A Publication of the International Endotoxin and Innate Immunity Society

ENDOTOXIN NEWSLETTER

October 2018

IEIIS - INTERNATIONAL ENDOTOXIN & INNATE IMMUNITY SOCIETY

Jason Barker, MD
Dept of Internal Medicine
University of Iowa
200 Hawkins Dr
Iowa City IA 52246 USA

Phone: 319 335 4594
Fax: 319 335 4194
Email: jason-barker@uiowa.edu

A Letter from the IEIIS President

Egil Lien

Dear Friends and Colleagues,

The fall is here, and it is time for another IEIIS meeting – this time a joint one with SLB. The biennial meetings are a cornerstone in IEIIS society life, and I hope to see many of you in Arizona. I think we have a great program and hopefully something for everyone – ligands, structures, immunology, signaling, pathogens and more. And of course – a lot of catching up to do with folks we have not seen in a while. I hope you enjoy the conference. Lots of thanks to everyone involved, in particular the co-organizers Darren Lee and David Underhill. Jennifer Holland from FASEB-SLB has also done a great job with assisting the organizers. Many others in IEIIS and SLB have also been contributing in different ways, thanks to all. Importantly – congratulation to all award winners! The awards are well deserved. Going forward, we are also aiming for IEIIS meeting off-year activities next year, and perhaps one or more smaller meetings. Stay tuned!

This newsletter is packed with good stuff for reading and I think it has great quality. Thanks in particular to Jason, and also to Nancy and all contributors. I hope we can continue with a good newsletter publishing routine over the next few years, but of course, we depend upon the contributions from members.

Since the last newsletter we also had a tragic incident with the way too early passing of Andrei Medvedev, who many of you knew. We will spend some time at the meeting remembering Andrei as a great scientist, friend and colleague.

In two years we are heading to Japan for the next meeting, organized by Koichi Fukase and colleagues, potentially in Kobe, Japan, October 18-21, 2020. We are communicating with the Japan Endotoxin and Innate Immunity Society and the Endotoxin and LPS focus group in Japan and hope to increase interactions towards the meeting.

I feel the society has increased activity, but we still need to reach out to many prospective members, both younger and older, and convince them of the benefits of membership. Tim Sellati remains as membership chair and that is an important position. Hongpeng Jia is heading the social media effort. Alison Scott has agreed to be a trainee reach-out and hopefully that can increase attention to trainees and various issues they face. All current members should also feel free to contact people they know who can be candidate members and recommend IEIIS.

In some ways it feels a bit unsatisfying to leave the position now when I have figured out a lot about how things work within the society. I remain optimistic about the future of the society, as we have many enthusiastic members. Thanks to everyone in different positions for input and help. The society is in very good hands with the transfer of the presidency to Koichi Fukase. Best of luck to him, and to all who have agreed to contribute. I have tried to get more people involved with various tasks, and hope that together we can keep the society vibrant and continue to have this as an excellent forum for endotoxin and innate immunity research.

Best wishes to all,

Egil Lien

Egil Lien
IEIIS President 2016-2018

Inside this issue:

2018 Biennial Meeting Awards	2
In Memoriam—Andrei Medvedev	4
In the News	4
Literature Reviews	7
IEIIS Now on Social Media	8
Careers: Job Opening Announcements	11
Meeting Program	13
Contact Us	15

Awards for the 15th Biennial IEIIS Meeting Chandler, Arizona USA October 2018

We are happy to announce some of the awardees for this year's IEIIS meeting. Below, we provide brief summaries of their work and their future plans. Please congratulate them and be sure to attend their talks.

FREDERIK B. BANG AWARD:

The Frederik B. Bang Award was established by the Stanley Watson Foundation to recognize a substantial body of significant research accomplishment by an outstanding senior investigator, whose contributions to the endotoxin field extend over many years.

The recipient of the Bang Award is chosen by the Bang Award Committee, the members of which were previously selected by the Executive Committee of the IES.

The Bang Award, which has been given every two years in conjunction with the biennial IES (now IEIIS) Conference, is accompanied by the presentation of a plaque to the recipient, along with a major cash award. The award is given to a scientist who has done outstanding work over many years in the broad field of endotoxin and innate immunity. By virtue of this award being given by the IEIIS, its substantial size, and the previous recipients, the Bang Award should be considered to be the preeminent award in the broad field which encompasses endotoxin and innate immunity research.

Previous Recipients
Frederik B. Bang Award

Jack Levin	*1985*
Chris Galanos	*1996*
Sheldon Greisman	*2000**
Ernst Rietschel	*2002*
Shoichi Kusumoto	*2004*
Christian Raetz	*2006*
Bruce Beutler	*2008*
Petter Brandtzaeg	*2010*
Shizuo Akira	*2012*
Stefanie Vogel	*2014*
Kevin J. Tracey	*2016*

** Awarded in 2002*

Chris Whitfield, 2018 Frederik B. Bang Awardee

by Stephen Trent

Chris Whitfield

I first became aware of the work of Dr. Chris Whitfield back in my postdoc days at Duke University in the laboratory of Dr. Chris Raetz. Lucky for me, Raetz was unable to attend a summer FASEB meeting on microbial polysaccharides and asked me if I would like to go and present my work in his place. This was a great opportunity for me as I was new to the field and I was able to spend time with folks like Miguel Valvano, Joanna Goldberg, and of course Chris Whitfield.

Over the years, Chris has made seminal contributions to understanding the structure and function of multicomponent molecular machines that assemble and export bacterial glycoconjugates, including lipopolysaccharides (LPS). Studies on the biosynthesis of bacterial glycans were revolutionized in the 1990s by emerging DNA sequencing technologies and the rapid expansion of sequence data. Capitalizing on this information required the capacity to validate biochemical activities using reliable structures of the natural products and these are areas in which Whitfield's group has made distinctive and field shaping contributions. In a series of pioneering studies the Whitfield laboratory revealed the major classes of enzymes and structural proteins required for assembly of bacterial glycans and helped lay the foundation for the field. He established model systems that serve as paradigms for mechanisms and pathways, spanning bacterial phyla. His work has also significantly impacted the development of candidate targets for new antimicrobial therapies and vaccines. His reputation as an international leader is reflected by ~170 publications in lead journals, as well as more than 150 invited lectures in academia, pharma, and at international meetings. He was a Canadian Institutes of Health Research (CIHR) Senior Investigator (the first from a non-medical University) before becoming a Canada Research Chair. Whitfield has received both early principal investigator and career achievement (Murray Award for Career Achievement/Roche award) prizes from the Canadian Society of Microbiologists. He was also elected to Fellowship in the American Academy of Microbiology (2006) and the Royal Society of Canada (2007).

From a scientific standpoint, Dr. Whitfield's accomplishments are highly impressive, but he has also been a champion for young scientists. After my talk at that FASEB meeting, Chris asked me if I was planning on going into academics. I wasn't totally honest in that moment and just stated that I was unsure, but really, I was unsure of myself. We chatted on and off at that meeting and he made it clear that the field could use people like me. Given my description of his accomplishments above, one can see how this encouragement would make a huge impression on a young postdoc. Of course, Chris Raetz, a wonderful mentor and friend, had also provided that same sincere encouragement, but hearing from someone other than my boss really influenced my path. It's like when someone else besides your mother tells you that you have a nice singing voice. Over the years, Chris Whitfield has shown this same encouragement and kindness to many scientists and he remains one of my scientific heroes. Dr. Whitfield is truly deserving of the Frederik B. Bang Award and the IEIIS is thrilled to award him not only for his scientific contributions, but for being a champion of others.

Awards for the 15th Biennial IEIIS Meeting, cont'd.

YOUNG INVESTIGATOR AWARDS:

Candidates for the Young Investigator Award must be pre- or post-doctoral students of no more than 35 years of age and must have submitted a poster abstract to the meeting. Award candidates are selected based on, among other things, the quality of their research as reflected in the submitted abstracts. Those selected this year are:

Courtney Chandler is a fifth year graduate student in the Program in Biochemistry and Molecular Biology at the University of Maryland, Baltimore. She works in the lab of Dr. Robert Ernst in the Department of Microbial Pathogenesis studying *Pseudomonas* pathogenesis. Part 1 of her project is the analysis of ~130 genomes of *P. aeruginosa* (Pa) with the goal of understanding better how Pa adapts to the lungs of cystic fibrosis patients. Part 2 of her project focuses on the role of lipid A hydroxylation in persistence and/or pathogenesis (this is the topic of her award lecture). Specifically, she is studying lpxO1 and lpxO2, the ß-hydroxylases that add 2-OH to the secondary acyl chains of lipid A in Pa. She's interested in (1) what hydroxylation is doing in a broad sense, since not all bacteria hydroxylate their lipid A, (2) what type of conditions trigger hydroxylation and why that may matter for function, and (3) how/why Pa has two lpxO genes, compared to other bacterial species which only have one. She intends to graduate in the spring, and future plans are to be determined at this point.

Yanyan Li, PhD, Harvard Medical School, completed her PhD studies in the laboratory of Dr. Robert Ernst, where she worked on the role of LPS modification enzymes in pathogenesis. She is now a postdoctoral researcher at Harvard Medical School working on the structural biology of LPS transport. Previously, her team helped delineate the structural basis of MsbA-mediated transport of LPS. At the meeting, she will discuss her new project studying another LPS transporter complex, LptBFGC. Specifically she will present high resolution cryo-EM structures that reveal the basis of stepwise LPS capture, elevation, and extrusion, each of which is coupled with distinct conformational arrangements. Her hope is that these newly identified structures will serve as good targets for the design of novel antibiotics.

THERESA L. GIOANNINI TRAVEL AWARD FOR WOMEN IN SCIENCE: *Theresa L. Gioannini Travel Awards for Women in Science began at the 2014 biennial meeting in memory of Dr. Theresa L. Gioannini: scientist, teacher, mentor, wife and mother extraordinaire. Her creativity and rigor made possible several seminal contributions concerning opiate and MD-2/TLR4 receptors. The awards are used to support the attendance and participation of women graduate students, post-docs, and junior faculty at IEIIS-sponsored meetings. The awardee selected this year is:*

Federica Agliano, PhD received her PhD at the University of Messina, Italy, dissecting the role of the Rab11-interacting protein FIP2 and TRAM in the TLR4 pathway and in immune responses against Gram-negative bacteria, leading to type I IFN induction in human macrophages. Currently she is a postdoc at the University of Connecticut Health Center, Department of Immunology. Her main studies focus on the role of long non-coding RNAs in regulating host responses to bacteria and their involvement in autoimmune diseases, such as lupus and rheumatoid arthritis.

TRAVEL AWARD: *IEIIS Travel Awards are chosen on the basis of review of the abstracts submitted and are directed toward student members of the IEIIS. The awardee selected this year is:*

Pontus Orning, University of Massachusetts, is a PhD candidate in the labs of Dr. Egil Lien and Dr. Kate Fitzgerald at the University of Massachusetts Medical School. His interest lies in the field of innate immunity and he's currently working on investigating how immune cells use inflammasomes and programmed cell death pathways to combat microbial infection. He is particularly interested in how bacteria have evolved mechanisms to evade the innate immune response and how host cells try to counteract this. Additionally, he is fascinated by anything CRISPR and how whole genome CRISPR activation and deletion screens can be used to learn more about the interplay between bacteria and host. Pontus is currently in the midst of finishing his PhD and wants to continue using these tools to study innate immunity in his future academic career.

In Memoriam—Andrei Medvedev

by Egil Lien

It was a sad day when I received news about the sudden and unexpected passing of Dr. Andrei E. Medvedev in late July while he was in Russia visiting his mother. Andrei was a great scientist and friend. He completed his PhD in Moscow and came to Terje Espevik's lab at NTNU in Norway in 1993 as a postdoc, where I met him. He moved to the US in 1996 to join Stefanie Vogel's lab at the Uniformed Services University of Health Sciences in Bethesda. In 2002 Stefanie and Andrei relocated to the University of Maryland, and Andrei moved through the ranks there, becoming an Associate Professor with his own lab. Later, he moved to the UConn Health Center in 2013.

Andrei's main research interests were signaling in the innate immune system and identifying the molecular mechanisms of host responses to serious infections. At NTNU he started to work with TNF receptors, NF-kB and later LPS and other ligands that interacted with receptors such as CD14 and CR3. At USUHS and U Maryland he focused more on endotoxin/LPS, and also was a part of the Toll-like receptor (TLR) "wave" that swept the innate immunity field at that time. One of his finest contributions was a paper in J Exp Med (2003) describing mutations in the IRAK-4 signaling molecule in a patient with recurrent serious bacterial infections and hypo-responsiveness to LPS. This strongly supported the view that TLR/IL-1/IL-18 signaling was a key component of human anti-bacterial defenses. Andrei was a well-funded and very productive scientist, perhaps especially known for solid investigations, great biochemistry, persistence and particular attention to details. He had many papers investigating mechanisms associated with endotoxin signaling and tolerance, the altered cellular state induced by an initial exposure to LPS before later challenge, also observed in vivo. Many of his papers studied TLRs and downstream signaling components, such as IRAK and Tollip. Lately he was also interested in lncRNA and their regulation of innate immunity.

Based upon his research, he was nominated for the IEIIS Sheldon E. Greisman Award early this summer and will receive this award posthumously. This is another testament to the high quality of his research.

Andrei Medvedev

Andrei was a long-time member of IEIIS, and very interested in society matters. He was often seen at the IEIIS meetings, he received a Young Investigator Award and was a scientific councilor, and helped with the Innate Immunity journal. He was a good and caring colleague with many collaborators and was always interested in other people's work.

While Andrei was known to be very serious about his research, he also had a great sense of humor. I especially remember a trip to a research retreat for our Department of Cancer Research at NTNU in the mid/early 90's. We had a chartered train ride that took a few hours, and after Andrei's arrival to Terje's lab the natural theme for the ride was Russia. We were served caviar and vodka shots, listened to Russian music, and some people even dressed up for the occasion. Andrei was brimming with joy and grinned for the whole trip. I was lucky enough to stay in regular email contact with Andrei even after our ways parted, and saw him at meetings, in Maryland, at UMass and at UConn, and he always greeted me with a big smile.

Andrei was a devoted family man and was very proud of his children Anton and Anastassia. After he started at UConn he commuted most weekends to his beloved wife Svetlana and their home in Maryland by car – a trip that takes at least 6 hours one way. Warm wishes go to Svetlana, Anton and Anastassia in this difficult time.

Andrei will be sorely missed by his colleagues and friends.

UConn has established a memorial fund in his name that will support presentations by young investigators. For those interested in contributing, the details are listed below.

UConn Foundation
Attn: Aaron Frankel
10 Talcott Notch Road Suite 100
Farmington, CT 06032, USA

Indicate "In Honor of Dr. Medvedev" on your donation

IN THE NEWS

Dr. Martine Caroff Recognized by the European Commission

Martine Caroff

Dr. Martine Caroff was recently recognized by the European Commission as a finalist in the EU Prize for Women Innovators 2018. Dr. Caroff is the Founder, Chief Scientific Officer, and Chairwoman of LPS-BioSciences (www.lpsbiosciences.com). Her company seeks to "make endotoxins accessible for the pharmaceutical industry and to offer a consistent range of services and developments to meet the needs associated with endotoxins."

One of her goals with the company is to create opportunities for young researchers, so please note the announcement of a job opening for a young researcher in this newsletter.

Dr. Caroff's finalist video can be viewed on YouTube at:
https://www.youtube.com/watch?v=n1qJJArF6m4&feature=youtu.be

Awards for the 15th Biennial IEIIS Meeting, cont'd.

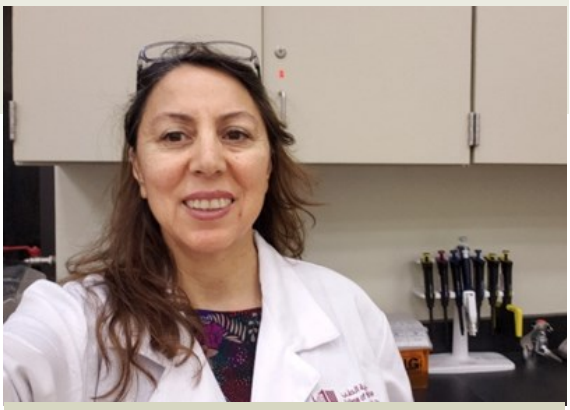
ALOIS H. NOWOTNY AWARD:

The Nowotny Award is bestowed upon a young investigator who has shown excellence in research, made a significant contribution to the study of endotoxins, shows potential for further scientific development, and whose research is close to that pursued by the late Professor Alois H. Nowotny. With the latter proviso, the award tends to be given to researchers whose hard work has a chemical or biochemical orientation with a focus on the study of the chemical nature of endotoxins. Nominations are made by the society membership prior to each biennial conference, and the recipients are chosen by the Governing Council.

Alison J. Scott, PhD, University of Maryland, Baltimore, has made important contributions to the field of endotoxin and innate immunity research and is a young and promising scientist performing high quality work. She has been involved in a number of studies including innovative investigations using new methods of combined advanced mass spectrometry and histology. These techniques can be termed molecular histology or mass spectrometry imaging, and consist of mass spectrometry directly on tissue samples. Some of these studies encompass identifications of *in vivo* biomarkers of disease, including those observed during infections. One such example is an excellent study of *Francisella* infections in mice, cited below. She is regarded as a highly collegial and positive scientist, always open for collaborations with others. Dr. Scott is currently Research Associate Professor. She earned her PhD in Robert Ernst's lab in 2015, and later did post-doctoral research with David Goodlett. We congratulate her for her achievements.

Representative publication: A.J. Scott et al. (2017) Host-based lipid inflammation drives pathogenesis in *Francisella* infection. *PNAS* 11:12596.

An Interview with Susu Zughaier, Qatar University, Doha, Qatar



Susu Zughaier, PhD, in her new laboratory at Qatar University

Q: Tell us about your work and your background with endotoxin and innate immunity research.

A: My interest in endotoxin and innate immunity research started during my PhD studies in the late nineties where I examined LPS biological activity in macrophages. I extracted LPS from different pathogens common in cystic fibrosis with focus on *Burkholderia cepacia* epidemic strains and compared their ability to induce inflammatory responses in macrophages. This work was just a year before the discovery of TLR4 as the LPS sensor. During my first postdoctoral studies in Professor Denis Kasper's lab at Harvard Medical School, I worked on vaccine immunology that strengthened my scientific skills. I then joined Professor David Stephens lab at Emory University where I investigated *Neiseria meningitidis* LPS structure-function at the dawn of TLR4 discovery. I established a functional innate immunity research laboratory. My interest in TLR research was extended to investigate how the innate immune system recognizes bacterial capsular polysaccharides that form the basis of several bacterial vaccines such as meningococcal and pneumococcal vaccines. My interest in host-pathogen interactions evolved into vaccine research focusing on developing nanotechnology based vaccines. My translational innate immunity research is focused on the immune modulatory effects of vitamin D, specifically how it regulates cellular iron metabolism via the hepcidin-ferroportin axis in macrophages. To date I published more than 45 research papers, two awarded patents and two provisional patent disclosures.

Q: Where was your old lab, and where is the new lab?

A: I was at Emory University in Atlanta until a year ago, I moved half way across the globe to Qatar University College of Medicine in Doha, Qatar.

Q: What motivated you to move and set up a new lab in a new country?

A: After 17 years of my career at Emory University, I was looking for a new challenge and a new experience. Many reasons contributed to this decision including the limited research funding opportunities. I visited Qatar multiple times where I participated in scientific conferences and got the chance to observe the investment in research infra structure which is very encouraging. I considered moving to Qatar to continue my scientific endeavors and give my family an international experience. Further, I am a proud naturalized US citizen; however, being a Palestinian Muslim woman from East Jerusalem I was not comfortable with the latest political climate and election campaign rhetoric in the US. Therefore, moving to Qatar was not just geographically closer to home where I grew up but I can relate to the local culture and experience what is described as "third culture".

Continued on Next Page

An Interview with Susu Zughaier, *cont'd.*

Q: What is financial support for research like in Qatar?
A: Qatar has invested significantly in building biomedical research infrastructure at the Ministry of Health related institutions, Qatar Foundation and Qatar University, the only state university. Scientists in Qatar can have access with regulated permission to data and biological material from centralized projects such as Qatar Biobank, Qatar Genome project and others. Further, scientists can apply to large grants from Qatar National Research Fund, the equivalent of NIH, which is also competitive. Qatar University provides laboratory spaces at no cost to researcher and access to all core labs. It also provides various grants such as seed funding, collaborative research grants and student research grants; therefore, I still write grants and compete for funding.

Q: What is the current focus of your lab?

A: In my lab I continue to focus on host-pathogen interactions specifically investigating macrophage innate immune responses and autophagy modulation during bacterial infections. I also collaborate with clinical microbiologists where we investigate genetic determinants of antibiotic resistance in Qatar. With my students, we utilize Qatar Biobank data to investigate the relation between vitamin D status and iron indices in healthy adults. In addition, I continue my international collaborations in the US working on *Neisseria gonorrhea* host-pathogen interactions and gonorrhea nanovaccine.

With my student in the lab

Very rewarding to have smart honor students training in my lab

Q: How have you and the family adapted to life in a new environment?

A: The drastic move was not easy for the family however, since Doha has a very large expatriate community and English is spoken everywhere, we adapted to the new life quite well. My daughters attend the American School of Doha that provides high quality education and sense of home. Doha has many attractions and leisure activities for families, in addition to cultural diversity and meeting new friends from all around the world. The weather is hot in summer but amazingly very good in winter and Spring. This is our second year living in Qatar and we do enjoy it very well.

Q: Will you be able to join the IEIIS/SLB meeting this fall, to catch up with old and new friends?

A: Yes indeed, I look forward to the upcoming meeting in Phoenix. I will be attending with two of my students who will present their research findings that they produced in my lab at Qatar University. We will present a flash talk and a poster titled "The role of hyperuricemia in modulating autophagy flux and inflammasome activation during bacterial infection in macrophages". I will also serve as co-chair for the second plenary session, and very excited to catch up with friends and build new collaborations.

LITERATURE REVIEWS

Hoping to enhance communication among IEIIS members and share valuable insights and contributions, we are again including reviews from members in the Newsletter. We encourage you to share your work or your perspectives, so feel free to send along any updates or mini-reviews of recent articles that you find interesting.

Sincerely,

Dr. Jason H. Barker
Scientific Councilor and Newsletter Editor, IEIIS
Inflammation Program, Internal Medicine, Infectious Diseases
University of Iowa
jason-barker@uiowa.edu

LPS-Induced Hemolymph Coagulation

Reviewer: Dr. Jerroldd P. Weiss
University of Iowa
Coralville, IA USA

Toshio Shibata, Yuki Kobayashi, Yuto Ikeda, and Shun-ichiro Kawabata (2018) Intermolecular autocatalytic activation of serine protease zymogen factor C through an active transition state responding to lipopolysaccharide. *J Biol Chem* 293:11589-11599

Jerrold Weiss

LPS-induced hemolymph coagulation in horseshoe crabs has provided a valuable example and model for study of the interaction of LPS with host proteins that lead to important functional changes in host defense. *Limulus* factor C is an LPS-binding serine protease zymogen that functions in hemolymph in concert with a second LPS-binding protease zymogen (*Limulus* factor B) in the LPS-triggered hemolymph coagulation cascade and also on the hemocyte cell surface in concert with a G protein-coupled receptor to trigger hemocyte activation in response to Gram-negative bacteria and cell-free LPS. Activation of both protease zymogens (factors C and B) is LPS-dependent but mechanistically distinct: activation of factor B is mediated by activated factor C whereas that of factor C is autocatalytic and thus could reflect either an **intra-** or **inter-**molecular activation mechanism.

This study provides several novel insights concerning the mechanism of factor C activation instigated by LPS binding. By analogy to the model of trypsinogen activation induced by a chymotrypsin-like cleavage of the Arg^{15}-Ile^{16} bond in trypsinogen, it has been postulated that a similar chymotrypsin-like cleavage of the Phe^{737}-Ile^{738} bond is necessary for expression of the serine protease activity of factor C. If so, the ability of the factor C zymogen to be activated in an autocatalytic fashion would appear to pose a mechanistic conundrum: i) how to explain the first activation event (much like an "immaculate conception"); and ii) how to explain the linkage targeted (Phe^{737}-Ile^{738}) when the proteolytic specificity of activated factor C is trypsin (not chymotrypsin)-like.

Substitution of the active site Ser^{941} ablated LPS-induced endo-proteolytic cleavage of factor C zymogen confirming that this was mediated by factor C (zymogen) and not a trace contaminating factor. However, neither substitution of Phe^{737} with Ala or Glu nor of Ile^{738} with Ala markedly affected LPS-induced nicking of factor C zymogen indicating that this activating fragmentation did not depend on chymotrypsin-substrate-like properties of this site. Perhaps, as the authors suggest, LPS binding of the factor C zymogen induces a conformational change around the 737 site that helps confer an activatable transition state of the zymogen.

Remarkably, substitution of Phe^{737} by proline (F737P) ablated LPS -induced cleavage of this mutant protein but <u>not</u> the ability of this mutant to cleave S941A factor C zymogen when both proteins were bound to LPS. Since S941A factor C zymogen cannot mediate its own cleavage at F737 ± LPS, the cleavage observed must reflect the <u>intermolecular</u> action of a neighboring LPS-bound (F737P) zymogen molecule that contains an intact Ser-bearing catalytic site. Whether or not the exclusive intermolecular (vs.intramolecular) action of the F737P factor C zymogen predicts an exclusive intermolecular activation mechanism of wild-type factor C zymogen when bound to LPS cannot be judged given the likely perturbing effects of the proline substitution on the conformation of this critical region. However, earlier findings by this group showing LPS dose-dependence of factor C zymogen activation that correlated with proximity between zymogen molecules as judged by protein cross-linking seems most compatible with an intermolecular mode of factor C activation. The binding of factor C zymogen to LPS-rich surfaces – whether aggregates of purified LPS or lipid A mimetics or outer membranes of Gram-negative bacteria – also seem most compatible with the LPS-induced intermolecular interactions to follow, either with factor B zymogen in hemolymph or G-protein coupled receptors on hemocytes.

A new inflammatory pathway sensing LPS biosynthesis carbohydrate intermediates

Pontus Orning[1,2], Egil Lien[1,2]

[1] Centre of Molecular Inflammation Research, Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, 7491 Trondheim, Norway.

[2.] Program in Innate Immunity, Department of Medicine, Division of Infectious Diseases and Immunology, UMass Medical School, Worcester, MA 01605, USA

Feng Shao and collaborators, including new IEIIS councilor Alla Zamyatina, recently reported on a pattern recognition receptor and its specific ligand - a carbohydrate PAMP (Zhou et al. 2018). Surprisingly, this was identified as the sugar ADP-d/l-glycero-β-d-manno-heptose (ADP-Hep), an intermediate in the LPS biosynthetic pathway, encoded by the *hldE* gene. The elegant and comprehensive paper contains screens both on the bacterial and host side to identify key players, in addition to structural investigation. ADP-Hep - including synthetic versions of the molecule - triggered NF-kB activation via a cellular sensor called Alphakinase-1 (ALPK1). Other pathway members include TRAF-interacting protein with forkhead-associated domain (TIFA), and TNF receptor-associated factor (TRAF) 6. The Type III secretion system of *Yersinia pseudotuberculosis* was aiding the transfer of the bacterial sugar to the host cell, but non-secretion system transfer also seems possible, perhaps via dedicated transporters. In addition, certain host adenylyltransferases could convert the ADP-Hep precursor d-glycero-β-d-manno-heptose 1,7-bisphosphate (HBP) into ADP-Hep-7-P, also capable of activating ALPK1. Could other bacterial components be metabolized into molecules triggering the same pathway? Structural analysis indicated direct binding of ADP-Hep to ALPK1.

The biological significance was tested by *in vivo* injection of ADP-Hep into mice, and the absence of ALPK1 blocked the inflammation. ALPK1 KO mice also appeared more sensitive to infections with the Gram-negative bacteria *Burkholderia cenocepacia* (Zhou et al. 2018), *Shigella flexneri* and *Helicobacter pylori* (Milivojevic et al. 2017; Zimmermann et al. 2017). It would be interesting to see how this pathway overlaps with and compares to other signals sensing Gram-negative bacteria, such as the TLR4 system.

Overall, this paper is a very interesting read and provides solid evidence for a new signaling pathway in innate immunity. Congratulations to Alla and all the authors.

References:

Milivojevic, M. et al., 2017. ALPK1 controls TIFA/TRAF6-dependent innate immunity against heptose-1,7-bisphosphate of gram-negative bacteria. *PLoS Pathogens*, 13(2).

Zhou, P. et al., 2018. Alpha-kinase 1 is a cytosolic innate immune receptor for bacterial ADP-heptose. *Nature*. 561 (7721), pp.122-126. Available at: http://www.nature.com/articles/s41586-018-0433-3.

Zimmermann, S. et al., 2017. ALPK1- and TIFA-Dependent Innate Immune Response Triggered by the Helicobacter pylori Type IV Secretion System. *Cell Reports*, 20(10), pp.2384–2395.

IEIIS NOW ON SOCIAL MEDIA

Dear Members,

In an effort to expand the outreach and enhance the awareness of our society to all related professionals, we have created several social media accounts as listed below. We are currently in the process to rejuvenise and update the contents, so any inputs and ideas to boost social exposure using these media are highly welcomed. Contributing high quality images from past meetings will be appreciated.

Please contact Hongpeng Jia at: hjia4@jhmi.edu if you can help with the ongoing effort

https://www.facebook.com/pg/International-Endotoxin-and-Innate-Immunity-Society-408088806381204/posts/?ref=page_internal

https://twitter.com/ieiisorg

https://www.linkedin.com/company/international-endotoxin-and-innate-immunity-society/

CHARMM-GUI LPS Modeler for Generation of LPS Structures from Various Gram-negative Bacteria

by Dr. Otto Holst
Research Center Borstel
Borstel, Germany

S. Jo, T. Kim, V.G. Iyer, and W. Im (2008)
CHARMM-GUI: A Web-based Graphical User Interface for CHARMM. *J. Comput. Chem.* 29:1859-1865

J. Lee, D.S. Patel, J. Ståhle, S-J. Park, N.R. Kern, S. Kim, J. Lee, X. Cheng, M.A. Valvano, O. Holst, Y. Knirel, Y. Qi, S. Jo, J.B. Klauda, G. Widmalm, and W. Im
CHARMM-GUI Membrane Builder with Glycolipids and Lipopolysaccharides for Complex Biological Membrane Simulations *In preparation*

http://www.charmm-gui.org/input/lps

LPS Modeler in CHARMM-GUI has been developed to facilitate the structure generation of a single LPS or LOS molecule (**Figure 1 A**). *LPS Modeler* takes an LPS/LOS sequence from the predefined LPS/LOS sequences as input data, i.e., the user can select the bacterial species, lipid A / core / O-antigen types, and the number of O-antigen RUs (**Figure 1 B**). Further, available O-antigens for a specific bacterium are provided as a table, so that they can be easily changed by clicking an O-antigen name (**Figure 1 B**). *LPS Modeler* currently supports experimentally identified LPS sequences of 15 bacterial species with 37 lipid A, 52 core, and 304 O-antigen types (**Table 1**), including all available *E. coli* O-antigen sequences in ECODAB. The predefined LPS/LOS sequences are stored in GRS (Glycan Reader Sequence) format on the server, which can be transferred to the client side upon request by the user.

The selected LPS/LOS sequence is automatically displayed in the CASPER format next to the core selection button or O-antigen text input box (**Figure 1 B**), as well as on the "Core Sequence" (**Figure 1 C**) and "O-antigen Sequence" (**Figure 1 E**) panels. Using these glycan sequence panels, the user can easily modify the carbohydrate types, linkage types, and chemical modifications, or can add or remove a carbohydrate or a chemical modification to/from the predefined sequence. In addition, with the presence of O-antigen RUs, the information for the core-O-antigen linkage is displayed (**Figure 1 D**), and the user can readily modify the linkage between core and O-antigen using the selection buttons.

Continued on Next Page

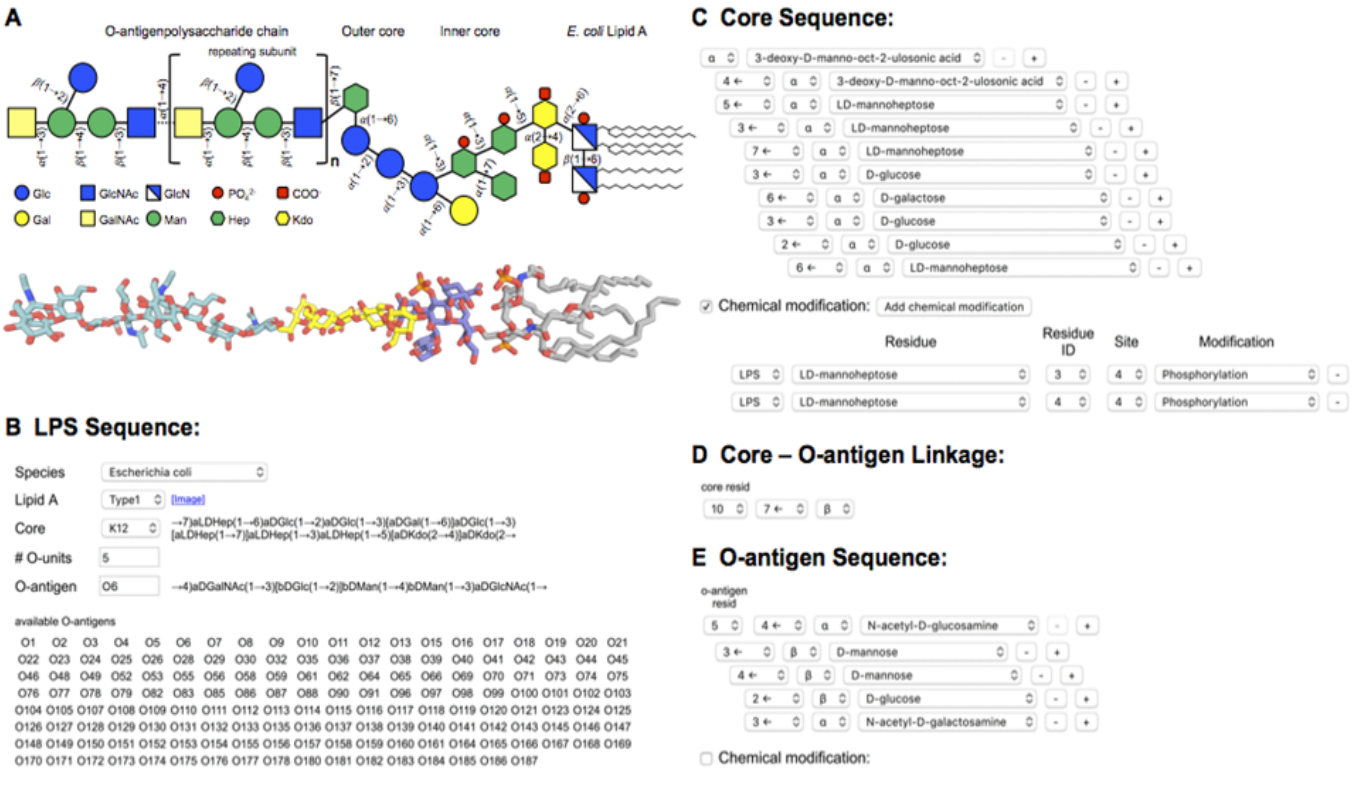
Table 1. Supported bacterial species with the number of lipid A, core, and O-antigen types in *LPS Modeler*.

Bacterial species	# of Lipid A types	# of Core types	# of O-antigen types
Acinetobacter baumannii	2	3	-
Burkholderia cepacia	3	1	-
Campylobacter jejuni	1	9	-
Chlamydia trachomatis	1	3	-
Escherichia coli	2	5	157
Helicobacter pylori	2	1	5
Klebsiella pneumonia	3	1	16
Moraxella catarrhalis	1	3	-
Neisseria gonorrhoeae	3	3	-
Neisseria meningitidis	3	8	-
Pseudomonas aeruginosa	5	3	32
Salmonella enterica	3	2	60
Shigella flexneri	1	1	19
Vibrio cholerae	5	3	15
Yersinia pestis	2	6	-
Total	37	52	304

Continued From Previous Page

If LOS is selected or a user puts zero in the "# O-units" text box to build rough LPS structure, the "Core-O-antigen Linkage" and "O-antigen Sequence" panels will be hidden to avoid confusion in identifying the selected sequence. Finally, based on reported chemical modifications or acylation patterns, there are more than one lipid A types available in a selected bacterial species, which user can check their chemical structures and choose one of available lipid A structures. Upon clicking on the next button, *LPS Modeler* generates a CHARMM input script using user-selected sequence information to build an all-atom LPS/LOS structure. All the input (CHARMM script) and output (LPS structure, connectivity information, and parameter) files can be downloaded by clicking the "download.tgz" button.

Fig. 1. *Structure of (A) LPS and (B-E) illustrative snapshots of LPS Modeler. (A) E. coli K-12 O6 with 2 repeating units. (B) Users can build a LPS sequence using bacterial species, lipid A, core, and O-antigen information. The selected LPS sequence is displayed on (C) "Core Sequence" and (E) "O-antigen Sequence" panels, and the linkage information between core and O-antigen is displayed in (D) "Core – O-antigen Linkage" section.*



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). The company addresses and meets the endotoxins related needs of the biggest industrial groups in human and animal health, cosmetics, agriculture, and agri-food sectors, through service delivery, production and partnership R&D. We are also working with academic laboratories to advance research on pathogens and conduct innovative projects in the vaccines and diagnostic domains.

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. To do this, you will accomplish the following tasks:

- Scientific responsibility of your team (manipulations, customer relationship, reports)
- Management of your team (security, organization, animation, training)
- Quality management (customer focus, standardization, feedback)
- Project management (project planning, tracking of time planned and carried out)
- Track costs associated with your missions (orders, budget, fundraising)

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:	**Desired behavioral skills:**
Experience in analytical Biochemistry: Structures of lipids, polysaccharides, LPS	Motivation for the team management, independence, good organization, seriousness and professionalism
Structural characterization by chromatography, Mass Spectrometry (MALDI) and NMR	Customer orientation Commitment toward results and profitability
Tests (colorimetry, spectroscopy) Purification through different techniques of chromatography and electrophoresis	Excellent communication, oral and written, in French and English
Manipulation of solvents, chemicals	Contributing to team spirit and good interpersonal skills

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

CASE WESTERN RESERVE UNIVERSITY
SCHOOL OF MEDICINE

Open Rank Faculty Position (tenure-track/tenured), Department of Molecular Biology and Microbiology, Case Western Reserve University (CWRU), Part of the CWRU - Cleveland VAMC Center for Antimicrobial Resistance and Epidemiology (Case VA CARES).

The Department of Molecular Biology and Microbiology at CWRU School of Medicine and the Case VA CARES (Center for Antimicrobial Resistance and Epidemiology) at the Louis Stokes Cleveland VA Medical Center are currently seeking applications for a 12-calendar month tenure track or tenured position at the **Assistant**, **Associate**, or **Full Professor** level. The newly created Case VA CARES center has the long-term goal of strengthening and expanding the existing research program targeted at understanding the mechanistic basis of antibiotic resistance. The center will aim to develop novel therapeutic approaches to combat multi-drug resistance organisms, and to translate these into therapies. Moreover, through the application of "-omic" technologies and rapid diagnostic procedures, the center will impact the management of patients with MDR infections, and help track outbreaks and facilitate the molecular epidemiology of MDR organisms. The center will also strengthen the education of trainees with regard to antimicrobial resistance. We encourage applications from highly qualified individuals with demonstrated experience in the areas of: **the molecular basis of antimicrobial action and resistance, alternative approaches to combating infections** (e.g. stimulating the immune system, or inactivating virulence mechanism), **animal models of infection with MDR organisms,** as well as **molecular epidemiology of MDR infections and bioinformatics**.

Successful candidates will establish a vigorous research program, participate in teaching activities, and interact productively with a nationally-ranked team of basic and clinical scientists interested in the overall areas of AMR microbiology and infectious diseases.

In addition to newly refurbished laboratory space and a generous start-up package, we offer a highly interactive environment with exceptional intellectual, infrastructural, and administrative support. We stress excellence in research and in teaching. All candidates should have a Ph.D. or M.D. degree and have completed at least 3 years of postdoctoral training. Candidates at the **Assistant Professor** level must have demonstrated a capacity for independent research and exhibit a high likelihood of attracting federal funding. At the **Associate** and **Full Professor** level, candidates should have a record of federal funding, an active research program, and evidence of a national/international reputation. Rank and salary will be commensurate with experience. The University offers partner benefits and is responsive to the needs of dual-career couples.

Interested applicants must email an application packet including a letter of application, curriculum vitae, brief statement of research goals and accomplishments, and 3 references as PDF files to: **MBIO-VAMC Search Committee** at: VAMBIO205@CASE.EDU . Only complete applications will be considered.

In employment, as in education, Case Western Reserve University is committed to Equal Opportunity and Diversity. Women, veterans, members of underrepresented minority groups, and individuals with disabilities are encouraged to apply.

Case Western Reserve University provides reasonable accommodations to applicants with disabilities. Applicants requiring a reasonable accommodation for any part of the application and hiring process should contact the Office of Inclusion, Diversity and Equal Opportunity at 216-368-8877 to request a reasonable accommodation. Determinations as to granting reasonable accommodations for any applicant will be made on a case-by-case basis.

"Myeloid Cells: Development, Environment and Inflammation"
PROGRAM

October 13-16, 2018
Sheraton Grand at Wild Horse Pass, Chandler, Arizona USA

Chairs: Darren Lee, *Oklahoma University College of Medicine*, *Dean McGee Eye Institute*, Egil Lien, *University of Massachusetts Medical School* & David Underhill, *Cedars Sinai*

Final program can be viewed online at: https://www.leukocytebiology.org/assets/docs/SLB2018/2018%20SLB_IEIIS%20Program%20Book.pdf

Saturday, October 13, 2018

Satellites - Multiple member led special interest satellite programs.

- *Enabling Technologies for Leukocyte Research*, Daniel Irimia, Harvard Medical School
- *Microbiome, Mucosal Immunology and Aging*, Rebecca Fuldner, NIA/NIH and Alan Landay, Rush
- *Emerging Concepts in NLR Sensing and Signaling*, Irving Coy Allen, Virginia Tech and Ed Miao, UNC Chapel Hill

Sunday, October 14, 2018

Poster Flash Talks - Selected abstracts by junior attendees provide short talks organized by topic.

MTTG (Members in Transition and Training) Session Lunch - Topic: State-of-the-art high-resolution imaging modalities (more details to come in spring 2018) organized by the SLB Members in Transition and Training Group

Award Talks

- *SLB Presidential Finalists* (Student and Junior Faculty/Postdoc categories)
- *IEIIS Young Investigator awards*
- *SLB's Dolph Adams* and *G. Jeannette Thorbecke award talks*
- *IEIIS' Alois H. Nowotny, Frederick B. Bang* and *Sheldon E. Greisman award presentations*

Keynote Lecture – SLB Keynote Awardee, More than a license to kill: the many roles of the leukocyte NADPH oxidase, Mary Dinauer, Washington University in St. Louis

Monday, October 15, 2018

Professional Development Workshop Breakfast – Topic: Team Science. Organized by the SLB Professional Development Committee

Plenary II: Myeloid Cell Development, Differentiation, and Novel Functions

- *TLR signaling, macrophage development, and Macrophage Activation Syndrome*, Jessica Hamerman, Benaroya Research Institute
- *Dendritic cell development and function*, Ken Murphy, Washington University St. Louis
- *Monocyte heterogeneity and origins*, Helen Goodridge, Cedars Sinai
- *Unconventional processing of IL-1 beta by neutrophils*, Eric Pearlman, University of California, Irvine

Poster Session Lunch

Concurrent Sessions 1-4:

Leukocytes in Immune Privilege Sites

- *Neuroprotective specialization for microglia in degenerative diseases of the retina*, Daniel Saban, Duke University School of Medicine
- *Obesity and Autoimmune Uveitis*, Darren Lee, Oklahoma University College of Medicine, Dean McGee Eye Institute

Best of JLB and Innate Immunity

- *Mediators and molecular pathways involved in the regulation of neutrophil extracellular trap formation mediated by activated platelets*, Mirta Schattner, Instituto de Medicina Experimental (IMEX)

Monday, October 15, 2018, cont'd.

- Top cited author from *Innate Immunity* TBA
- SLB W&D Paper of the Year Awardee
- IEIIS Theresa L. Gioannini Awardee

Inflammatory Signaling in Leukocytes

- *Initiation and Regulation of Innate Immunity*, Jonathan Kagan, Boston Children's Hospital, Harvard Medical School
- *Cytotoxic lymphocytes activate caspase-7 in target cells to clear bacteria*, Ed Miao, University of North Carolina School of Medicine, Chapel Hill

Neutrophils and Phagocyte Functions

- *F. tularensis BLPs and TLR1 regulate human neutrophil lifespan*, Lee-Ann Allen, University of Iowa, Carver College of Medicine
- *The cytoskeleton and the pericellular coat dictate the responsiveness of phagocytic receptors*, Sergio Grinstein, University of Toronto

Plenary III - Metabolism & Physiology in Inflammation and Immunity

- *Host-microbe interactions: harnessing co-evolution to treat disease,* Janelle Ayres, Salk Institute
- *Fueling Phagocyte Functions*, Daniel McVicar, NIH/NCI
- *Innate Immune Recognition and Signaling in Drosophila*, Neal Silverman, University of Massachusetts Medical School
- *Mechanisms of chronic inflammation associated with microbial dysbiosis in a Rhesus Macaque model of environmental enteric disease*, Ilhem Messaoudi, University of California, Irvine

Tuesday, October 16, 2018

Women and Diversity Workshop Breakfast – Topic: Effectively Communicating Our Science to the Public. An educational session organized by the SLB Women and Diversity Committee.

Plenary IV - The Microbiome in Inflammation and Immunity

- *Commensal fungal metabolism and host immunity*, Yan Shi, Tsinghua University

Tuesday, October 16, 2018, cont'd.

- *Host Immunity to Commensal Fungi*, David Underhill, Cedars Sinai
- *Microbial Dysbiosis drives age-associated inflammation which impairs myeloid development*, Dawn Bowdish, McMaster University
- Title TBA, Speaker TBA

Poster Session Lunch

Concurrent Sessions 5-6:

Ligands of Innate Immunity: Structure & Function

- *Recent examples of structure and structure-function analysis of LPS and lipid A*, Otto Holst, Research Center Borstel
- *Structure Matters – Modification of the Lipid A Component of Lipopolysaccharide (LPS) LPS Alters Host Immune Responses*, Bob Ernst, University of Maryland

Host Receptors and Microbes

- *Single-cell Dynamics of Pyroptosis in M. tuberculosis infected macrophages*, Trude Flo, Norwegian University of Science and Technology
- *Mechanisms controlling innate immune responses to nucleic acids*, Kensuke Miyake, University of Tokyo, Institute of Medical Science

Plenary V - Inflammation and cell death in host-pathogen interactions

- *Detecting and Responding to Microbial Viability*, Julia Blander, Weill Cornell Medicine
- *Bacterial type III secretion system effectors regulate of IL-1b production and cell death*, Egil Lien, University of Massachusetts Medical School
- *Sensing and Reacting to Pathogens at the Skin Barrier*, Gabriel Nunez, University of Michigan
- *Novel strategies for targeting innate immune responses to influenza*, Stefanie Vogel, University of Maryland School of Medicine

Meeting Adjourns

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**
  (2018 meeting joint with SLB: October 14-16, Arizona, USA)
- **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
Tim Sellati (USA)
IEIIS Membership Chair
Phone: 001 518 986 0287
Email: timothy.sellati@gla.org

To Submit Articles for Future Newsletters
Jason Barker (USA)
IEIIS Newsletter Editor
Phone: 001 319 335 4594
Email: jason-barker@uiowa.edu

Dues and Subscription Questions
Amy Hise (USA)
IEIIS Treasurer
Phone: 001 216 368 5036
Email: amy.hise@case.edu

To Update Contact Information
Nancy Pollman (USA)
IEIIS Administrative Assistant
Phone: 001 406 546 6492
Email: IEIIS@aol.com