actin reorganization, chemotaxis, and IL-8 production. The targets of p38 MAPK that mediate these functions are largely unknown. To map the signal transduction pathways from p38 MAPK to these functional responses, a pro-

teomic approach was performed in which recombinant active p38 MAPK and [^{32}P]ATP were added to lysates from unstimulated human neutrophils. Proteins were separated by two-dimensional gel electrophoresis (2DE), phosphoproteins were visualized by autoradiography, and these proteins were identified by mass spectometry. Phosphorylation of MRP-14 by p38 MAPK was confirmed by an in vitro kinase reaction using purified MRP-14. The site of phosphorylation of MRP-14 by p38 MAPK was identified by tandem mass spectrometry to be Thr-114.

Phosphorylation of MRP-14 by p38 MAPK in intact neutrophils was examined by [^{32}P]orthophosphate loading, followed by fMLP stimulation in the presence and absence of a p38 MAPK inhibitor, SB203580. 2DE separation of neutrophil proteins and autoradiography showed that MRP-14 was phosphorylated following fMLP stimulation, and this phosphorylation was blocked by SB203980. The effect of MRP-14 phosphorylation by p38 MAPK on co-localization with the actin cytoskeleton was determined by confocal microscopy of Triton X-100 permeabilized neutrophils. A small amount of MRP-14 was associated with cortical F-actin in unstimulated cells. fMLP stimulation resulted in increased F-actin at sites of lamellipodia formation. A marked increase in MRP-14 staining occurred at the base of lamellipodia, but was excluded from the leading edge. This redistribution of MRP-14 was inhibited by pretreatment with SB203980. In conclusion, p38 MAPK phosphorylates MRP-14 on Thr-114 in human neutrophils, and this phosphorylation regulates MRP-14 interaction with the actin cytoskeleton.

LB8 (PS2 - 66)

Inflammatory Macrophages from Mice Fed Ethanol and Infected with *Salmonella enterica* serovar Typhimurium produce higher levels of TNF-α then Macrophages from Infected Control Mice.

Mike P. Burrows, Debbie Vidlak, Jennifer Van Evera, Jennifer Strachota, Thomas R. Jerrells Ph.D. Pathology and Microbiology, University of Nebraska Medical Center, Omaha, Nebraska,

The adverse effects of alcohol consumption on the immune system are well documented, and are associated with increased susceptibility to and increased severity of certain infections. Studies have shown that alcohol alters the function of cells of the innate immune system, specifically monocytes and macrophages(Mϕ). *Salmonella enterica* serovar Typhimurium infection of mice is a model system for *S. typhi* in human beings, and infects the liver and spleen. Ethanol (EtOH) consumption is associated with an inhibition of clearance of *Salmonella* from the liver and spleen, which results in more inflammation in these organs. One effect of alcohol exposure of mononuclear phagocytes is an increase in the production of TNF-α. In the inflammatory response to *S. enterica* the majority of TNF-α is produced by inflammatory Mϕ recruited from the blood to the liver and the spleen. The aim of this study was to examine alcohol's effect on inflammatory Mϕ production of TNF-α during an infection with *S. enterica*. Mice were provided EtOH with a Lieber-DeCarli liquid diet pair feeding protocol for a period of one week, or a chronic model of EtOH in drinking water for 4 to 6 weeks. Mice were euthanized five days after infection, serum was collected, as well as liver and spleen tissue for Mϕ isolation. The isolated cells were plated and LPS was added to induce TNF-α production. Inflammatory Mϕ from the spleens of EtOH-fed mice produced 2 to 3 times more TNF-α then Mϕ from control animals. TNF-α was also increased in the serum of EtOH-fed animals compared to control animals. Other pro-inflammatory cytokines (IL-6, MCP-1, IL-10) were unaffected by the presence of alcohol as measured in the serum and inflammatory Mϕ cytokine culture supernate. These data support the suggestion that mechanisms shown by others to be altered in resident Mϕ by alcohol may also exist in inflammatory Mϕ, which could result in the increased liver damage noted in *Salmonella*-infected mice that consume alcohol. Supported by RO1 AA 12450 and T32 AA 7582

LB9 (PS2 - 67)

EFFECTS OF ALCOHOL AND SURGERY ON IFN-γ PRODUCTION OF SPLENIC T-CELLS IN A MURINE MODEL OF GRAM-NEGATIVE PNEUMONIA AND ENDOTOXINAEMIA.

R. Kleinwächter[1], N. Lanzke[1], L. Sargsyan[1], A. Lehmann[1], F. Bast[1], D. Groneberg[2], C. Spies*[1]. [1]Department of Anesthesiology and Intensive Care [2]Department of Pediatric Pneumonology and Immunology, Charité-University Medicine of Berlin, Campus Mitte, Germany.

Background: The frequency of infections is increased in alcoholic patients. Additionally there is an increased postoperative infection rate in long-term alcoholic patients, which may be due to the impairment of adequate cytokine-production. The pro-inflammatory IFN-γ as the master cytokine of the Th1 and Tc1 subset promotes the cellular immune response and acts therefore as inductor for subsequent immune defense.

Aim of the study: In order to investigate the influence of alcohol together with surgical stress on the host response, we detected the IFN-γ-production of splenic lymphocytes within a murine operative infection and endotoxin model.

Methods: BALB/c mice were pretreated with ethanol (3mg/g body weight) or NaCl i.p. over 8 days. A median laparotomy was performed on day 8. In a randomised design two days post-op, one group of mice was challenged with LPS i.p. to induce endotoxinaemia, another group was given *Klebsiella pneumoniae* intranasally to cause pneumonia.

Mice were sacrificed, spleens were removed, cells were isolated and IFN-γ production of splenic Th1- and Tc1-lymphocytes was determined by FACS-analysis.

Statistics: Data are shown as median and range. Statistical analysis was performed with non-parametric tests (Mann-Whitney-U). A p value of less than 0.05 was considered significant.

Results: A local infection caused a significant decrease of IFN-γ in CD4+ lymphocytes in EtOH-treated operated mice ($p=0.003$). After surgery LPS induced a significant decrease of IFN-γ in CD4+ T-cells within both, NaCl- and EtOH-, groups ($p=0.003/<0.001$). Along with surgery EtOH-injection provoked a significant decrease of IFNγ in CD4+ T-cells in infected animals ($p=0.003$).

With surgery IFN-γ production in CD8+ cells was significantly decreased after LPS-injection compared to animals treated solely with NaCl and EtOH respectively ($p=0.019/0.003$). Both, surgery and EtOH together significantly reduced IFN-γ in CD8+ lymphocytes in LPS-injected mice ($p=0.003$). EtOH/LPS-treated operated mice showed a significant decrease of IFN-γproduction in CD8+ T-cells compared to EtOH/*Klebsiella*-treated operated animals ($p<0.001$).

Regarding the clinical rating, LPS-treatment put the animals into a poor condition contrary to the local infection, which affected the mice after one day of infection only moderately.

Conclusions: Thus, surgical stress resulted in immune suppression in CD4+ and CD8+ splenic lymphocytes, which might aggravate the adverse alcohol effect on the immune response. Whereas CD4+ T-cells were already influenced by a local infection after alcohol-treatment, CD8+ T-cells were only responsive to a systemic process. Furthermore, the alcohol-effect became apparent in T-helper-cells during pneumonia unlike in cytoxic T-cells where a distinct difference between Ethanol- and NaCl-treated mice was seen only in mice administered LPS.

LB10 (PS2 - 68)

Killing of *Salmonella typhimurium* by synthetic cecropin A-like peptides; role of α-helical stability and length of the lipopolysaccharide.

Åse Björstad*, Huamei Fu, Claes Dahlgren, Johan Bylund, Department of Rheumatology and Inflammation Research, University of Göteborg, Sweden.

Antibacterial peptides are a part of the innate immune system in a variety of different species including humans. Many of these peptides, including the cecropin-like peptide Hp(2-20) from *Helicobacter pylori*, have also been shown to act on immuno-competent cells. It is well established that cecropins have the ability to assume an amphipathic, α-helical structure, and breakage of this structure in Hp(2-20) reduces the antibacterial effect and abolishes the proinflammatory activity. A C-terminally truncated cecropin A peptide that structurally resembles Hp(2-20), failed to activate neutrophils, and computer-based structural simulations revealed a difference between the two peptides in the stability of their α-helical structures. A hybrid peptide with amino acid substitutions (12 gly→phe and 13 glu→ser) stabilizing the α-helical structure of the truncated cecropin A peptide, did not introduce any proinflammatory activity. The bactericidal activity was, however, increased towards all bacterial strains tested. The difference in activity between the peptides was most pronounced in killing *Salmonella typhimurium* MR10, a deep rough strain lacking most of the lipopolysaccharide (LPS). The smooth strain *S. typhimurium* MS was less sensitive to the peptides, but the effect was not directly related to the length of the LPS as illustrated by the fact that another rough strain (MR0) was killed to the same extent as the smooth strain. Moreover, expression of a full length LPS in the semi rough strain LT2-M1 increased rather than decreased the susceptibility of these bacteria. The outer membrane as a whole, and not the length of the LPS, is the essential part for bacterial survival in a hostile environment created by antibacterial peptides.

LB11 (PS1- 69)

***Salmonella* colitis in mice is modulated by prostaglandin formation and by Nramp1.** Heungjeong Woo*, Joshua Fierer. Division of Infectious Disease, Department of Medicine, U.C. San Diego, and VA Healthcare, San Diego, CA.

Nramp1 is a transmembrane protein that is expressed in macrophages in the late lysosomal compartment where *Salmonella* localize. Nramp1 mutants are more than 1,00x more susceptible to systemic *Salmonella* infections, but nothing is known about the role of this protein in intestinal infections. Mice do not develop intestinal pathology after oral infection with *Salmonella* unless they are pre-treated with an aminoglycoside. Pre-treated mice develop colitis and have frank diarrhea. We used this model of *Salmonella* gastroenteritis to study the role of host responses in the pathogenesis of this disease. Mice were pre-treated with streptomycin 10 mg by oral route and one day later were orally infected with *S. typhimurium* 14028. As a measure of intestinal colonization we determined the number of *Salmonella* colony forming unit (CFU) in the feces after infection, we weighed and measured the colon on the third day after infection to quantitate the diarrhea, and we made histologic sections of the colon for H&E staining. We compared the infections in B6 Nramp1 mutant) and congenic B6 mice that vary only in their Nramp1 allele. The BL/6 mouse had more *Salmonella* in their feces, more diarrhea and more intense inflammation in their cecums than BL/6 congenic mouse. Because *Salmonella* invasion of cultured epithelial cells induces PGE2 synthesis we treated both B6 and B6 congenic mice with indomethacin to inhibit cyclooxygenase activity. Indomethacin treated mice had less serious colitis with less diarrhea, but they had more *Salmonella* in their feces. These findings suggest that macrophages play an important role in the pathogenesis of *Salmonella* gastroenteritis. They also show that prostaglandins are necessary for diarrhea to occur, though the cells that make the prostaglandins have not been identified. This also implies that diarrhea is a primitive host defence mechanism against invasive bacteria.

LB12 (PS1 - 70)

Replenishment Of Intracellular Calcium After fMLP Stimulation Of Human Polymorphonuclear Neutrophils

Jens Martin Herrmann[1], John Bernardo[2], Heidi Long[2], Kurt Seetoo[2], Mary B. McMenamin[2], Kim Otto2, Lewis V. Wray, Jr.[2], Thomas E. Van Dyke[1], Elizabeth R. Simons. [1]Boston University - Goldman School of Dental Medicine, 100 E. Newton St., [2] Boston University School of Medicine, 715 Albany St., Boston, MA.

During infections human polymorphonuclear neutrophils (PMN) are stimulated and guided toward invasive antigens by gradients of chemoattractants such as formyl-Met-Leu-Phe (fMLP). Chemotaxis is followed by degranulation when a critical concentration of chemo-attractant is reached. The objective of this study was to model the PMN activation process with these two sequential steps, using the PMN's cytoplasmic calcium ($\Delta[Ca^{2+}]_i$) and pH (ΔpH_i) changes as measures of PMN response. Sequential stimulation of PMN was performed with 10^{-8} M fMLP by incubating PMN at 37 ∞C in KRP (PBS +0.9 mM Ca^{2+} +1.5 mM Mg^{2+}); if desired EGTA was added 15 sec. before the 1st or the 2nd stimulus in order to chelate the extracellular Ca^{2+}+ pool ($[Ca^{2+}]_{out}$). $\Delta[Ca^{2+}]_i$ and ΔpH_i were monitored with the fluorescent probes indo-1 and BCECF (Molecular Probes^{TM}), respectively, on a F4500 fluorimeter (Hitachi^{TM}) or a FACS 440 flow cytometer (Becton & Dickinson^{TM}) as previously described. Each stimulus elicited an immediate rise in $\Delta[Ca^{2+}]_i$ and, after a concomitant drop in the ΔpH_i, an alkalinization of the cytoplasm. The impact of a re-stimulation on $\Delta[Ca^{2+}]_i$ was measured after 5 min. of further incubation. Chelating of $[Ca2+]_{out}$ with EGTA 15 sec. prior to the 1st stimulation reduced the initial response slightly but abrogated a 2nd high transient so that only the gradual late increase attributed to influx from the medium via Ca^{+2} channels occurred. When the $[Ca^{2+}]_{out}$ was chelated 15 sec. prior to the 2nd stimulation, the transient $\Delta[Ca^{2+}]_i$ "spike" was present but smaller than the initial one. Each time the fMLP elicited $\Delta[Ca^{2+}]_i$ nearly completely from intracellular stores. No replenishment of these stores occurred within 5 min. even when $[Ca^{2+}]_{out}$ was available, implying that the lowering of $\Delta[Ca^{2+}]_i$ after the initial high transient "spike" did not indicate replenishment. The source of PMNs Ca^{2+}-homeostasis came from the external milieu since, if no $[Ca^{2+}]_{out}$ was available (EGTA), no 2nd transient spike occurred. (Support: Alexander-von-Humboldt Foundation, NIH grants DK31056, HL76463, DE13499 & RR00533)

LB13 (PS1 - 71)

Protein kinase D (PKC-mu) is involved in inflammatory signalling in response to bacterial flagellin. Nicholas Graham, Arnawaz Kaleem, Theodore Steiner*. Division of Infectious Diseases, University of British Columbia, Vancouver, BC

Bacterial flagellin is a potent activator of innate immune responses. Toll-like receptor (TLR)-5 is required to recognize and generate signals in response to flagellin; conversely, flagellin is the only known activator of TLR5. Like other TLRs, TLR5 signals through its intracellular TIR domain, ultimately leading to NF-kappaB activation and inflammatory responses. However, the details of this signalling pathway are not fully known. We identified a motif in the TIR domain of TLR5 that contains a putative target site for the serine-threonine kinase protein kinase D (also known as protein kinase C-mu). PKD is required for intracellular signalling in response to various growth factors and oxidant stress. We hypothesized that PKD could phosphorylate TLR5 and modu-

late responses to flagellin. To test this, we studied production of interleukin (IL)-8 from Caco-2 intestinal epithelial cells and HeLa cells. We found that the nonspecific PKC/PKD inhibitor Gö6976 reduced flagellin-induced IL-8 promoter activity and IL-8 protein release from Caco-2 cells, but did not affect NF-kappaB activation. The inhibitor Gö6983, which is active against "typical" PKC isoforms but inactive against PKD, did not reduce IL-8 production, suggesting that the effect of Gö6976 was a result of PKD inhibition. We also found an increase in PKD kinase activity in cells treated with flagellin for 15 min. Moreover, co-immunoprecipation experiments suggested that TLR5 forms a complex with PKD and other signalling proteins within this early time frame. Finally, we engineered a TLR5 construct with the putative PKD target serine mutated to an alanine (TLR5 S805A). HeLa cells transiently transfected with TLR5 S805A release about half as much IL-8 as cells transfected with wild-type TLR5 following flagellin stimulation, suggesting that PKD activity is required for full responses to flagellin. In summary, our findings suggest that PKD is involved in proximal signalling responses to bacterial flagellin. Future experiments will be needed to determine whether PKD directly interacts with and phosphorylates TLR5.

LB14 (PS2 - 69)

Inflammatory responses of mononuclear phagocytes to *Chlamydial* lipopolysaccharide. *Yuko Tsutsumi-Ishii[1], Kazunori Shimada[2], Hiroyuki Daida[2], Rudolf Toman[3], Isao Nagaoka[1].
Departments of [1]Host Defense and Biochemical Research, and [2]Cardiology, Juntendo University, School of Medicine, Tokyo 113-8421, Japan, [3]Department of Rickettiology and Chlamydiology, Institute of Virology, Slovak Academy of Sciences, 84245 Bratislava, Slovak Republic

Chlamydia pneumoniae infection is known to be associated with atherogenesis. Previous studies have suggested that chronic inflammatory responses to *C. pneumoniae* may contribute to the promotion of atherosclerosis in aortic lesion. However, the precise mechanism of *Chlamydia*-related atherogenesis remains largely unclear.

Among *Chlamydia*-derived bioactive components, lipopolysaccharide (LPS) is one of the most important virulence factors. LPS from *C. pneumoniae* is structurally unique in that Lipid A domain, a toxic center of LPS, has longer but less acyl chains than those of enterobacterial LPS such as *Escherichia coli*. Thus, we investigated the inflammatory responses of monocytes/macrophages to *Chlamydial* LPS. FACS analysis showed that *Chlamydial* LPS could bind to human peripheral monocytes and murine macrophage-cell line RAW264.7 in CD14- and LPS-binding protein (LBP)-dependent manner. In agreement with this, human monocytes and RAW264.7 cells could produce inflammatory cytokines (TNF-α and IL-6) following *Chlamydial* LPS stimulation. Of note, these cells were less responsive to *Chlamydial* LPS than *E. coli* LPS. Binding study with immobilized recombinant LBP indicated that the binding of *Chlamydial* LPS to LBP was approximately 2-fold less than that of *E. coli* LPS. Furthermore, an affinity of *Chlamydial* LPS to recombinant CD14 was 4-fold lower than that of *E. coli* LPS.

These results suggest that differences in the affinities of *Chlamydial* LPS and *E. coli* LPS to LBP and CD14 substantially influence the monocyte/macrophage responses to these LPS.

LB15 (PS2 - 70)

DIFFERENTIAL REQUIREMENTS FOR NF-κB p65 TRANSLOCATION, TNF RELEASE AND INTERFERON-β INDUCTION BY HUMAN MACROPHAGES INGESTING LISTERIA MONOCYTOGENES POINT TO A CYTOSOL-SPECIFIC IMMUNE RESPONSE.

Thornik Reimer*, Thomas W. Jungi. Institute of Veterinary Virology, University of Bern, Switzerland.

L. monocytogenes (LM) is a gram-positive facultative intracellular bacterium escaping the phagolysosmal compartment following phagocytosis. Using murine macrophages as targets, various virulence genes governing phagolysosomal escape, cytosolic replication and cell-to-cell spreading of LM have been described. However, the armamenture of macrophage effector pathways against intracellular pathogens is variable between mammalian species. To address whether intracytosolic LM mount an immune response different from phagolysosomally restricted congenic strains, human monocyte-derived macrophages (HMDM) were infected with wt LM or a congenic hly- strain lacking the hemolysine gene necessary for phagolysosomal escape in macrophages. Nuclear translocation of the NF-κB subunit p65, TNF release, and transcription of the ifnb gene were monitored. It was found that (i) the NF-κB subunit p65 translocates to the nucleus within 30 min. p.i. irrespective of the subcellular localisation of LM, and regardless of whether ingested bacteria were viable or had been heat-killed. This was distinct from reports on findings in murine macrophages. (ii) Only viable LM of either strain mount a strong TNF response in unstimulated MDM, suggesting that nuclear translocation of p65 is necessary but not sufficient for upregulation of TNF synthesis. This requirement for viability could be overcome by priming HMDM with IFN-γ before infection. (iii) Only wt LM but not hly- LM induced the expression of the ifnb gene. Although the significance of interferon-β (IFN-β) in the control of a bacterial cytosolic infection remains to be determined, it is shown for the first time in human macrophages, that cytosolic localisation of LM ensues a strong IFN-β mRNA signal which is governed by criteria other than or in addition to p65 nuclear translocation and TNF production. Using HMDM as host cells, we show that LM able to escape to the cytosol may induce a host defense response differing from that elicited by dead or phagolysosomally restricted bacteria.

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Abdalla, Hana (S)
Linkoping Univ
Fac of Health Sci / Div Med Microbiol
Linkoping, 58185
Sweden
46-13-222055
46-13-224789
hanab@imk.liu.se

Abshire, Michelle Y. (S)
Univ of Virginia
Dept of Microbiol
1300 Jefferson Park Ave
Jordan Hall 7040
Charlottesville, VA 22908
(434) 924-9995
ma6t@virginia.edu

Abu Kwaik, Yousef (M)
Univ of Louisville Coll of Med
Dept of Microbiol & Immunol
319 Abraham Flexner Way, 55A
Rm 316
Louisville, KY 40202
(502) 852-4117
(502) 852-7531
abukwaik@louisville.edu

Ahmad, Ali (M)
Univ of Montreal
Dept of Microbiol & Immunol
3175 Cote Ste Catherine
Rsr Ctr - Rm 2724
Montreal, Quebec H3T 1C5
Canada
(514) 345-4931, x6157
(514) 345-4801
ahmada@justine.umontreal.ca

Ali, Majid (S)
Univ of Sheffield
Cardiovasc Rsr Unit
Clinical Sciences Centre
Northern General Hosp
Sheffield, South Yorkshire S5 7AU
United Kingdom
44 1142714576
44 1142619587
m.ali@shef.ac.uk

Bauer, Susanne (S)
Lund Univ
Dept of Cell & Molec Biol
Tornavagen 10 - BMC, B14
Lund, SE-22184
Sweden
46-46-2224839
46-46-157756
susanne.bauer@medkem.lu.se

Bidani, Akhil (M)
Univ Texas Hlth Sci Ctr
Div of Pulm & CCM
6431 Fannin / MSB 1 270
TX, Houston 77030
(713) 500-6826
(713) 500-6829
akhil.bidani@uth.tmc.edu

Birmingham, Cheryl (S)
The Hospital for Sick Children
Inf, Imm, Inj & Rpr Prgm
555 University Ave
Toronto, ON M5G 1X8
Canada
(416) 813-7654, x3555
(416) 813-5028
cheryl.birmingham@utoronto.ca

Bjorstad, Ase (S)
Univof Gothenburg
Dept of Rheumatol
Guldhedsgatan 10
Gothenburg, 413 46
Sweden
46 31 342 49 27
46 31 82 39 25
ase.bjorstad@rheuma.gu.se

Bohlson, Suzanne S. (S)
Univ of California, Irvine
Dept of Molec Biol & Biochem
2419 McGaugh Hall
Irvine, CA 92697
(949) 824-3266
(949) 824-8551
sbohlson@uci.edu

Boudreau, Robert T. M. (S)
Dalhousie Univ
Dept of Microbiol & Immunol
5778 South St, Apt. 417
Halifax, NS B3H 4N5
Canada
(902) 422-2059
(902) 494-5125
rtmboudreau@hotmail.com

Bouton, Amy H. (M)
Univ of Virginia
Dept of Microbiol
HSC - Box 800734
Charlottesville, VA 22908
(434) 924-2513
(434) 982-1071
ahb8y@virginia.edu

Brown, Stephan L. (S)
Meharry Med Coll
Dept of Biochem
Nashville, TN 37208
(615) 500-6411
sbrown111@hotmail.com

Burelout, Chantal (S)
Laval Univ - CRRI
Ctr De Recherche En Immunol-Rheumatol
2705 Blvd Laurier, Rm T1-49
Quebec, QC G1V 4G2
Canada
(418) 654-2772
(418) 654-2765
chantal.burelout@crchul.ulaval.ca

Burrows, Michael P. (S)
Univ of Nebraska Med Ctr
Dept of Pathol & Microbiol
668 South 41st St
Wittson Hall - Rm 4024
Omaha, NE 68198
(402) 559-8311
mburrows@unmc.edu

Choudhry, Mashkoor A. (M)
Univ of Alabama At Birmingham
Dept of Surg
1670 University Blvd - G094
AL, Birmingham 35294
(205) 975-9712
(205) 975-9715
mashkoor.choudhry@ccc.uab.edu

Collin, Marika (S)
William Harvey Rsr Inst
Dept of Exp Med, Nephrol & Crit Care
Queen Mary - Univ London
Charterhouse Square
London, EC1M 6BQ
United Kingdom
44-20-78826025
44-20-72511685
m.collin@qmul.ac.uk

Conrad, David M. (S)
Dalhousie Univ
Dept of Microbiol & Immunol
5850 College St -Rm 7E
Halifax, NS B3H 1X5
Canada
(902) 494-6242
(902) 494-5125
dmconrad@dal.ca

Correll, Pamela (M)
Pennsylvania State Univ
Dept Vet Sci
105 Henning Bldg
PA, University Park 16802
(814) 863-0128
(814) 863-6140
phc7@psu.edu

Costa Rosa, Luis (M)
Univ of Sao Paulo
Dept of Cellular Biol
Av Prof Lineu Prestes, 1524
Rm 302
Sao Paulo, 05508-900
Brazil
55-11-30917227
55-11-30917402
ggrosa@icb.usp.br

Daley, Jean M. (M)
Brown Univ / RI Hosp
Dept of Surg
593 Eddy St, NAB 214
Providence, RI 02903
(401) 444-5889
(401) 444-8052
jdaley@lifespan.org

Dame, Tarah M. (S)
Stony Brook Univ
Dept of Molec Gen & Microbiol
5120 Ctr for Inf Dis
Ctr for Molec Med - Rm 280
Stony Brook, NY 11794-5120
(631) 632-4226
(631) 632-4294
tdame@notes.cc.sunysb.edu

Descoteaux, Albert (M)
Univ De Quebec
Institut Armand-Frappier
531 Des Prairies
Quebec, Laval H7V 1B7
Canada
(450) 687-5010 x4465
(450)686 5301
albert.descoteaux@inrs-iaf.uquebec.ca

Dobson, Wendy N. (S)
Univ of Toronto
Dept of Med Gen & Microbiol
1 King's College Circle
Med Sci Bldg, Rm 4381
Toronto, ON M8Z 3R4
Canada
(416) 946-5308
(416) 978-6885
w.dobson@utoronto.ca

Dolganiuc, Angela (S)
Univ of Massachusetts Med Sch
Dept of Med/Gastroenterology
55 Lake Ave North
MA, Worcester 01655
(508)856-5279
(508) 856-4770
Angela.Dolganiuc@umassmed.edu

Faunce, Douglas E. (M)
Loyola Univ Med Sch
Dept of Surg
2160 S 1st Ave
Bldg 110 - Rm 4221
IL, Maywood 60153
(708) 327-2663
(708) 327-2813
dfaunce@lumc.edu

Gray-Owen, Scott D. (M)
Univ of Toronto
Dept of Med Gen & Microbiol
1 King's College Cir, Rm 4381
Toronto, ON M5S 1A8
Canada
(416) 946-5307
(416) 978-6885
scott.gray-owen@utoronto.ca

Guy, Michael K. (M)
Colorado Serum Company
4950 York St
Denver, CO 80216
(303) 295-7527
(303) 295-1923
mguy@colorado-serum.com

Harrison, Rene E. (M)
Univ of Toronto
Dept of Life Sci
126 S Military Trail
Toronto, ON M1C 1A4
Canada
(416) 287-7377
(416) 287-7642
harrison@utsc.utoronto.ca

Heaney, Mark L. (M)
Memorial Sloan-Kettering Cancer Ctr
Dept of Med & Prog of Molec Therapeut
1275 York Ave
NY, New York 10021
(212) 639-2275
(212) 772-8550
m-heaney@ski.mskcc.org

Hmama, Zakaria (M)
Univ of British Columbia
Dept of Med
2733 Heather St
D452, HP East
Vancouver, BC V5Z 3J5
Canada
(604) 875-4111, x68076
(604) 875-4013
hmama@interhange.ubc.ca

Hudson, Krischan J. (S)
Univ of Virginia
Dept of Microbiol
1300 Jefferson Park Ave
Jordan Hall 7040
Charlottesville, VA 22908
(434) 924-9995
kjh6n@virginia.edu

Jerrells, Thomas R (M)
Univ of Nebraska Med Ctr
Dept of Pathol & Microbiol
986495 Nebraska Med Ctr
NE, Omaha 68198-6495
(402) 559-8304
(402) 559-4077
tjerrell@unmc.edu

Jog, Neelakshi (S)
Univ of Louisville
Dept of Nephrol
570 S. Preston St
Donald Baxter Bldg - Ste 1025
Louisville, KY 40202
(502) 852-0014
(502) 852-4384
jami.vance@kdp.louisville.edu

Johansson, Helena M. (S)
Lund Univ
Dept of Cell & Molec Biol
Tornavagen 10
Lund, SE-22184
Sweden
46-46-222-9845
46-46-157756
helena_m.johansson@medkem.lu.se

Johansson, Carin (S)
Linkoping Univ
Dept of Molec & Clin Med
Linkoping, 58185
Sweden
46-13-222051
carjo@imk.liu.se

Kerfoot, Steven M. (S)
Univ of Calgary
Dept of Med Sci
3330 Hospital Dr, NW
Calgary, Alberta T2N 4N1
Canada
(403) 220-3012
(402) 286-1267
skerfoot@ucalgary.ca

Kim, Kyeong Ah (S)
Yonsei Univ Coll of Med
Dept of Parasitol & Trop Med
134 Sinchon-dong, Seodaemun-gu
Seoul, 120-752
Korea
82-2-361-5290
82-2-363-8676
ruddk97@hanmail.net

Kim, Bosook (S)
Inst for Basic Rsr
Dept of Dev Neurobiol
1050 Forest Hill Rd
Staten Island, NY 10314
(718) 494-4890
(718) 494-4884
kbs6666@hanmail.net

Larina, Liudmila L. (M)
Korea Advanced Inst of Sci & Tech
Dept of Matl Sci & Engrg
373 Kusong-dong, Yusong-gu
Taejeon, 305-701
South Korea
82-42-869-42-80
82-42-869-3310
llarina@yahoo.com

Leibovich, S Joseph (M)
UMDNJ-New Jersey Med Sch
Dept of Cell Biol & Molec Med
185 S Orange Ave - MSB G 677
NJ, Newark 07103
(973) 972-5404
(973) 972-7489
leibovic@umdnj.edu

Lee, Hannah S. (S)
Univ of Toronto
Dept of Molec & Med Gen
1 King's College Circle
Med Sci Bldg, Rm 4381
Toronto, ON M5S 1A8
Canada
(416) 946-5308
(416) 978-6885
hsw.lee@utoronto.ca

Lerm, Maria (M)
Linkoping Univ
Dept of Molec & Clin Med
Linkoping, 58185
Sweden
46-13-224779
46-13-224789
marle@imk.liu.se

Levine, Jerrold S. (M)
Univ of Illinois At Chicago
Dept of Med/Nephrol
820 South Wood St
MD-793 / Rm 479 / CSN
Chicago, IL 60612
(312) 413-1178
(312) 996-7378
jslevine@uic.edu

Lonnbro, Per (S)
Lund Univ
Dept of Cell & Molec Biol
Tornavagen 10 - BMC, B14
Lund, SE-22184
Sweden
46-46-222-44-88
46-46-157756
per.lonnbro@medkem.lu.se

Mackenzie, Simon (M)
Univ Autonoma De Barcelona
Dept of Cell Biol - Anim Physiol Unit
Edificic, Campus De La UAB
Bellaterra, Barcelona 08193
Spain
34-93-5814127
34-93-5812390
simon.mackenzie@uab.es

Marsh, Rachel A. (S)
Univ of Rochester Med Ctr
Dept of Surg
601 Elmwood Ave - SURG
Rochester, NY 14642
(585) 275-3965
(585) 275-8513
rachel_marsh@urmc.rochester.edu

Marty, Caroline (S)
Univ of Illinois At Chicago
Dept of Pharmacol
835 S Wolcott - Rm E403, MSB
Chicago, IL 60612
(312) 996-7857
cmarty1@uic.edu

McIntire, Ramsey H. (S)
Univ of Kansas Med Ctr
Dept of Anat & Cell Biol
3901 Rainbow Blvd
Kansas City, KS 66160
(913) 588-7260
(913) 588-7180
rmcintire@kumc.edu

Ming, Wenyu (M)
Indiana Univ Sch of Med
Dept of Pediatrics
1044 W Walnut St, R451A
Indianapolis, IN 46202
(317) 274-5543
(317) 274-8908
wming@iupui.edu

Minielly, Robin C. (S)
URMC
123 Jordache La
Spencerport, NY 14559
(585) 746-6756
robin_minielly@urmc.rochester.edu

Moreland, Jessica G. (M)
Univ of Iowa
Dept of Pediatrics
200 Hawkins Dr
Iowa City, IA 52242
(319) 356-1615
(319) 353-8597
jessica-moreland@uiowa.edu

Nielsen, Katie R. (S)
Univ of Iowa - Carver Coll of Med
Inflammation Program
2501 Crosspark Rd, D137 MTF
Coralville, IA 52241
(319) 335-4323
(319) 335-4194
katie-nielsen@uiowa.edu

Norman, Keith E. (M)
Univ of Sheffield
Cardiovasc Rsr Unit
Clinical Sciences Centre
Northern General Hosp
Sheffield, South Yorkshire S5 7AU
United Kingdom
44 1142714665
44 1142619587
k.norman@shef.ac.uk

Owen, Katherine A. (S)
Univ of Virginia
Dept of Microbiol
1300 Jefferson Park Ave
Jordan Hall 7040
Charlottesville, VA 22908
(434) 924-9995
(434) 982-1071
ko4q@virginia.edu

Pearlman, Eric (M)
Case Western Reserve Univ
Center for Global Hlth & Dis
10900 Euclid Ave
OH, Cleveland 44106-7286
(216) 368-1856
(216) 368-4825
exp2@po.cwru.edu

Perl, Mario (S)
Rhode Isl Hosp / Brown Univ
Dept of Surg Rsr
593 Eddy St
Providence, RI 02903
(410) 444-6706
(401) 444-3278
mperl@lifespan.org

Pestonjamasp, Kersi N. (S)
Univ of California San Diego
Cancer Center
10865 Altman Row
San Diego, CA 92121
(858) 822-3895
kpestonjamasp@ucsd.edu

Rasmusson, Birgitta (M)
Linkoping Univ
Dept of Molec & Clin Med
Linkoping, 58185
Sweden
46-13-222061
46-13-224789
birra@imk.liu.se

Reynolds, Craig W (ED)
NCI-FCRDC Bldg 1052 Rm 253
Biol Res Br
PO Box B
MD, Frederick 21702-1201
(301) 846-5693
(301) 846-1494
reynoldsc@ncifcrf.gov

Riant-Varadaradjalou, Sonia (S)
NIAID/NIH
Laboratory of Allergic Dis
10 Center Dr, MSC 1881
Bldg 10, Rm 11C208
MD, Bethesda 20892-1881
(301) 496-8745
(301) 480-8384
svaradaradjalou@niaid.nih.gov

Rice, Andrew P. (M)
Baylor Coll of Med
Dept of Molec Virol & Microbiol
One Baylor Plaza
Houston, TX 77030
(713) 798-5774
(713) 798-3490
arice@bcm.tmc.edu

Rogers, Thomas J. (M)
Temple Univ Sch of Med
Fels Inst for Canc Res & Molec Biol
3307 N Broad St
PA, Philadelphia 19140
(215) 707-3215
(215) 707-4743
rogerst@temple.edu

Ryu, Jae-Sook (M)
Hanyang Univ Coll of Med
Dept of Parasitol
Sungdong-Gu
Haengdang-Dong 17
Seoul, 133-791
Korea
82-2-2290-0683
82-2-2281-6519
jsryu@hanyang.ac.kr

Sarantis, Helen (S)
Univ of Toronto
Dept of Med Gen
1 King's College Circle
Med Sci Bldg, Rm 4381
Toronto, ON L4K 1H1
Canada
(416) 946-5308
helen.sarantis@utoronto.ca

Schorey, Jeff S. (M)
Univ of Notre Dame
Dept of Biol Sci
129 Galvin
Notre Dame, IN 46556
(574) 631-3734
(574) 631-7413
schorey.1@nd.edu

Shah, Chandrabala (S)
London Sch of Hyg & Trop Med
Dept of Inf & Trop Dis
Keppel St
London, WC1E 7HT
United Kingdom
0207-927-2806
0207-323-5687
chandrabala.shah@lshtm.ac.uk

Sim, Seobo (S)
Yonsei Univ Coll of Med
Dept of Parasitol
Sinchon-dong 134, Seodaemun-gu
Seoul, 120-752
South Korea
82-2-361-5298
82-2-363-8676
ssim@yumc.yonsei.ac.kr

Smith, Adam (S)
The Hospital for Sick Children
Inf, Imm, Inj & Rpr Prgm
555 University Ave
Toronto, ON M5G 1X8
Canada
(416) 813-7654, x3555
(416) 813-5028
ac2smith@hotmail.com

Smyth, Mark J. (M)
Peter MacCallum Cancer Inst
Cancer Immunol Prgm
Locked Bag 1, A'Beckett St
Melbourne, 8006
Australia
61-3-9656-3728
mark.smyth@petermac.org

So, Nancy S. (S)
Univ of Toronto
Dept of Molec & Med Gen
1 King's College Circle
Toronto, ON M5S 1A8
Canada
(416) 946-5308
(416) 978-6885
nancy.so@utoronto.ca

Szeto, Jason (S)
The Hospital for Sick Children
Dept of Infection, Immunity, Inj & Rpr
555 University Ave
Toronto, ON M5G 1X8
Canada
(416) 813-7654, x1464
(416) 813-5028
jszeto@uottawa.ca

Taylor, Addison (M)
Baylor Col of Med
Dept of Med/Hypertension
6565 Fannin / MS F504
TX, Houston 77030
(713) 798-4721
(713) 793-1087
ataylor@bcm.tmc.edu

Tejle, Katarina (S)
Linkoping Univ
Dept of Molec & Clin Med
Linkoping, 58185
Sweden
013-222055
013-224789
katte@imk.liu.se

Walsh, Mary C. (S)
Brigham & Womens Hosp/Harvard Med Sch
Dept Anesthesia -CETRI
75 Francis St / Thorn 1315
MA, Boston 02115
(617) 732-6890
(617) 278-6957
mwalsh@zeus.bwh.harvard.edu

Williams, Keisha C. (S)
LSU Health Sci Ctr
Dept of Physiol
3912 S. I-10 Service Rd, #332
Metairie, LA 70001
(504) 309-0943
kwill6@lsuhsc.edu

Wu, Yan (S)
The Scripps Rsr Inst
Dept of Immunol
10550 N Torrey Pines Rd
La Jolla, CA 92037
(858) 784-8536
(858) 784-8218
yanwu@scripps.edu

Zhang, Sean X. (S)
Toronto Western Hospital
Dept of Rheumatol
399 Bathurst St, MC 13-415
Toronto, ON M5T 2S8
Canada
(416) 603-5456
xzhang@uhnres.utoronto.ca

Zhang, Xueqing (S)
Univ of Massachusetts
Dept of Pediatrics
364 Plantation St
Worcester, MA 01604
(508) 856-6757
xueqing.zhang@umassmed.edu

Program-at-a-glance

Wednesday, October 20

1:00-5:30pm ALCOHOL AND IMMUNOLOGY RESEARCH INTEREST GROUP WORKSHOP (Dockside 1)

4:00 – 7:00pm SLB COUNCIL MEETING (Dockside 4)

Thursday, October 21

8:30-11:30am ALCOHOL AND IMMUNOLOGY RESEARCH INTEREST GROUP (Harbour Salon C)

9:00-5:00pm REGISTRATION (Harbour Foyer)

9:00-12:00 Noon SLB COUNCIL MEETING (Pier 6)

12:30-2:30pm KEYNOTE ADDRESSES (Harbour Ballroom)
Chairs: J. Fierer and S. Goyert

2:50-3:55pm PLENARY 1: HOST RESPONSE TO PATHOGENS: NOVEL CELLULAR MECHANSIMS (Harbour Ballroom)
Chairs: J. Fierer and S. Goyert

4:00-5:15pm PRESIDENTIAL STUDENT AWARD PRESENTATIONS (Harbour Ballroom) Chair: D. Mosser

5:15-7:30pm PRESIDENTIAL RECEPTION, POSTER SESSION 1 AND EXHIBITS (Harbour Foyer and Pier 4/5)

8:00-10:00pm STUDENT/POSTDOC MIXER. The Harbour Sports Grille.

Friday, October 22

8:00-9:00am POSTER WORKSHOP I: (Harbour Salon A) Chair: S. Goyert

9:00-5:00pm REGISTRATION (Harbour Foyer)

9:00-11:30am PLENARY 2: ANTIMICROBIAL EFFECTORS OF INNATE IMMUNITY (Harbour Salons B & C)

11:30-1:00pm LUNCH ON YOUR OWN

11:45-12:45pm GUIDELINES FOR PUBLISHING DIGITAL ART. Sponsored by Cadmus. (Lunch provided, pre-registration required)

1:00-3:00pm CONCURRENT SYMPOSIA 1 AND 2

1:00-3:00pm SYMPOSIUM 1: HOST RESPONSE TO INTRACELLULAR PATHOGENS (Harbour Salons B & C)
Chairs: M. Swanson and N. Reiner

1:00-3:00pm SYMPOSIUM 2: INNATE AND ADAPTIVE IMMUNE RESPONSES TO INFECTION: ENDOTHELIAL CELLS, LYMPHOCYTES AND NK CELLS. (Harbour Salon A)
Chairs: M. Furie and A. Malik

3:20-5:20pm CONCURRENT SYMPOSIA 3-4

3:20-5:20pm SYMPOSIUM 3: CELLULAR SIGNALING MECHANISMS IN RESPONSE TO INFECTION (Harbour Salon A) Chairs: M. Olivier and C. Karp

3:20-5:20pm SYMPOSIUM 4: INNATE AND ADAPTIVE IMMUNE RESPONSES: NEUTROPHILS AND MONOCYTES
(Harbour Salons B & C)
Chairs: E. Kovacs and J. Suttles

5:30-6:45pm 2004 MARIE T. BONAZINGA AWARD Sponsored by Accurate Chemical and Scientific Corporation (Harbour Salon B and C)
S.N. Vogel.

6:45-8:45pm MARIE T. BONAZINGA AWARD RECEPTION, POSTER SESSION 2 AND EXHIBITS (Harbour Foyer and Pier 4/5)

Saturday, October 23

8:00-9:00am POSTER WORKSHOP II: (Harbour Salon A) Chair: J. Fierer

9:00-10:55am PLENARY 3: HOST DEFENSES AGAINST PATHOGENS
(Harbour Salons B & C)
Chairs: S. Grinstein and P. Gros

10:55am *JOURNAL OF LEUKOCYTE BIOLOGY* DOLPH ADAMS AWARD (Harbour Salons B & C)
J. Banchereau.

11:45-12:45pm MEET-THE-SPEAKER LUNCH (FOR STUDENTS AND POST-DOCS, PRE-REGISTRATION REQUIRED) (Dockside 4)

11:30-1:00pm LUNCH ON YOUR OWN

12:30pm GENERAL SLB MEMBERSHIP MEETING
(Harbour Salon A)

1:00-3:00pm CONCURRENT SYMPOSIA 5 AND 6

1:00-3:00pm SYMPOSIUM 5: CELLULAR MECHANISMS OF INFLAMMATION (Harbour Salons B & C)
Chairs: P. Kubes and M. Cybulsky

1:00-3:00pm SYMPOSIUM 6: INNATE AND ADAPTIVE IMMUNE RESPONSES: CYTOKINES/ CHEMOKINES/RECEPTORS
(Harbour Salon A)
Chairs: D. Remick and O.M.Z. Howard

3:20-5:20pm CONCURRENT SYMPOSIA 7 AND 8

3:20-5:20pm SYMPOSIUM 7: PATHOGENESIS OF SEPSIS AND SHOCK
(Harbour Salon A)
Chairs: A. Ayala and P. Ward

3:20-5:20pm SYMPOSIUM 8: INNATE AND ADAPTIVE IMMUNE RESPONSES: DENDRITIC CELLS AND MACROPHAGES
(Harbour Salon B & C)
Chairs: D. Mosser and E. Raz

7:00pm AWARDS BANQUET (Harbour Ballroom)