Dear Friends and Colleagues,

I am hoping you all have had a good first half of 2018. I am just back from the Toll meeting, lots of interesting science going on with innate immunity and LPS, and I think we will see more progress from many groups at the IEIIS meeting in Arizona this fall.

The early deadline for our joint meeting with SLB is coming up fast, please remember to register as an IEIIS member! Our new 2-year membership will keep you on the lists even in meeting off-years, so you have one less thing to worry about in those years. The membership fee will instantly pay off when you sign up for the meeting. You can find links to membership and meeting registration pages at [www.IEIIS.org](http://www.IEIIS.org).

The meeting is in Arizona, USA, October 14-16, 2018. There are also some pre-events happening October 13, so check the schedule carefully before making your travel arrangements. David Underhill (IEIIS and SLB), Darren Lee (SLB) and myself have put together a program we hope you will enjoy. The presenters are from a variety of topics related to interests of both societies, as it typically is for these joint meetings. There should be plenty of presentations on both bacterial components and innate immune responses. There are also many opportunities for oral and poster presentations, so the organizers hope you will come and present your work. The venue is the Wild Horse Pass Resort, 20-30 minutes outside Phoenix, Arizona.

Importantly, there are a number of awards related to the meeting. Many students/trainees can receive travel awards. Also, the IEIIS awards - Nowotny, Bang, Greisman, Young Investigator, Gioannini Women in Science – will be awarded at the meeting. If you want to nominate someone, please contact me at egil.lien@umassmed.edu.

The survival of any society is dependent upon enthusiastic and involved members. I hope some of you will feel for contributing to IEIIS. I know the Society has made a major difference in the careers of many scientists, and has provided a forum for exchange of ideas, reagents, results and protocols. One important advantage is to get career advice and support from more senior members. This is also important in order to continue the recruitment and establishment of future scientists working with endotoxin and innate immunity. If you want to nominate someone (or even yourself) to IEIIS office, please contact me. We need new names for councilors, and also for president-elect.

We are aiming for another Newsletter issue before the meeting, so please contact Jason or me if you want to contribute! We may also ask some members to write short pieces for the next issue.

I am hoping to see you all in Arizona in October!

All the best,

Egil Lien

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We are excited to present the 15th biennial IEIIS meeting and 51st annual SLB meeting in a beautiful Southwestern US setting, a short travel (20-30 minutes) from Phoenix. This is the 4th time IEIIS and SLB (Society for Leukocyte Biology) join forces – past joint meetings (2006, 2010, 2014) have been very successful.

We are assembling a great program. Proposed session topics include: Inflammation and cell death in host-pathogen interactions; Myeloid cell development, differentiation and novel functions; Ligands of Innate Immunity: structure and function; Metabolism and physiology in inflammation; Best of JLB and Innate Immunity; Neutrophils and phagocyte functions; Metabolism and Physiology in inflammation; Leukocytes in immune privilege sites; inflammatory signaling; host receptors and microbes; the Microbiome in inflammation and immunity. There are also some pre-meeting sessions October 13 that are interesting.


There are plenty of opportunities for presenting your work! We will have plenary sessions, break-out sessions, selected oral presentations from abstracts, award presentations, and of course plenty of time for networking and catching up with your colleagues and friends.
UPDATES FROM MEMBERS

Hoping to enhance communication among IEIIS members and share valuable insights and contributions, we are again including updates from members in the Newsletter. We are particularly fortunate to have a career retrospective from Dr. Jean-Marc Cavaillon, which includes his perspective on many of the seminal endotoxin discoveries of the last 4 decades. We also include two updates from the labs of IEIIS members: Dr. Holger Heine (Borstel) describes his recent work on the mechanisms of induction of inflammation by archaea, and Dr. Alla Zamyatina (Vienna) highlights her recent publication on the ability of novel synthetic glycans to modulate MD-2/TLR4 and caspase-4/11 activation.

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. We hope to see you in Chandler, Arizona this October at the joint IEIIS/SLB meeting!

Sincerely,
Dr. Jason H. Barker
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My Life with Endotoxins

With this title I don't mean my life with the 40 grams of endotoxin present in my belly, enough to kill 40,000 people, I mean my life with this lyophilized white powder present in a test tube or in a vial, purified by my friends or bought from a Greek letter Company, sometimes hard to solubilize but always displaying great power and a lot of properties when added to cells in vitro or once injected in animals; in brief, one of the most fascinating molecules in Nature and a great tool for immunologists.

Life of Scientists is made of misfortunes, and failures are our daily bread (disappointing experiments, wrong hypothesis, rejected papers and discarded grants…). But life is also made of chances, voluntary choices, opportunities, luck and encounters. It happened by chance that endotoxins have been the leading theme of my life, it has been my choice to further study them, particularly when they lead to the status of tolerance, they offered me the opportunity to study their most potent action, i.e. their capacity to induce cytokines, as well as to study sepsis patients in whom they can be so harmful. They offered me the opportunity to encounter wonderful colleagues and great scientists with a common interest in these fascinating molecules, some offered me the precious gift of their friendship, some offer me their trust, many, thanks to their support, helped me to continue my way in one of the most difficult and challenging job, of course, I mean research.

My first steps in the field of endotoxin

My first encounter with endotoxin occurred while I was a third-year student at the Paris-South Sciences University, when I joined the laboratory of Dr. Ladislas Szabo, an expert biochemist, working on the endotoxin of *Bordetella pertussis*. For this voluntary summer training period, I was accompanied by two other students (Nicole Haefner-Cavaillon and Martine Caroff). This elegant, old-fashioned dressed and highly educated Hungarian scientist was regularly offering us some Latin quotations, while his colleagues in his lab were offering us our first dosages of sugars.

When it was time to make a choice for a master degree, I asked a famous professor, which field of biology would have the most promising future: "Immunology" was his answer. Then, I asked Dr. Szabo if he knew anyone in the field of Immunology. He gave me the name of Prof. Anne-Marie Staub, a prestigious immunochemist working on *Salmonella* endotoxin at Institut Pasteur. She kindly welcomed me in her lab and I worked on rabbit cross-reacting antibodies against *S. johannesburg* LPS and other structures containing N-acetyl galactosamine, the immunodominant sugar of this specific LPS (i.e. Forssman antigen on sheep red blood cells and human group A red blood cells). I stayed in her lab for a PhD, studying the capacity of rabbit immune cells to recognize the endotoxin after injection of the whole bacteria. This work was co-directed by Dr. Constantin Bona who then made a prestigious career on idiotypes at Mount Sinai Hospital in New York. He was working in Louis Chedid's Lab, one of the most passionate researchers I ever met (the co-discover of the adjuvant properties of muramyl dipeptide).

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Taking advantage of the Canadian experience

For what was still mandatory, my military duties, I crossed the Atlantic and joined Dr. Bernhard Cinader at the University of Toronto where I worked on rabbit cellular immunity and immune cells crosstalk in response to mitogens. Nicole, my wife, was on the upper floor, in Keith Dorrington’ laboratory, where she worked on Fc receptors. Back in France we decided to combine our respective Canadian acquired expertise, and studied the LPS receptor on rabbit macrophages, and we showed that serum factors were required for binding and activation. But too young, too powerless, we failed to discover CD14, TLR4, soluble CD14, LBP and other key elements involved in the binding of LPS to its receptor, but still we were the first to demonstrate that on macrophages there was a membrane component able to bind LPS, and corresponding to the definition of a receptor (i.e. specificity, saturability, reversibility). Thanks to the endotoxins, I was among the very first at Institut Pasteur to work on cytokines, and more precisely on interleukin-1, then assessed as “lymphocyte activating factor” in a biologic test. To be honest, in fact my very first publication on cytokines was made on gamma-interferon induced by streptococcal superantigens while I was working in the laboratory of Prof. Joseph Alouf, a specialist of bacterial exotoxins, who had succeeded Anne-Marie Staub. This paper, the second demonstration that a superantigen could induce cytokine was co-authored with Luc Montagnier (my only paper co-signed with a Nobel prize winner!). Cytokines became my second passion, and I wrote the first book in French on cytokines, and was for a while associate-editor of the Journal ”Cytokine”. I like to mention that my life in Research started in 1974, the exact year Stanley Cohen (Nobel prize 1986 with Rita Levi-Montalcini) coined the word “cytokine”. With Nicole, and the help of Martine Caroff who became an internationally recognized leader in the field of biochemistry of endotoxins, we deciphered the relationships between the structures of LPS and its capacity to induce cytokine production, establishing a key role of the inner core region.

From rabbits to humans

But my motivation was to leave the world of the rabbits to enter into that of the real world of humans. I have always been convinced that the final goal of my immunological research would be to understand the events occurring in real life of human beings. The failure to save septic patients with experimental approaches that saved thousands of mice from septic shock is an illustration that one needs to describe and understand the cellular and molecular events in humans. Nevertheless, when my first attempt to obtain an autonomous group at Institut Pasteur was rejected, Prof. Patrice Debré, a famous French MD/PhD told me: “Why do you want to study humans when there are so many nice models with KO mice?”. Despite his question and my failure, I remained convinced to pursue my studies in humans and preferred what Prof. Petter Brandzaeg (Oslo), a famous specialist of meningococcal infections, wrote in his thesis: “Human diseases should be studied in the diseased humans”. But at that time, the HIV virus was not yet a challenge for humanity, and (amazingly) only one unit at Institut Pasteur was working with humans, that of Prof. Bernard David, a specialist of allergy. Thus, in exchange of some efforts to be a bit involved in studies on allergy, he kindly welcomed me and allowed me to pursue my works on endotoxin. In fact, my most satisfying and rewarding work was made in allergy. It was the significant improvement of ten chronic hemodialyzed patients who experienced terrible allergic reactions after each dialysis session. We succeeded in ending these events by changing the ethylene-treated complement activating membrane to γ-irradiated and complement non-activating ones, and by filtering the dialysis baths. Isn’t it our role to work to improve humanity welfare? Of course, this is an extremely modest contribution, but still I am proud of it, and ten people truly appreciated what we have done for them. Amazingly, the paper relating the observation has never been cited except once 13 years after its publication! This exemplifies the relativity of the impact of research, the impact of publications and the impact factors… Our interest for chronic hemodialyzed patients had emerged thanks to Nicole who was working with MDs on these patients and with whom we had demonstrated the hypothesis that the circulation of blood leukocytes on poorly biocompatible membranes could let to the production of interleukin-1 (IL-1). Because I rapidly understood that the presence of detectable cytokines was reflecting the tip of the iceberg, we craftily and successfully looked for IL-1 within the circulating monocytes.

Translational research

Three major lucky events occurred while I was working in David's lab. He offered me the technical help of a young, bright and hard-working technician, Catherine Fitting, who since then has been working with me till the end of my group. As she is a left-handed person, while I am a right-handed one, it was very convenient to work together under the hood without hindering ourselves! The second event was the venue of a Chilean post-doc, Carlos Muñoz. He had been working with Charles Dinarello, one of my scientific heroes, and was mastering the dosages of tumor necrosis factor (TNF) and IL-1β by radioimmunoassays while we were only using bioassays (ELISAs were not yet available). The third event was the encounter of Dr. Jean Carlet, an Intensive Care Unit doctor who was the first MD I met who accepted working with a scientist. In France the border between MDs and PhDs was and remains rather thick despite what Charles Richet (French Nobel Prize, 1913) had said in 1888: ”To oppose the physician to the physiologist and the scientist to the clinician, means that one has not understood anything about physiology or medicine!”. Then, all together we published the first complete analysis demonstrating the altered immune status of septic patients' monocytes, an event reminiscent of the endotoxin tolerance phenomenon. Interestingly, this time the paper had a good impact offering the basis of the so-called "compensatory anti-inflammatory response syndrome" (CARS), a concept coined by Roger Bone. I have to admit that this investigation was a curiosity-driven investigation rather than a research based on a specific hypothesis. Subsequently, we described the same phenomenon in neutrophils, T-lymphocytes and...
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My Life with Endotoxins

NK cells. We were very much involved illustrating the cytokine storm in sepsis, correlating the IL-8 levels with outcome, showing that RANTES (CCL5) is a rare cytokine of which the levels inversely correlate with outcome and that an anti-inflammatory cytokine, namely TGFβ, is also enhanced. We established that measuring cell-associated cytokines was a useful tool. These efforts were very poorly evaluated by my peers, and the word “descriptive” was often used to disqualify our work. (As Prof. A. Casadeval reminded us in a conference, astronomy is only a descriptive science, and there is nothing negative in this research).

Together with another medical doctor, Christophe Adrie, we made interesting works linking the occurrence of endotoxin translocation and the immunological status of patients resuscitated after cardiac arrest or after cardiac surgery. Endotoxin translocation was not a new topic for us since we had observed it in 1993 in patients undergoing abdominal aortic surgery, associating the event with a local production of TNF as assessed by measurements made in the portal vein. Later, we showed that similarly, translocation of peptidoglycan structures was occurring after abdominal aortic surgery.

I was highly lucky when a wonderful, young and bright scientist, Minou Adib-Conquy, decided to join me after her thesis. She had agreed to introduce molecular biology in my group and she made key contributions to decipher the mechanisms underlying endotoxin tolerance and the hyporeactivity of patients’ monocytes to LPS activation. With Catherine and Minou we created the research unit "Cytokines & Inflammation" at Institut Pasteur. Her death, while she was only 47 has been a very painful misfortune.

Another key event in my life was to cross paths with Dr. Shaw Warren. He introduced me to the world of reality at a time HA-1A anti-LPS antibody (Centoxin) was a controversial possibility to cure sepsis patients. We showed that unfortunately this antibody had no neutralizing effects. It was a time when FDA was very strict, considering that one successful study was not sufficient to put a product on the market. Later on, as seen with Xigris (Activated protein C) to treat sepsis patients, FDA licensed the product after only one positive study and allowed the marketing of a product that was finally withdrawn ten years later for lack of efficacy. Shaw Warren who had already worked at Institut Pasteur with Louis Chedid who studied the adjuvant and polyclonal B-cell activating properties of LPS, and who was the father of the concept of a universal antibody against LPS, spent one sabbatical with me. Moving to Paris with his whole family, I admired this effort. Then, we started to ask ourselves why mice are 100,000 fold more resistant to endotoxin than humans. This lead to his on-going efforts to find within mouse serum factors able to protect them against endotoxins. It also explains why I am advocating that the future will be in "murinizing" humans to render them as resistant as mice to LPS.

A love story with IE(IIs)

My links with the International Endotoxin and Innate Immunity Society (IEIIS) started at its birth. Indeed, in 1986 I was attending the "International Symposium on endotoxin" in Bari (Italy) when Joe Berry and Alois Nowotny established the foundation of the International Endotoxin Society (IES). At that time, I would have never predicted that my life would be closely associated with this Society. This offered a great opportunity to interact with my peers who became my friends and it is comforting to see they are still my friends! Unfortunately, Joe Berry died at age 76 in February 1987 during a conference in Washington. Then, Alois Nowotny took over the founding of the Society established in 1987, and was its first president. Nicole and I were founding members. In 1994, the Society established a new journal “the Journal of Endotoxin Research” (now Innate Immunity), and since its creation I have been within the Editorial board, kindly renewed by its successive editors, David Morrison, Jack Levin, and Otto Holst.

The Society used to have an American president followed by an European and an Asian one. In 1996, I was elected as "president-elect", on competition with Emilio Jirillo of the University of Bari (Italy) supported by his German colleagues Marina Freudenberg and Chris Galanos (Freiburg, Germany).

Fighting Dogma

In 1995, I was convinced that endotoxin tolerance was not specific to LPS. But it was against the prevailing dogma. Indeed, reading carefully the literature it was fascinating to see how some authors avoided putting forward their results because they were not fitting with the dogma. Nowadays, the cross-tolerance of inflammatory signals and of most ligands (PAMPs as well as DAMPs) of the pattern recognition receptors (PRRs) is well accepted. Isn’t it fascinating to observe that although scientists should be the most open-minded people, they are highly conservative, love to put everything in boxes, establishing definite dogma. Another interesting study was exemplifying the concept of compartmentalization when we showed that murine alveolar macrophages were reluctant to display endotoxin tolerance.

In a review, I addressed the dogma that classifies cytokines as pro- or anti-inflammatory ones, and provided many examples that illustrate that it is not correct. Another dogma I have been fighting against was the two-wave concept of the inflammatory reaction occurring during sepsis: a systemic inflammatory response syndrome (SIRS) followed by the occurrence of CARS. In 2001, I published a figure in Journal of Endotoxin Research illustrating that it was not to be the case, and that in fact both events were almost concomitant. During the following decade the most famous scientists continued to publish in the most prestigious journals the two-wave concepts. Indeed, as early as 1995, three teams had published that in sepsis patients, the IL-10 plasma levels were correlating with those of IL-6, IL-8 or TNF. How could it be the case if both SIRS and CARS were not concomitant? Nowadays, people admit that both events are concomitant. Djillali Annane, a famous French ICU doctor invited me to co-write a review on septic shock for The Lancet. Amusingly it was called by the French students the ABC of sepsis (based on the names of the three authors: Annane, Bellisant, Cavaillon).

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I was strongly supported by the very Francophile Ernst Rietschel (Borstel, Germany), who had been president from 1990 to 1992. The results were very tight. In 1998, in Santa Fe, I succeeded David Morrison. During the handover, I came to him with a beret, which I put on his head, a baguette and a bottle of wine that I gave him. With such a French looking appearance, it was easier to succeed this distinguished US scientist. I gave myself several goals I could achieve thanks to the wonderful help of the most efficient secretary one may expect, Jon A. "Tony" Rudbach (1937-2008): increasing the number of members, reinforcing its international ground, editing the Newsletter regularly, and establishing a conference in Paris. The conference was a great success with 261 abstracts from 32 countries and 420 participants. In Paris, I was happy to transmit the gavel to my friend Robert (Bob) Munford who organized a most successful meeting in Washington, DC, two years later.

To conclude
In 2011, Martine Caroff created her start-up “LPS BioSciences” and invited me to be a co-founder. The work performed by this start-up is just amazing and illustrates that mastering the world of endotoxin remains essential and useful for the many Companies which request the expertise of LPS-BioSciences.

The Greisman award in 2012, and my nomination as Honorary Life Member in 2014 conveyed by the Governing Council of the IEIIS, were great honors. I understand it also meant I was now old enough to get them, but it is a very nice way to compensate the ageing process! It is now time to leave the room for the young generation, hoping it will share with the old guys their fascination for this molecule.

How Archaea Induce Inflammatory Responses

by Tim Vierbuchen and Holger Heine
Division of Innate Immunity
Research Center Borstel, Borstel, Germany


The importance of the microbiota on health and immune homeostasis is widely accepted and the interaction between the microbiota and our body is currently subject to numerous ongoing studies. However, most of these studies are focusing on bacteria alone, although viruses, fungi and archaea are also part of this complex microbial community. Recent studies have shown that archaea are present at nearly every part of the body but their contribution to health and disease is not understood, and no archael pathogen has been identified yet. Even though archaea are prokaryotes like bacteria, they form a distinct domain with structurally different membrane and cell wall components as well as unique metabolic pathways. Methanogenic archaea are important players of the microbiota as they live in a syntrophic relationship with several fermentative bacteria. These bacteria are dependent on the consumption of H₂ by archaea since a low H₂ partial pressure is required for efficient fermentation.

The gut-associated methanogenic archaeon Methanosphaera stadtmanae has been identified as a strong inducer of pro-inflammatory responses and it is suggested to be involved in inflammatory diseases. Yet, the mechanism of how this archaeon is sensed by the immune system has not been evaluated until now. This is of great interest as no archaea-derived microbe-associated molecular pattern (MAMP) has been described so far. In our recent study, published in Frontiers in Immunology, we unraveled the receptors, archaenal structures and signaling pathways that are engaged upon activation of human innate immune cells by M. stadtmanae.

After phagocytosis of M. stadtmanae by myeloid cells such as monocytes or dendritic cells, the archaeon induces secretion of pro-inflammatory cytokines including IL-1β as well as expression of type I and III interferons. Using CRISPR/Cas9-generated knock out cells, we demonstrate that the response is dependent on the adapter molecule MyD88 and on UNC93B1, a molecule important for endosomal trafficking of nucleic acid-sensing TLRs. In detail, human TLR8 and TLR7 function as main receptors for recognition of M. stadtmanae and its RNA. As mice are lacking functional TLR8, M. stadtmanae is only recognized by TLR7 in murine bone marrow-derived dendritic cells (BMDCs). Moreover, this archaeon induces a TLR8-dependent activation of the NLRP3 inflammasome with hallmarks of the recently described LPS-induced alternative pathway. In contrast to canonical NLRP3 activation, the TLR8-dependent pathway does not rely on a ‘second signal’ and does not lead to formation of ASC specks (pyroptosomes).

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For the first time, our results describe specific recognition of an archaeon by human immune cells at the molecular level. As some studies indicate a potential connection of *M. stadtmanae* to inflammatory bowel disease and lung hypersensitivity, these findings might help to understand how archaea are involved in inflammatory diseases. There is a great need to further investigate the interplay between archaea and the human body, as the role of these organisms is probably vastly underestimated.

*M. stadtmanae* is taken up by myeloid immune cells through phagocytosis. Inside the phagolysosome, the archaea are degraded, and archaeal RNA is released. The RNA is recognized by TLR7 and TLR8 and a signaling cascade is induced leading to the nuclear translocation of the transcription factors IRF5 and NF-κB. These transcription factors induce the expression of type I and III interferons as well as proinflammatory cytokines. Through a yet unknown mechanism, TLR8 additionally activates the NLRP3 inflammasome. This process yields to activation of caspase-1 which in turn processes pro-IL-1β into its active form. In contrast to canonical inflammasome activation, potassium efflux is not a feature of *M. stadtmanae*-induced inflammasome activation.

**Activation model of human monocytes by *M. stadtmanae***

References


Therapeutic Immunomodulation


Therapeutic immunomodulation has grown to one of the most attractive strategies for treatment of acute and chronic diseases ranging from antibiotic-resistant infections and sepsis to autoimmune disorders and cancer. TLR4 plays a key role in immunoprotection against infection and in boosting adaptive immunity. Although TLR4 is intensively exploited as a target for development of vaccine adjuvants and anti-sepsis drug candidates, regulated activation of the TLR4-mediated pro-inflammatory signaling has not yet been achieved. Rational therapeutic exploitation of the TLR4 complex is hindered by several obstacles:

- profound and unpredictable effects on the TLR4 activation inflicted by subtle variations in the chemical structure of Lipid A (which is heterogeneous within bacterial species);
- a lack of evidence on how diverse Lipid A variants are discriminated by the TLR4 complex in terms of the binding mode and the resulting biological effect;
- species-specificity (e.g. human vs. mice) in ligand recognition by the TLR4 system hampers estimation of future therapeutic efficacy based on in vivo data.

Activation of TLR4 is interrelated with induction of protease activity of a cytosolic LPS receptor caspase-4/11 which leads to cell death by pyroptosis and is deeply implicated in the development of sepsis. The structural basis of caspase-4/11 activation by LPS and lipid A is currently unknown.

Lipid A is based on the intrinsically flexible three-bond linked β (1→6)-diglucosamine backbone which can spontaneously adjust its molecular shape (i.e. the relative orientation of GlcN rings) upon binding by the proteins. Recently we recognized and demonstrated that not the chemical structure of lipid A alone, but the 3D-molecular shape of the TLR4-MD-2-bound lipid A is decisive for expression of TLR4 stimulating or TLR4 antagonist activity. To verify our concept, we exchanged the flexible β(1→6) glycosidic linkage of lipid A with an exceptionally rigid two-bond (1→1′) glycosidic linkage and developed on this basis synthetic unnatural TLR4 ligands: lipid A mimetics or LAMs. The biological activity of LAMs relies on both chemical and 3D-tertiary structure inflicted by a specific molecular shape of the (1→1′)-linked disaccharide backbone which depends on the anomic configuration around (1→1′)-glycosidic linkage.

Thus, LAMs based on a β(1→1′)α - linked diglucosamine backbone entailing planar oriented sugar rings furnished potent species independent (human and mouse) TLR4 antagonists with nanomolar affinity for TLR4/MD-2, whereas LAMs derived from a rigid α(1→1′)α - linked disaccharide scaffold with “twisted” relative arrangement of sugar rings brought about powerful TLR4 agonists exhibiting picomolar affinity for both human and mouse MD-2/TLR4 complex. Importantly, the 3D architecture of 1,1'-linked disaccharide backbone of LAMs reflects tertiary structure of the β(1→6)-linked diglucosamine backbone of the TLR4-MD-2-bound Lipid A found in the co-crystal structures. In this way we achieved predictable and regulated modulation of NF-κB signaling through controlling the efficiency of TLR4 complex dimerization by LAMs and their chemical modification.

Next, we designed first molecularly defined caspase-4/11 ligands able to either activate or inhibit inflammatory caspases and developed unique sugar-based immunostimulating molecules which can dissect TLR4 and caspase-11 activation. Exploring possibilities for dissecting TLR4 and caspase-4/11 activation pathways by molecularly defined ligands is crucial to foster the development of novel vaccine adjuvants and immunotherapeutics targeted at the resolution of inflammation.

We demonstrate the merits of advanced synthetic chemistry and “chemical” understanding of biological processes for a breakthrough in the understanding of structural basis of TLR4 and caspase-4/11 activation.

References:
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.
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 [IEIS@aol.com](mailto:IEIS@aol.com) or contact one of these individuals directly:

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