

A Letter from the IEIIS President



Koichi Fukase

Dear Friends and Colleagues,

More than a year and a half has passed since COVID-19 pandemic started. The 16th IEIIS meeting, scheduled to be held last year, had to be postponed to this year. Although there is still no end in sight to the pandemic, we would like to hold the 16th IEIIS meeting on October 12-15, 2021, as a hybrid-type conference. All oral sessions will be held at the Kobe international conference center or virtually. Invited lectures will also be delivered on-demand. Poster sessions will be held virtually. The deadline for the advance registration and abstract submission has been extended to September 13. Please join from the following URL (<https://congress.academicbrains.jp/ieiis2021/>).

Best regards,

Koichi Fukase

Koichi Fukase
IEIIS President 2018-2021
Chair, 2021 IEIIS 16th Meeting

16th Biennial Meeting of the International Endotoxin and Innate Immunity Society



Oct 12-15, 2021 - Kobe International Conference Center, Japan

Chair: Koichi Fukase (Osaka University)



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WELCOME TO KOBE, 2021
Check meeting updates on the web sites:
<https://www.ieiis.org/>



September 2021

IEIIS - INTERNATIONAL ENDOTOXIN
& INNATE IMMUNITY SOCIETY

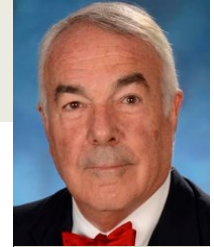
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Update from Dr. Alan Cross: Jerrod Brammer Manuscript Published



Alan Cross

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Dr. Alan Cross's graduate student, Jerod Brammer, also a member of the IEIIS, just published a manuscript in *Infection and Immunity*: "A non-lethal murine flame burn model leads to a transient reduction in host defenses and enhanced susceptibility to lethal *Pseudomonas aeruginosa* infection" (Posted Online 21 June 2021; *Infect Immun* doi: 10.1128/IAI.00091-21).

Dr. Brammer showed that following the burn there is a sequestration of neutrophils within a seroma, thereby rendering the mouse functionally neutropenic. High Mobility Group Box 1 (HMGB1), a TLR4 agonist, increased after the burn and preceded the increase in pro-inflammatory cytokines. With *Pseudomonas* infection superimposed upon the burn wound, the HMGB1 level increased 10-fold until death. HMGB1 signaling was inhibited with a small molecule inhibitor, P5779, which binds MD2 at a site distinct from that for LPS and mortality was significantly decreased. These studies identify a DAMP or alarmin, HMGB1, released following the burn as a potential therapeutic target in the treatment of burn wound sepsis. ▲

Update from Drs. Bob Ernst & Alison Scott: Method to Determine Lipid A Structure Directly from Gram-Negative Bacterial Colonies



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It's been our long-standing effort to identify and characterize lipid A structures among Gram negative bacteria to better understand how lipid A influences bacterial fitness and pathogenesis. In collaboration with biotech start-up Pataigan, co-founded by Dr. Ernst, we developed a method to determine lipid A structure directly from Gram-negative bacterial colonies and/or clinical samples called Fast Lipid Analysis Technique (FLAT). This technique uses minimal sample with a citric acid-based buffer to cleave lipid A directly on a stainless-steel plate. This plate can then be used to analyze lipid A structure using matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry (MS). Given that Gram-negative bacteria each have a distinct lipid A signature, this method allows for rapid diagnosis and identification of Gram-negative species and can give indicators of antibiotic resistance. Furthermore, postdoctoral fellow Hyojik Yang recently developed an extension of this technique, called FLAT^m, to investigate the chemical structure of lipid A through tandem MS. By fragmenting the lipid A, we can define its chemical structure in under two hours, avoiding the traditional, time-, labor-, and sample-intensive techniques used previously. We hope to use this technique to better identify Gram-negative pathogens in human clinical samples and to better investigate the lipid A of Gram-negative bacteria that have yet to be thoroughly characterized.

As an extension of this work, graduate student Richard D. Smith is finalizing the development of a lipid-based MALDI-TOF assay to rapidly detect colistin resistance in *Enterobacter* species. *Enterobacter* species are labelled a high priority due to their ability to become multi-drug resistant (MDR) after persistent antibiotic use. Colistin (polymyxin E) is commonly used as a last-resort antibiotic to treat MDR *Enterobacter* infections, yet this has accelerated the emergence of resistance to polymyxins including colistin. Colistin resistance is primarily mediated through modification of the terminal phosphate moieties of lipid A, and thus these modifications can be used as predictions of resistance. Using a collection of minimally passaged *Enterobacter* clinical isolates, we determined minimum inhibitory concentrations (MICs) and conducted killing assays for colistin and then correlated these results with lipid A structures as determined by FLAT and MALDI-TOF MS. Our results suggest analysis by FLAT can identify lipid A structural modifications associated with colistin resistance. Due to the rapid nature of FLAT and the ability to directly analyze clinical samples without the need for culture, this assay has the potential to help better inform clinicians about decisions surrounding antibiotic therapy and help mitigate the risk of unnecessary use of antibiotics in the clinic. ▲

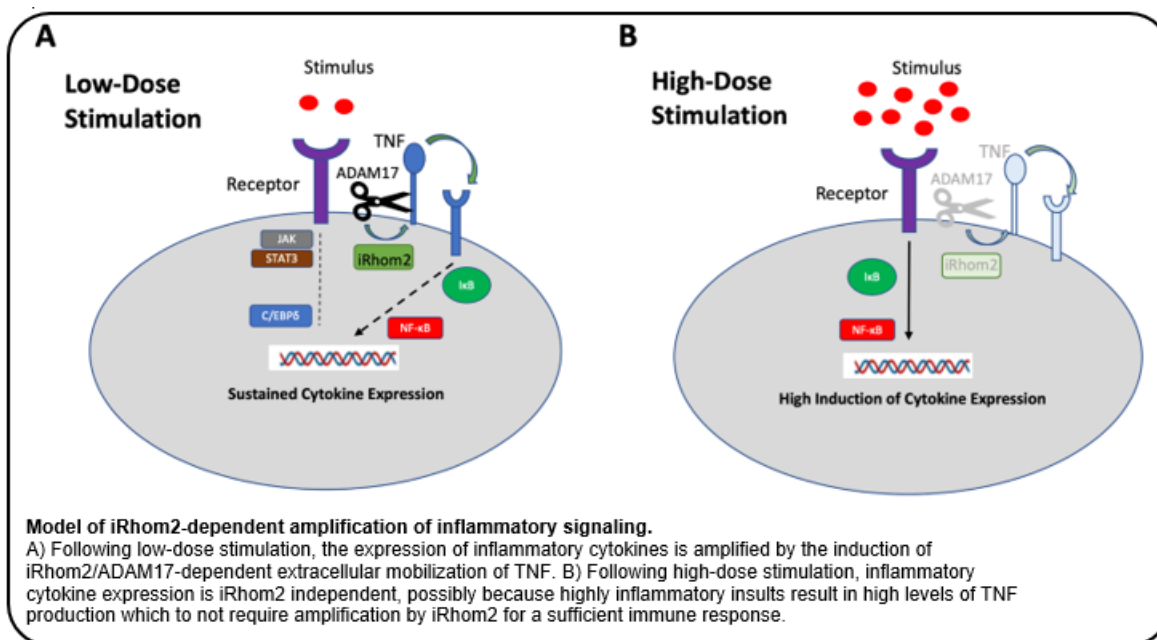
Update from Dr. Thorsten Maretzky, a new member of the IEIIS: Understanding the Regulation of Inflammatory Cytokines from a Metalloprotease Perspective



Thorsten Maretzky

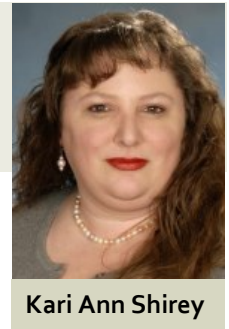
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Dysregulated tumor necrosis factor (TNF) signaling in immune cells is implicated in a wide range of immunopathologies, particularly with respect to chronic low-grade inflammation, a common comorbidity in cardiometabolic and autoimmune diseases. TNF signaling is regulated via the inactive rhomboid protein 2 (*iRhom2*), a highly conserved, catalytically inactive member of the rhomboid intramembrane serine protease family. Recent studies have shown that *iRhom2* regulates the release of TNF through maturation and trafficking of a disintegrin and metalloproteinase (ADAM) 17 from the endoplasmic reticulum to the cell surface, where it can be activated. Deficiency of *iRhom2* leads to a tissue-specific loss of ADAM17 activity in immune cells. Using *iRhom2*-deficient bone marrow-derived macrophages, our laboratory has recently shown that *iRhom2*-dependent expression of TNF mRNA and protein is manifest at low (pM) but not higher (nM) concentrations of LPS and dependent on both extracellular mobilization of TNF and cellular TNF receptors (*see model slice below*). In addition, our results demonstrate that LPS-induced IL1 β mRNA expression as well as C5a-induced expression of TNF mRNA are also selectively *iRhom2*-dependent at doses of either agonist that produced only weak induction in the absence of *iRhom2*. These findings show that otherwise weak stimuli of inflammatory responses can be substantially amplified by *iRhom2*/ADAM17-dependent mobilization of extracellular TNF that can drive a feed-forward regulatory mechanism. In summary, our findings imply that the immune response to multiple insults is differentially regulated by ADAM17 activation based upon the concentration of the insult, and that *iRhom2* plays a key role in modulating the innate immune response to a wide range of challenges wherein inflammation plays a role in the onset of pathology. ▲



Skurski J, Dixit G, Blobel CP, Issuree PD, Maretzky T. The Threshold Effect: Lipopolysaccharide-Induced Inflammatory Responses in Primary Macrophages Are Differentially Regulated in an *iRhom2*-Dependent Manner. *Front Cell Infect Microbiol.* 2020;10:620392. Epub 2021/02/16. doi: 10.3389/fcimb.2020.620392. PubMed PMID: 33585287; PMCID: PMC7878383.

Two Updates from Dr. Kari Ann Shirey: Novel Role of Neuroendocrine Molecules in the Pathogenesis of Influenza Infection



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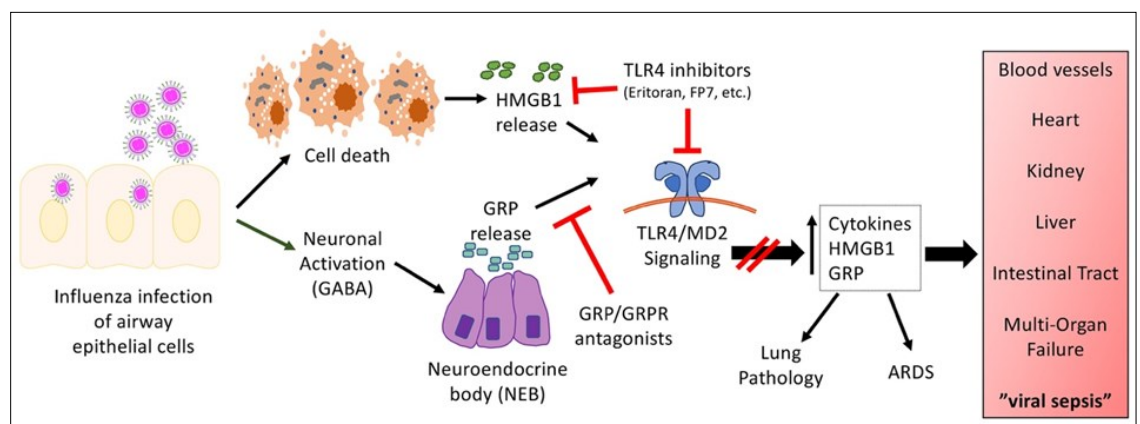
In collaboration with Dr. Frank Cuttitta at the National Cancer Institute, NIH, Frederick, we have been exploring the novel role of neuroendocrine molecules in the pathogenesis of influenza infection. We have published that a host-derived protein, Gastrin releasing peptide (GRP) produced by specialized pulmonary neuroendocrine epithelial cells (PNEC) in response to neuronally-derived gamma-aminobutyric acid (GABA), also contributes to influenza-induced cytokine production, pathology, and lethality by synergistically working with TLR4. Ongoing work is focusing on further delineating the cellular and molecular mechanisms by which GRP and GABA elicit influenza-induced disease. In addition, Dr. Shirey recently presented a seminar on this work at the University of Maryland School of Medicine, Center for Vascular and Inflammatory Diseases entitled, "Novel Neuroendocrine Role in the Host Response to Influenza Infection."

Shirey KA, Sunday ME, Lai W, Patel MC, Blanco JCG, Cuttitta F, Vogel SN. 2019. Novel role of gastrin releasing peptide-mediated signaling in the host response to influenza infection. *Mucosal Immunol.* 12:223-231.

We recently published a review that focuses on the role that TLR4 plays in the development of viral-induced acute lung injury and the potential for therapeutic targeting to mitigate disease.

Abstract: Respiratory viral infections have been a long-standing global burden ranging from seasonal recurrences to the unexpected pandemics. The yearly hospitalizations from seasonal viruses such as influenza can fluctuate greatly depending on the circulating strain(s) and the congruency with the predicted strains used for the yearly vaccine formulation, which often are not predicted accurately. While antiviral agents are available against influenza, efficacy is limited due to a temporal disconnect between the time of infection and symptom development and viral resistance. Uncontrolled, influenza infections can lead to a severe inflammatory response initiated by pathogen-associated molecular patterns (PAMPs) or host-derived danger-associated molecular patterns (DAMPs) that ultimately signal through pattern recognition receptors (PRRs). Overall, these pathogen-host interactions result in a local cytokine storm leading to acute lung injury (ALI) or the more severe acute respiratory distress syndrome (ARDS) with concomitant systemic involvement and more severe, life-threatening consequences. In addition to traditional antiviral treatments, blocking the host's innate immune response may provide a more viable approach to combat these infectious pathogens. The SARS-CoV-2 pandemic illustrates a critical need for novel treatments to counteract the ALI and ARDS that has caused the deaths of millions worldwide. This review will examine how antagonizing

TLR4 signaling has been effective experimentally in ameliorating ALI and lethal infection in challenge models triggered not only by influenza, but also by other ALI-inducing viruses.



Shirey KA, Blanco JCG, Vogel SN. 2021. Targeting TLR4 signaling to blunt viral-mediated acute lung injury. *Front. Immunol.* 02 July 2021 <https://doi.org/10.3389/fimmu.2021.705080>

READ MORE!

Dr. Alla Zamyatina and Dr. Holger Heine recently contributed to a research paper and a review to *Frontiers in Immunology*

Zamyatina, A., and H. Heine. (2020) Lipopolysaccharide Recognition in the Crossroads of TLR4 and Caspase-4/11 Mediated Inflammatory Pathways. *Front Immunol* 11, 585146. <https://doi.org/10.3389/fimmu.2020.585146>

Heine, H., F. Adanitsch, T. T. Peternelj et al. (2021) Tailored Modulation of Cellular Pro-inflammatory Responses with Disaccharide Lipid A Mimetics. *Front Immunol* 12, 631797. <https://doi.org/10.3389/fimmu.2021.631797>



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Biochemistry Group Leader (M/W)

Company:

LPS-Biosciences is an innovative Biotech SME established in 2011 with strong expertise in bacterial endotoxins and structural analysis with 40 years of research at the French National Center for Scientific Research (CNRS).

Missions:

As part of the development of our activity in biotechnology and growth of our team, we are looking for a scientific manager. Reporting to the head of laboratory, you will be managing a team of technicians working for our clients in the vaccine field. This will include planning and execution of research projects, quality control management, as well as budget of your team.

Required profile:

Young PhD in analytical biochemistry having a first experience of at least 2 years post-doctoral or company, and willing to manage a team.

Desired technical skills:

- Experience in analytical Biochemistry: Structures of lipids, polysaccharides,
- LPS. Structural characterization by chromatography, Mass Spectrometry (MALDI) and NMR Tests (colorimetric, spectroscopy)
- Purification through different techniques of chromatography and electrophoresis.
- Manipulation of solvents, acids, alkali.

Contract:

- Permanent position to be filled as soon as possible
- Place: Orsay in Essonne (91) France, near Paris, accessible by RER B and national road 118

Please send candidacy CV and motivation letter to recrutement@lpsbiosciences.com



Renew Your Membership Now!

<https://www.ieiis.org/Membership%20subscription>

IEIIS members are entitled to a 20% reduced article processing rate for the society's official journal *Innate Immunity* as well as a discounted registration rate to attend the society's highly-regarded biennial international scientific and business meeting. The meeting sites alternate between the USA, Japan, and Europe, providing international opportunities for scientific interaction with researchers in wide-ranging and related areas of work.

Other benefits of membership include:

- **Joining a network of experienced scientists who can give advice and help on project and career issues/development**
- **Speaking/presenting at internationally attended meetings**
(2021 meeting: October 12-15, Kobe, Japan)
- **New 2-year discounted membership rate**
- **Involvement in smaller meetings during main meeting off-years**
A unique opportunity for trainees, and young and mid-level investigators to meet with highly accomplished scientists whose seminal discoveries underpin the fields of endotoxin biology and innate immunity
- **Ability to apply for student travel grants for the IEIIS biennial meetings**
Includes up to \$750 USD and a waiver of registration fees
- **IEIIS Newsletter**
News about members and meetings; special articles and contact information
- **Opportunities**
Become involved via Council or committee membership
- **Vote in IEIIS elections**

Where to Ask . . .

Need to update your address information? Want to pay your dues but are not sure how? You can get answers to these and all other questions related to your IEIIS membership from the following locations:

To contact the Society for any inquiry, email us at IEIIS@aol.com or contact one of these individuals directly:

Membership

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