

A Letter from the IEIIS President



Koichi Fukase

Dear Friends and Colleagues,

IEIIS had a successful 2018 fall meeting in Arizona, and I have really reconfirmed that IEIIS is developing in the integrated multidisciplinary research field. I would like to encourage interdisciplinary fusion research and further promote the IEIIS society development. Some updates:

2020 MEETING: We are planning an attractive program for the next IEIIS meeting, which will be held on October 18-21, 2020, at the Kobe International Conference Center. Kobe, a historical port city in Western Japan, located close to Osaka and Kyoto, is famous for Kobe beef, Japanese sake and beautiful night view. Keynote lectures will be given by Prof. Shizuo Akira (Osaka University) and Prof. Hiroshi Kiyono (The University of Tokyo). We look forward to welcoming and meeting you in Kobe.

MEMBERSHIP DRIVE: We are starting a membership drive to increase membership numbers. This will be coordinated with the help of our new Membership Chair, Tim Sellati. New for this year is the 2-year membership. There are many advantages with membership ability to join interesting meetings and present your research, you will get a useful network of contacts, you can get advice on career choices and experiments, publish in the *Innate Immunity* journal, and more. This is a good opportunity for you and your friends to become or stay affiliated with the Society!

WEBSITE: At the website you will find information about the Society; ability to join or re-join; contact information for officers, councilors and other people in key positions; information about upcoming events and meetings; awards, and more. If you have any input, please contact Holger at hheine@fz-borstel.de

***InI* JOURNAL:** Our great journal *Innate Immunity* continues to publish high quality reports. New developments are that *InI* has become an open access journal, which will make papers freely available.

THANKS: Many contribute to the IEIIS. Special thanks to Egil Lien, President 2016-2018 and Editor-in-Chief of *InI*; Jason Barker, Editor of *Endotoxin Newsletter*; our Treasurer Amy Hise; other councilors, and officers and key persons; including our Administrative Assistant, Nancy Pollman, for all the work benefitting IEIIS.

If you have any comments or ideas with regard to the Society, please contact me at koichi@chem.sci.osaka-u.ac.jp.

Best regards,

Koichi Fukase
IEIIS President 2018-2020

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January 2020

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

In Memoriam: Ulrich Seydel (1941-2019)

By Andra B. Schromm, Thomas Gutschmann, and Klaus Brandenburg

We are writing to share word of the passing of Ulrich Seydel. After a long, exhausting, and brave battle against cancer Ulrich died on 22 May 2019. Ulrich was a long standing member of the international endotoxin society (IES) and the international endotoxin and innate immunity society (IEIIS). He was a pillar of the IES/IEIIS from the early days on and served the society in many ways. He was an active contributor at the IEIIS Conferences, served as a council member and took over the baton from Jack Levin as Editor-in-Chief of the IEIIS Journal *Innate Immunity*. His research contributions and his long standing personal commitment to endotoxin research had great impact on our understanding of the structure-function relationship and the biology of endotoxin and was honored by awarding him the status as an Honorary Life Member of the IEIIS.



Ulrich Seydel

Ulrich was born in 1941. He was a physicist by training, worked in his early career on explosions of hot wires in the field of Solid State Physics, but very early found his interest in the field of biophysics and microbiology driven by the aim to reveal the function of microbial membranes. Ulrich became Professor of Physics at the University of Kiel in 1985. At the Research Center Borstel, Germany, where he was head of the Division of Biophysics from 1979 - 2006, he made essential contributions in the field of endotoxin research. He developed new model systems to investigate the outer membrane of Gram-negative bacteria. Among these, self-constructed customized systems were established that enabled the generation of asymmetric planar lipid membranes as a model system. He studied the electrophysiology

of porins and the membrane attack complex by complement proteins, pore-forming antimicrobial peptides and antibiotics.

As a physicist, he always tackled biological questions also with the view of thermodynamics, equilibrium behavior and physico-chemistry. The aggregation behavior of lipids was his special field of interest and he made tremendous contributions in characterizing the physical behavior of endotoxins and in providing comprehensive knowledge regarding the structure-function relationship of endotoxin. The discovery that specific lipid conformations which can be measured in the aggregated state of endotoxin by small-angle X-ray scattering experiments are associated with the immunological activity as well as antagonistic activity of the respective LPS coined the term "endotoxic (supramolecular) conformation".

An outstanding characteristic of Ulrich was his ability to develop new ideas beyond established concepts. His expertise in the physics of lipids provided new insights in our understanding of endotoxin biology and we think many of us have learned through him the importance of physico-chemistry of endotoxins. He was truly an interdisciplinary scientist, who discussed and collaborated with many scientists in the field and many of us will miss him as a friend.

While Ulrich was very serious end engaged with science, he also was a great mentor and accompanied more than 40 young scientists from physics, biology and chemistry in their diploma and doctoral theses. He was committed to support young scientists, the initiation of the Borstel PhD Mentoring Program and co-founding of the Research and School Program to name only two of several of his activities. Within his research group he especially enjoyed lab outings that usually ended at his house, where he fired the barbecue in his garden and invited us to be his guests. He loved to discuss scientific questions in this relaxed atmosphere. His collaborators and guests who visited the Research Center Borstel or attended conferences have enjoyed his hospitality, his open house, and his friendship beyond science. Ulrich had a great sense of humor, he always had a hearty joke to tell and enjoyed to challenge and dispute scientific hypothesis with the "floret".

Ulrich will be sorely missed by his friends and colleagues.



Our thoughts and gratitude go to his wife Hiltrud, his three children who all became devoted to science as well, and the two young grandchildren.

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

IEIIS 2020

Oct 18-21, 2020 - Kobe International Conference Center, Japan

Chair: Koichi Fukase (Osaka University)

It is a great pleasure and honor to host the 16th biennial IEIIS meeting, which will be held October 18-21, 2020, at the Kobe International Conference Center. Kobe, a historical port city in western Japan, located close to Osaka and Kyoto, is famous for Kobe beef, Japanese sake, and beautiful night views.

We are planning an attractive program. Proposed sessions include the following topics: mucosal immunity; vaccines and adjuvants; ligands of innate immunity, structure, and function; lectins and immune-regulation, sterile inflammation, innate immunity and metabolic diseases, extracellular micro vesicles and immune-regulation, inflammatory signaling, host receptors and microbes; gut-microbe and immune-regulation.

We hope that you will join us to exchange current research discoveries while renewing old friendships and establishing new ones. We will also provide good opportunities, especially for young scientists and students, to meet and interact with top scientists working in this field to expand their knowledge.

SAVE THE DATES!!



WELCOME TO KOBE, 2020
Check meeting updates on the web sites:
<https://www.ieiis.org/>





Dr. Jack Levin: Golden Goose Award

Dr. Jack Levin recently received a Golden Goose Award at a ceremony which was held at the Library of Congress in September. This improbably named award is given by the American Association for the Advancement of Science (AAAS) to recognize federally funded biomedical research which was initially thought to have little likelihood of any significant impact. This year Dr. Levin received one of these awards for the discovery, early development and use of the Limulus Amebocyte Lysate (LAL) test for the detection of bacteria endotoxins in parenteral drugs, intravenous fluids, and implantable medical devices. An estimated 17,000,000 (not a typo) Limulus tests are now performed annually throughout the world. Biomedical research laboratories have also found it very useful to determine if bacterial endotoxin is present in various reagents.

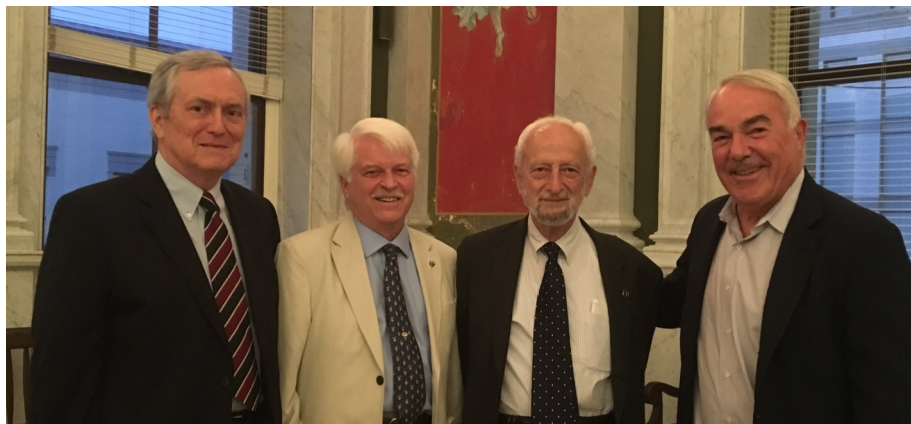
Dr. Jack Levin with the Golden Goose Award at the Library of Congress, 10 September 2019

The 2019 Golden Goose Award was reported in a recent issue of *Science* (*Science* 365, Issue 6460, pp. 1390-1391, 2019)

Jack Levin, a hematologist, and the late Frederik Bang, also a medical doctor, were awarded a Golden Goose Award for “The Blood of the Horseshoe Crab” research that led to the development of a screening test known as the Limulus amebocyte lysate test, which can detect minute concentrations of bacterial endotoxin, a component of all dangerous Gram-negative bacteria.

The test is based on an extract of blood cells, known as amebocytes, from the distinctive blue blood of the Atlantic horseshoe crab. The cells contain a blood-clotting mechanism triggered by the presence of bacterial endotoxin. The test serves as an effective detection tool that today prevents the use of intravenous fluids, injected drugs, and implantable medical devices that contain potentially dangerous concentrations of endotoxins.

Also in attendance were IEIIS members Dr. Robert Munford and Dr. Alan Cross.

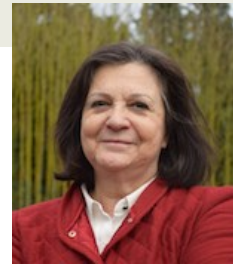


Dr. Jack Levin (3rd from left) joined by Dr. Tom Novitsky (2nd from left), one of the founders of Associates of Cape Cod, which translated Jack’s discovery into a commercial product. Also pictured are Dr. Alan Cross (right) and Dr. Robert Munford (left).

Dr. Martine Caroff wins the European Union Women Innovator Entrepreneurs Award for 2019

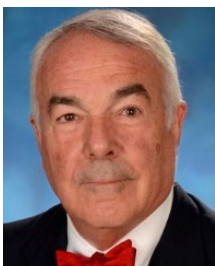
You may recall that last year, Dr. Martine Caroff was selected as one of the nine finalists for the European Union Women Innovator Entrepreneurs award. Congratulations are in order, as she was recently selected as one of four winners of the prize for 2019. The award recognizes women who have founded a successful company and brought an innovation to market. She will be investing the prize funds in the second company that was created last year. She notes, “There is a life after an academic career in LPS...and the two companies are going on with endotoxin research.”

For more information, visit https://ec.europa.eu/info/research-and-innovation/funding/funding-opportunities/prizes/eu-prize-women-innovators/eu-prize-women-innovators-2019_en



Martine Caroff

Update from Dr. Alan Cross



Alan Cross

Alan Cross, Professor of Medicine
Department of Internal Medicine
University of Maryland School of Medicine
Baltimore, MD USA
410-706-5328
across@som.umaryland.edu

We have been collaborating with the Nosocomial Vaccine Corporation, Affinivax and Astellas Pharmaceuticals to develop a novel 12-valent vaccine for *Klebsiella* and *Pseudomonas* based on the Multiple Antigen-presenting System (MAPS) developed by Zhang et al (PNAS 2013;110(33):13564-69). It is based on the O polysaccharides of 4 *Klebsiella* and 8 *Pseudomonas* strains and includes pathogen-relevant carrier proteins. We presented an abstract of this work at the World Vaccine Congress held in Washington DC in April, 2019. In addition, we recently published a review entitled “Progress towards the development of *Klebsiella* vaccines” in Expert Review of Vaccines¹. In addition, we developed a *Klebsiella/Pseudomonas* conjugate vaccine².

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IN THE NEWS

Update from Dr. Paul Kosma



Paul Kosma

**Prof. Dr. Paul Kosma, Department of Chemistry
University of Natural Resources and Life Sciences–Vienna
Muthgasse 18, 1190 Vienna Austria
+43 1 47654-7735
paul.kosma@boku.ac.at**

We have recently finished a synthetic study in collaboration with Miguel Valvanos group from Queens University in Belfast to generate substrates for bacterial aminoarabinose transferases which are responsible for an antibiotic resistance mechanism by covalent modification of the phosphate groups in lipid A but also via formation of a glycosidic linkage to Kdo/Ko residues in the core domain.

We could show that an easily accessible truncated version of the AraN donor (replacing the undecaprenyl portion by the short-chain monoterpene nerol) is sufficiently reactive with membrane preparations of the enzyme. The enzymatic reaction is highly specific for the anomeric configuration of the AraN-phosphate and the configuration of the double bond in the lipid part. Using Kdo2-Lipid A as the acceptor, we could show by MS that the Burkholderia cenocepacia enzyme transfers the amino-sugar to the lipid A phosphate(s). This novel activated AraN-donor should be highly valuable in future biochemical studies and for the development of suitable inhibitors of the transferase reaction to overcome polymyxin B and colistin resistance seen in bacterial infections. The paper has been electronically published ahead of print in ChemBioChem.

Olagnon, C., J. Monjaras Feria, C. Grünwald-Gruber, M. Blaukopf, M. A. Valvano, and P. Kosma. (2019) Synthetic Phosphodiester-Linked 4-Amino-4-deoxy-L-arabinose Derivatives Demonstrate that ArnT is an Inverting Aminoarabinosyl Transferase. *Chembiochem*, Epub ahead of print <https://doi.org/10.1002/cbic.201900349>

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/>

Update from Dr. Nilofer Qureshi



Nilofer Qureshi

Dr. Nilofer Qureshi, Professor
Director - Shock/Trauma Research Center, Director, Molecular & Cellular Immunology
Department of Biomedical Sciences, Section: Microbiology
University of Missouri- Kansas City School of Medicine
Kansas City, MO USA
816-235-1056
qureshin@umkc.edu

NOVEL MECHANISMS MEDIATING THE SEPTIC SHOCK SYNDROME AND RELATED INFLAMMATORY DISEASES: THE PIVOTAL ROLE OF THE UBIQUITIN-PROTEASOME SYSTEM

A synopsis of work by the laboratory of Nilofer Qureshi, Ph.D.

Severe sepsis and septic shock are life-threatening diseases caused primarily by bacteria and associated bacterial toxins. These diseases adversely affect the health of >18 million people globally/year with an approximate 35-50% mortality. Despite the implementation of strategic therapeutic interventions, there are currently few, if any, effective drug therapies for treatment of these diseases, mainly because the mechanisms mediating the shock state remain to be fully defined. Our own studies to address this important issue initially focused on a determination of the structures of HPLC purified enterobacterial LPS, a well-documented primary microbial toxin known to be responsible for septic shock.¹⁻⁵ We then capitalized on the use of highly purified LPS substructures to establish the underlying mechanisms involved in inflammatory cell activation, highly likely to be central to septic shock pathogenesis. We found that a biologically-inert, but closely related, LPS structure blocks the binding and internalization of highly toxic LPS in a mouse macrophage cell line, strongly suggesting that LPS could either trigger inflammatory cell activation either from the cell surface and/or by directly entering the cells through caveoli, and receptor mediated endocytosis.

Based on these important findings, we established that LPS rapidly binds to the subunits of intracellular proteasomes.⁶ This observation provided strong evidence to support the conclusion that LPS-mediated multiple signaling pathways may well be regulated, at least in part, by the proteolytic activities of the cells' proteasome. Proteasomes are well-recognized as cytoplasmic organelles containing at least three well-characterized proteolytic activities that can be induced to transform into another form, termed inducible proteasomes.⁷ This is an ATP-driven process, that is fueled by glucose. The relatively short-lived regulatory proteins (such as IκB) to be degraded are first ubiquitinated by E1, E2 and E3 ligases, and then degraded by the Ubiquitination-Proteasome System.⁷ However, the link between this change in

composition of the proteasome subunits and initiation of disease-causing inflammation had not, to date, been elucidated. For more than a decade, and based upon these collective observations summarized above, our group has been actively addressing the role of intracellular proteasomes in the modulation of inflammatory responses induced by LPS, and other microbial products in both mouse and human inflammatory cells.

In this respect, we have shown that all mammalian cells have a complement of proteasomes, but their subunits in different cell types differ significantly, as well as their capacity to be reprogrammed in various cell types in response to LPS. These reprogramming events result in substantial changes in regulation of cell signaling capacity, and consequent regulation of expression of cytokines, control of cell cycles, metabolic events, and hormonal functions. Specifically with respect to inflammatory mediator cells tissue macrophages predominantly express X, Y, Z-type proteasomes (low chymotrypsin-like, CT-like/post acidic, PA ratio). The chymotrypsin-like activity of X degrades proteins at the non-polar amino acid tryptophan, tyrosine residues, the post-acidic activity Y degrades proteins at the aspartic and glutamic residues, and trypsin-like activity Z degrades proteins at the trypsin and arginine residues), while white blood cells from the same species predominantly express the inducible LMP7, LMP2 and LMP10-type subunits, (high CT-like/PA ratio). These different types of proteasome's proteases affect responses that, perhaps not surprisingly, differ rather significantly. In response to LPS exposure, for example, X, Y and Z-type subunits of proteasomes are replaced by inducible proteases LMP7, LMP2, and LMP10, which are newly synthesized proteasomes in a variety of inflammatory cell types, including primary macrophages, RAW 264.7 mouse macrophage cell line, CD14+ monocytic cells, and human PBMCs. Of potential importance, we have shown that, during the course of LPS-mediated inflammation, monocytes/macrophages (MO/Mφ)^{6,8-13} play a

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critical role in exacerbating or resolving disease-mediating cellular responses by priming naïve resident host inflammatory cells for selective host responsiveness. This, in turn, contributes to either enhancement or suppression of inflammation (SIRS), inflammatory cell proliferation,^{6,8-13} and/or development of hyporesponsiveness (tolerance). In addition, the induction of expression of T cell-specific cytokines is also dependent on the type of proteasome proteases present, and these cytokines can also affect the regulation of expression of specific subunits of the proteasome.^{14,15}

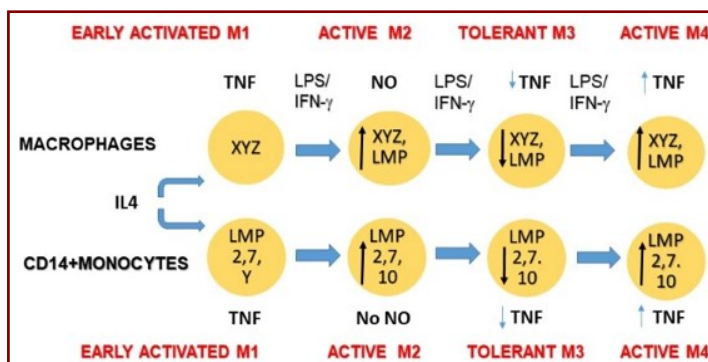


Fig. 1 LPS activates innate immunity by modulating the level of expression of subunits of proteasomes in macrophages. The cells are usually maintained in early activated form and possess XYZ type proteolytic subunits that are upregulated by LPS to switch to LMP type protease subunits. Then all proteasome subunits are downregulated during development of tolerance and LPS can no longer activate cytokines, such as TNF- α . These dormant tolerant cells can be re-activated in response to IFN- γ and LPS.

Collectively, these findings support the concept of a relatively novel and (for this discussion) simplified mechanism for regulation of innate immunity, as summarized schematically in Fig. 1: The host macrophages usually exist in either an “early” activated mode 1 or as resting cells predominantly expressing XYZ-type proteasomes, when activated in response to LPS, synthesize and release multiple cytokines and signaling mediators, primarily via signaling through the MyD88 pathway. These cells are known to be activated in response to LPS via the transcription factor *NF- κ B*, after phosphorylated and ubiquitinated *I κ B α* is degraded by the proteasome. The primary macrophage mediators include TNF- α , IFN- γ , growth factors, and others involved in multiple signaling pathways. This results in an amplified activation of other inflammatory cells with a consequent upregulation of gene expression of LMP7, LMP2, and LMP10 (high CT-like/PA ratio) proteasome protease subunits. Generally these proteins appear within 8-24 hr. of initial LPS-mediated activation and results in further differentiation of macrophages and dendritic cells and induction of synthesis and release of NO and other mediators. Specifically, this requires that the macrophages in active

phagocytosis mode 2 acquire the capacity to induce P-IRF3; NO, IFN- β , STAT-1P and STAT-3P in response to LPS (This finding is based on results of our experiments with LMP7/LMP10 knockout mice).^{9,10}

Such M ϕ are able to respond robustly to LPS and/or IFN- γ (derived primarily) from T and NK cells), thereby promoting NO release for targeting infectious microbes invading the host. After achievement of the phagocytosis mode 2 state, the cells naturally progress to a “tolerant” mode 3, where they become relatively refractory to LPS stimulation (thereby, allowing the healing process to begin). In this state, no new proteasome subunits are being induced, in large part, because of relatively low levels of expression of *NF- κ B*. At this stage the proteasomes are subject to ubiquitination and degradation. Exposure of tolerant cells to IFN- γ (which is known to upregulate expression of the LMP subunits) followed by renewed LPS stimulation, serves to reverse the state of tolerance/refractoriness and render the cells functionally active again.¹³ Alternatively, in the absence of an external agonist the cells can proceed towards a state of autophagy (Atg genes) or apoptosis, possibly due to the hypoxia inducing factor-1A (HIF-1A) and nuclear factor erythroid 2-related factor 2, (Nrf2) transcription factor proteins that are normally degraded by the proteasome under control conditions, but are stabilized when the proteasome’s proteases are downregulated, and these allow the cells to remain viable under hypoxic conditions, until new cells and proteasomes are generated.

In conclusion, these changes in the types of protease subunits manifest in the cell are reflective of actual switching their proteasome proteolytic activities from predominantly low ratio of CT-like/PA activity in the un-induced cells to high ratio of CT-like/PA activity in response to LPS. This switching in the proteasome’s proteolytic activities serves to effectively regulate the extent of degradation of signaling proteins involved in LPS-induced TLR4 and other signaling pathways, at precise times and stages during the development and regulation of the host innate immune response. In this respect, the cellular proteasomes have the capacity to regulate several transcription factors, degradation of signaling mediators, synthesis of cytokines, hormones, cell-cycle proteins, rate-limiting enzymes, enzymes involved in metabolism, pyruvate kinase, HMG-CoA reductase, inflammasomes, RNases, kinases, helicases, receptors, enzymes involved in epigenetic changes, and hundreds of other proteins and enzymes, in other words, virtually all critical events occurring in a cell.

Now specifically with respect to severe sepsis and septic shock, a severe downregulation of gene expression of LMP proteasome subunits frequently occurs in PBMC’s of late-stage septic shock patients, as compared with normal individuals,¹⁶ suggesting that such cells are likely to be in the tolerant mode. Sometimes the host

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can be in tolerance for weeks and become susceptible to nosocomial infections. Dysregulation of this Ubiquitin-Proteasome System has the potential to lead to serious defects in the development and implementation of host inflammatory processes. Of relevance, we have recently established that several highly effective proteasome modulators present in relatively common food in human diets, and drugs,¹⁷⁻²⁰ can serve to either upregulate or downregulate expression of these proteases in PBMC's. Still to be determined is the extent to which these may be either beneficial or harmful to the host, depending on the progressive stage of disease of the patient.

The above summary represents one of the first times that an immune cell's function (PBMCs, macrophages and monocytes) has been characterized based on structure/function of its proteasome subunits. This information can be expected to be pivotal for the future development of effective treatment strategies for treatment of sepsis, as well as perhaps diabetes, cancer, heart, and neurological diseases.

(This work was supported mainly by NIH grants).

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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**
(2020 meeting: October 18-21, 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

Tim Sellati (USA)
IEIIS Membership Chair
Phone: 001 518 986 0287
Email: timsellati@gmail.com

To Submit Articles for Future Newsletters

Jason Barker (USA)
IEIIS Newsletter Editor
Phone: 001 319 335 4594
Email: jason-barker@uiowa.edu

Dues Payments

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