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ENDOTOXIN NEWSLETTER

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NEWSLETTER EDITOR

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A Letter from the President

Who we are

For more than a century, studies of Gram-negative bacterial endotoxins have helped propel major advances in knowledge of mechanisms mediating innate immune recognition, responses, and resolution. While the revelations of the past two decades have underscored the diversity of "danger"-associated molecular patterns that trigger innate immune responses, the abundance and near ubiquity of endotoxins and their remarkable potency continue to distinguish these unique glycolipids. These properties have sustained and expanded interest in the potential beneficial and harmful roles of endotoxins in an increasing array of physiologic and patho-physiologic settings. Progress in the structural analyses of endotoxin molecules from an increasing array of Gram-negative bacteria and in the genetic and biochemical mechanisms producing structurally and functionally distinct endotoxins have revealed novel aspects of bacterial evolution and adaptation and of immune regulation, and helped guide the design and development of new immune modulators. A perusal of the biological, chemical, and biomedical literature underscores the continued vitality and expanding reach of endotoxin-related research.

Jerrold Weiss

The mission of the **International Endotoxin and Innate Immunity Society (IEIIS),** as that of the International Endotoxin Society that preceded the IEIIS, is to promote the exchange of ideas and new data among investigators of endotoxin biology and innate immunity and to support and promote the career development of our younger and more junior colleagues.

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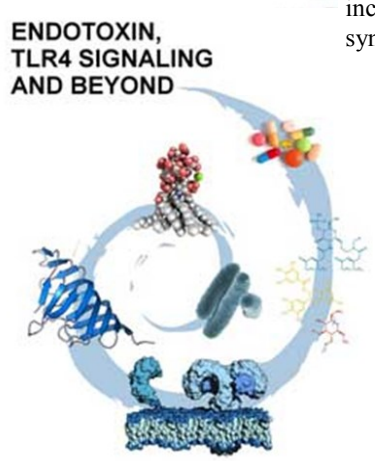
Highlights of Milano Meeting

by Jerrold Weiss



Endotoxin, TLR4 Signaling, and Beyond, was held on August 21, 2013 at the Villa Forno, Cinisello Balsamo in Milano, Italy. The symposium was instigated by Jerry Weiss and organized by Francesco Peri and Francesca Granucci as a satellite meeting of the 15th International Congress of Immunology that began the next day in Milano. There were roughly 60 attendees and participants (see picture on Page 2), including 16 invited speakers from 6 countries. The symposium was strongly supported by the IEIIS.

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A Letter from the President

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Key to our society's evolution has been the role that endotoxin-related research played in the discovery and characterization of innate immune recognition and response systems directed not just at Gram-negative bacteria but all microbe- and danger-associated perturbations of homeostasis.

Our society is distinguished by its global international membership and unique in its integrated focus on the chemistry, biology, physiology, and translational biology of microbe (pathogen)-associated molecular patterns, including but not limited to Gram-negative bacterial endotoxins, and their interactions with innate immune recognition and response systems.

Our efforts to meet our mission are manifest in many ways, including (co-) sponsorship of meetings, publication of manuscripts in the journal sponsored by the IEIIS, Innate Immunity, and less formal interactions through our society website (http://IEIIS.org) and Newsletter. The modernization of the IEIIS website should greatly enhance efforts to make the IEIIS more visible and vital, especially in the periods between its international biennial meetings.

As in all communities, the function and impact of the IEIIS depends on the participation and engagement of its members – i.e., those who have been and/ or are currently advancing endotoxin and innate immunity-related research.

Equally importantly, our members need to encourage the membership and participation of their students and younger colleagues to help the IEIIS keep pace with the inroads of endotoxin- and innate immunity-related research into previously unchartered territories. The generations of scientists, many now Honorary Lifetime Members of the IEIIS that helped build the IES/IEIIS, provide an invaluable historical perspective that should further enrich the benefits of membership. I am hopeful that the current revamping and modernization of the IEIIS website and Newsletter will further this dialog.

Best wishes. I look forward to seeing you in the near future,

Jerry Weiss, President of IEIIS

Highlights of Milano Meeting

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As the title of the symposium suggested and promised, subjects presented and discussed ranged from the structural and functional properties of natural and synthetic agonists and antagonists of As the title of the symposium suggested and promised, subjects presented and discussed ranged from the structural and functional properties of natural and synthetic agonists and antagonists of TLRs, including TLR4, TLR2, and TLR13, novel approaches and insights concerning TLR and C-type lectin activation and signal/ transduction, TLR-dependent and -independent functions and actions of CD14, and expanding functional contexts in which innate immune sensory and response systems may be operative, including in Alzheimer's disease and in other neuro-pathologies.

Most remarkable and rewarding were the very active and animated discussions that followed each presentation and continued long into the Italian summer night over dinner and wine.

Dr. Peri has been offered the opportunity to orchestrate a special issue in the journal Molecular Immunology to help encapsulate in greater detail the high quality science that was presented at the symposium. This issue should be forthcoming in early spring, 2014 and will be posted on the IEIIS website to help alert those interested readers. An editorial summarizing the major conceptual insights presented and discussed at the symposium will also be forthcoming at about the same time in the IEIIS journal, Innate Immunity.

Awards from the 12th Biennial IEIIS Meeting Tokyo, Japan, October 2012

by Alan Cross and Jerrold Weiss

YOUNG INVESTIGATOR AWARDS: *Awarded to pre-or post-doctoral students <35 years of age who submitted abstract for poster presentation at the biennial meeting. Nominees were submitted by the nominee's research mentor and reviewed by members of the IEIIS governing council.*

Brittany Needham: a pre-doctoral student mentored by Stephen Trent (Institute of Cellular and Molecular Biology, The University of Texas at Austin, USA). Her selected abstract/ poster was entitled: "*Modulating the innate immune response by combinatorial engineering of endotoxin."*

Rebecca Coll: a post-doctoral student mentored by Luke O'Neill (School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Ireland). Her selected abstract/poster was entitled: "*GSTO1 is a novel redox regulatory component of the TLR4 and TLR1/2 signaling pathways*."

More extensive descriptions by Brittany and Rebecca highlighting their work and career progress are included on page 10 of this newsletter.

ALOIS H. NOWOTNY AWARD: *Awarded to a young investigator who has shown excellence in research, has made significant contributions to the study of endotoxins, shows potential for further scientific development, and whose research is close to that pursued by Dr. Alois H. Nowotny (structure, function and immunochemistry of endotoxins).*

Yukari Fujimoto, Ph.D. Dr. Fujimoto received his Ph.D. from Osaka University, Japan, in 2002 and is currently Associate Professor, Laboratory for Natural Products Chemistry, Department of Chemistry, Graduate School of Science, Osaka University. Major research accomplishments have included chemical synthesis of defined structures and partial structures of lipid A/LPS, peptidoglycan fragments, *S. aureus*-derived lipopeptides, and various glycoconjugates for characterization of the structural determinants of their immunostimulatory activities.

SHELDON E. GREISMAN AWARD: *First established in 2010 by vote of the IEIIS governing council in honor of Sheldon E. Greisman, M.D., whose contributions helped provide a foundation for understanding host responses to endotoxin. Many of his observations provided a conceptual basis for current clinical innate and adaptive immunity research. Awardees will be recognized for their substantial and original contributions which have led to an increased understanding of the interactions between microorganisms and innate immunity, insights that provide new opportunities and directions for the development of diagnostic and therapeutic approaches.*

Jean-Marc Cavaillon is the 1st recipient of the Greisman award. Dr. Cavaillon received his Ph.D. and Dr. Sc. in Immunology from the University of Paris in 1977 and 1980, respectively. He has been at the Institut Pasteur since then, becoming Head of the Unit "Cytokines & Inflammation" in 2001 and Professor in 2008. Dr. Cavaillon has made numerous contributions to the studies of innate immune responses to infection and non-infectious insults, with a focus on mechanisms involved in cytokine induction and their protective and potentially pathologic consequences, including changes in subsequent immune responsiveness (e.g., endotoxin tolerance). His efforts have epitomized the goals of translational biology, combining basic research at the bench

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Photos Taken at Symposium in Baltimore Honoring Dr. Greisman December 2007

From left to right:

Drs. Alan Cross, Sheldon Greisman, and Robert Munford

From left to right:

Drs. Ernst Rietschel, Sheldon Greisman, and Richard Hornick

REMEMBERING OUR PAST MEMBERS & MENTORS ...

Shozo Kotani: Pleasure and Fruits of Interdisciplinary Collaboration in Endotoxin

by Shoichi Kusumoto

I would like to dedicate this short article to late Prof. Kotani who gave us the first chance to join the research field of immunostimulating bacterial cell components and to Dr. Masaru Inage who was my first doctoral student and made an outstanding contribution to the initial step of our synthesis. He was unfortunately involved in a serious railway accident near Osaka and passed away in 2005.

One afternoon of late fall in 1972, Prof. Tetsuo Shiba and I sat in the office of Prof. Shozo Kotani, a microbiologist at the same University. He told us that cell wall peptidoglycan ubiquitously occurring in all bacterial cells enhances the immunological responses of higher animals. We accepted his request for a collaboration by synthesizing several compounds corresponding to partial structures of peptidoglycan and soon succeeded in identifying N-acetylmuramyl-L-alanyl-D-isoglutamine (muramyl dipeptide, MDP) as the smallest immunostimulating structure of peptidoglycan. Though the same conclusion was independently reported by the group of Edger Lederer of CNRS even slightly earlier than us, the result was an important lesson which told us that a certain definite structural part can represent the function of the entire macromolecular glycoconjugate. We also learned that organic chemistry can contribute to solving important biological problems by providing with homogeneous key molecules free from any possible contamination from natural sources.

While working on peptidoglycan, we came to know a more interesting cell wall component, "endotoxin". Though ninety years had already passed since Richard Pfeiffer first described it in 1882, endotoxin was not well known among organic chemists. Its potent and multiple biological activities and complex and yet ambiguous chemical structure made endotoxin a highly attractive target of chemical endeavor. During the long research history on the structure and functions of endotoxin, several epoch-making contributions were made by Otto Westphal and Otto Lüderitz at the Max Planck Institute, Freiburg,

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Chris Raetz

by Doug Golenbock and Russell Bishop

Doug Golenbock *(excerpted from his talk at the XIIth biennial IEIIS international meeting, Tokyo, October, 2012)*

Chris was a great friend. He was just one of my many mentors, but certainly the one who taught me the most about science. Not just how to design experiments, but how to think about science.

I was the first MD to work in Chris's lab. Chris was an MD who had a great distrust of MD's who did science. I would like to think that I helped changed that but I really think his distrust of MDs was entirely related to the fact that he considered himself to be a world class scientist but a rather untrustworthy physician. He could barely draw blood, he once admitted.

We started off rather poorly together, primarily because I was all thumbs in the lab. Thanksgiving Day 1985, I had a small incident involving 5 mCi of ^{32}P, and Chris thought maybe it was time for me to go see patients again. However, after a discussion together, he finally agreed to give me a chance to prove I could make discoveries. I got all the ^{32}P cleaned up the way he wanted and after that, things were a lot smoother. Our conversation had convinced him I wanted to learn to be a scientist, and that was a career goal that Chris always respected.

Chris told me that one needed to learn to trust one's students. He said that this was not easy. One example Chris told me concerned his legendary post-doctoral student, Masahiro Nishijima. What Masahiro probably doesn't know was that Chris initially thought Masahiro's screen for E. coli mutants in PtdCholine metabolism was flawed. But, out of the screen came the discovery of lipid X. Chris said to me that many of the best discoveries in his lab were all like this. You tell the post-doc not to do something, he does it anyway, and you discover something really novel. He had a long list of such discoveries that he loved to tell me about. These conversations always demonstrated a key element of Chris Raetz as mentor: he had a great love and respect for his students and always gave them credit for their hard work and accomplishments. This is not to say that Chris did not feel he had a heavy hand in the things students and post-docs did right, things he talked about constantly. But Chris appreciated that nothing got accomplished on the basis of a mentor's genius alone.

I stayed on in the Raetz lab. My four years in Chris Raetz's laboratory were, simply put, the most intellectually thrilling years of my life.

Chris ultimately left the University of Wisconsin to go to Merck, hoping to use his expertise in lipid metabolism to make life-saving drugs. He did well at Merck, but one could sense his growing unhappiness at not being more intimately involved in his science.

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Anne-Marie Staub

by Jean-Marc Cavaillon

Anne-Marie Staub passed away on December 30th, 2012. She was born on November 13, 1914, in Pont-Audemer en Normandy where the family had moved after the beginning of World War I. Her maternal grandfather was a tanner, like Louis Pasteur's father. Her paternal grandfather, Charles Staub (1846-1918) was headmaster of Lycée Buffon; close to Institut Pasteur, and Louis Pasteur was a witness of his marriage. Her father, André Staub started to work at Institut Pasteur in Charles Chamberland's laboratory.

Anne-Marie Staub

When she joined the Institut Pasteur, she started to work with Daniel Bovet and her works first published in 1937 led to the discovery of the first antihistamines and were the foundation of the Nobel Prize awarded to Daniel Bovet in 1957. Bovet's boss, Ernest Fourneau, prevented continuation of A-M. Staub's work with Bovet. After spending time in the laboratory of her father who was then the head of the veterinarian vaccines unit, she joined Pierre Grabar in 1941, who was back from a sabbatical with Michael Heidelberger in New York. She worked there on Bacillus anthracis. To improve her expertise on carbohydrate biochemistry, she spent 6 months with Prof. Claude Rimington at the University College Hospital Medical School of London. Because of her expertise on anthrax, she was offered two additional years in London with a grant from the Medical Research Council and worked in Sir Paul Fildes's group with Dr. G. P. Gladstone.

Back in Paris, she was offered to head the group of immunochemistry in the Vaccine unit and started her work on the biochemical characterization of O-antigens of Salmonellae. In a meeting in Roma in 1953, Zoltan Ovary introduced her to Otto Lüderitz. It was the beginning of a long and fruitful collaboration with O. Lüderitz and his boss Otto Westphal of the Max-Planck-Institut für Immunbiologie in Freiburg as illustrated by numerous papers and reviews

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Malcolm B. Perry

by Martine Caroff

Malcolm B. Perry was born in Birkenhead near Liverpool, UK, in 1930. He was attracted by Chemistry as an 8 year-old boy, having a "laboratory" built by his father in a shelter at the bottom of his garden. From that time on, his passion never faltered. He received his PhD and Doctor of Science degrees respectively in Organic Chemistry and Biochemistry in Bristol and moved to Queen's University in Canada in 1954 where he became Research Professor in the Medical School.

His research started with the analysis of Streptococcal pneumoniae capsular polysaccharides, now components of the Pneumovax vaccine. He realized the first chemical syntheses of heptoses, aminohexoses, deoxysugars: a long list of components of bacterial capsular polysaccharides & lipopolysaccharides. He established collections of methylated sugars and methods for structural analysis such as gas chromatography of acetylated and partially methylated carbohydrates.

In 1962 he moved to the National Research Council in Ottawa where he became a Principal Research Officer in the Bacterial pathogenesis section. Much of his research involved the analysis of LPS of medically important pathogens described in more than 350 papers. During his long and fruitful career he characterized the O-chain structure of major pathogens including those of Francisella tularensis, Burkholderia pseudomallei and mallei, E.coli

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Ladislas Szabo

by Martine Caroff

Ladislas Szabo was born in Hungaria in 1922. He emigrated to France where he received his PhD degree in 1952 from the Université de Paris.

He started his research in the Laboratory for Organic Chemistry in the Centre for Research on Normal and Cancer Cells, in Villejuif, before moving to Université de Paris Sud, Orsay, where he spent most of his career. He was a famous synthetic chemist specialized in phosphorylated sugars. This led him to find good natural models in LPS and especially in those of Bordetella pertussis for which bacteria were available from vaccine industries. In addition to chemistry, he also oriented part of his team to structural analysis, and then also introduced a group of Immunologists in the team in the early 1980s. He can be seen as a visionary for having gathered early the three specialties in this way in a single laboratory.

He synthesized the first Kdo molecule at the exact same time, and by chance following the same route as Malcolm B. Perry did in Canada. They published in different journals in 1969. Dr. Szabo later decided to start the syntheses of lipid A components while structural chemists, in the group, were demonstrating the anomery of glucosamine I of natural lipid A. Many structures and chemical mechanisms were described in the following years while the structure of Bordetella pertussis LPS was unveiled, and collaboration with Malcolm B. Perry

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REMEMBERING, cont'd.

Shozo Kotani

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Germany. They elaborated an efficient method of extraction of bacterial cells by hot aqueous phenol, which affords protein -free lipopolysaccharide (LPS). They then showed that mild acid hydrolysis of LPS liberates its lipophilic component, named lipid A, which exhibits all the biological functions of endotoxin including both detrimental and beneficial activities. Further new knowledge on the structure and functions of lipid A came out from the group of Lüderitz and Ernst Rietschel of the same institute: the chemical structure of lipid A isolated from *Salmonella minnesota* R595 mutant was deduced to be an *N,O*-polyacylated 1,4'-bisphosphorylated β(1-6) glucosamine disaccharide. The latter phosphorylated disaccharide was referred to as the hydrophilic backbone of lipid A. Though the exact number and locations of fatty acyl groups on the backbone were not determined, we felt the above rough structural information was already sufficient for the start of our synthesis.

When we solved several difficult problems and completed the multistep synthesis of the first target, i.e., 2,2'-*N*- and 3,4,6'-*O*-acylated disaccharide bisphosphate, we contacted Dr. Lüderitz at Freiburg and asked him to test our synthetic specimens for biological activity. We thereby expected everything would be correctly done there because they certainly had the highest level of knowledge, information, and techniques to study endotoxin. This contact fortunately led to the start of good and long term collaboration between the two groups, but still some more time was required until we were to reach a happy end to the story. Namely, contrary to our expectation, none of our synthetic preparations showed definite endotoxic activity. We had to conclude that something was wrong in our synthesis. Having compared natural lipid A and the synthetic molecule, we recognized that their physicochemical properties and hence their chemical structures were different.

It then seemed to be essential to purify the main component of natural lipid A and determine its precise structure until with the exact number, location and chain length of individual acyl groups. Lipid A obtained from *Escherichia coli* Re mutant was used for this analysis according to the advice of Dr. Chris Galanos of Freiburg who knew this bacterium produces a rather homogeneous lipid A. The main component of lipid A was successfully isolated in a pure state after some chemical modifications and chromatographic purification. Chemical as well as detailed spectroscopic analyses by the latest NMR and MS techniques led us to conclude the complete structure of *E. coli* lipid A. Whereas the previously proposed structure of the hydrophilic backbone was correct, the position of acylation had to be revised. We believed this was the first complete structural elucidation of lipid A, but again another research group, that of Nilofer Qureshi and Kuni Takayama at Wisconsin, independently, and possibly even a bit earlier than us, reported the identical structure for lipid A of a heptoseless mutant of *Salmonella typhimurium*. They isolated this component by repeated HPLC purification and determined the structure with the aid of NMR and MS analyses.

Endotoxin research is by itself a multidisciplinary science covering microbiology, immunology, biochemistry, medicinal science to biophysics, so that anyone may join freely in making an important contribution.

In any case, the goal of our investigation, i.e., synthetic reproduction of endotoxic compound, seemed to be already very close. The first synthesis according to the new information was started and completed in November 1983. The purified product was sent to Freiburg and, this time, proved to show the expected endotoxic activity. This was the first synthetic and endotoxic lipid A obtained one hundred and one years after the discovery of bacterial endotoxin. We still exactly remember this exciting and happy moment. Now, no one could oppose the idea that lipid A is the endotoxic principle of LPS. Various structural analogues of lipid A were then isolated from various bacterial cells and some have been synthesized. Some of the synthetic lipid A was distributed among many research groups for very fine experiments and have served as a certain standard. The relationships among chemical structures, biological activities, and physicochemical properties of lipid A were well documented.

The community of endotoxin researchers is, as I felt, quite tolerant and open to newcomers and because of this comfortable atmosphere I already have spent a few enjoyable decades. Endotoxin research is by itself a multidisciplinary science covering microbiology, immunology, biochemistry, medicinal science to biophysics, so that anyone may join freely in making an important contribution. We were really lucky just to have come on a right stage of the development of the research and able to do something to the field. After the discovery of Toll like receptors around the end of twentieth century, our understanding of innate immunity system was very much improved. Even under this situation, I believe endotoxin research, because of its multidisciplinary nature, ever expands in various, even unexpected, directions, to the great benefit of human beings. ▲

Chris Raetz

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Just before leaving Merck, Chris called me to tell me that he had been offered a job at Duke. The price of leaving Merck was enormous. No one knew then, of course, that Chris would die young, but even in consideration of this, he simply tossed away millions in guaranteed income to return to academia.

Chris Raetz

It was then that I realized that Chris was all about the science. Chris loved science. Indeed, he loved to refer to himself as a science nerd. And everyone he worked with became part of that love. In retrospect, knowing Chris as I came to know him, the chance to move back to the job he loved made this decision a no brainer, and indeed, Chris's best work was yet to come.

Chris was enormously proud of his students and often recited me a long list of their accomplishments, both during and after their tenure in his lab. Despite the fact that he was the King of lipid A biosynthesis, his talks were always full of acknowledgements to his students. This is really what Randy Hampton referred to when he talked about the "Raetz survivors club". It was not a reference to surviving some stressful period of one's life. It was survival from Chris's overwhelming influence, his un-remittent interest in your work, and the impulsive way that he sucked up and thrived on the science being done in his lab. It was a wonderful feeling knowing your latest discoveries would be part of Chris's raison d'etre in short time. I, for one, always wanted to produce for Chris as a result.

I want to tell you a little bit about Chris as career advisor, because I think this also tells you a little bit about what type of person he was. In 1990, I went to Chris and asked him to hire me at Merck. After my request, he became uncharacteristically quiet. After this incredibly pregnant pause he said, "Doug, why would you want to work for me? That works well for me, but I am not certain you know what that means. Everything you discover at Merck will be considered to be my discovery. You would hate that. You are the type to want people to give you credit for your own discoveries. You can have a job at Merck if you really want it, and I think that with your MD training you will do very well here, but I strongly advise against it." I have often thought back upon that career advice, since it obviously led to me leaving NJ, the state in which my father was born, and moving to Boston.

When I left Merck, my friend and "brother from another mother", Randy Hampton, and I published a paper in Nature. Chris was the senior author. It seemed that lipid A binds to class A scavenger receptors, and our evidence was incontrovertible. Still young and naïve, I told Chris that I was certain he, Randy and I were destined to do this again in a few years. Chris's response was "never mind about Nature, focus on JBC. That is where the real science is." Like everyone else, Chris was thrilled by a Science or a Nature paper, but JBC was where Chris thought real discoveries were published. JBC, for Chris, was where the hard work of science was reported. When I got tenure at UMass, he said to me, "you are proof that one can be successful with JBC."

Chris was great to go to meetings with. He knew everything about everyone and their work, was openly critical and admiring at the same time. He always gave a great talk. In the pre PowerPoint days, Chris would have a box of slides in his hand. Often, just minutes before his talk, he would stand up and would seemingly randomly choose a handful of slides one by one from the box and load his carousel. He would then proceed to give a terrific and usually brilliant talk. One morning in Helsinki, I was eating breakfast with Chris. I complained that my talks were never spontaneously brilliant, like his or Sam Wright or Richard Ulevitch. They seemed, at least to me, painfully contrived. I just couldn't believe that without practice, those guys could get up and give such amazing presentations. Chris said to me, "spontaneous? Don't believe it! We practice our talks all the time! I spent an hour last night putting together my slides and talking to the wall as if it were an audience."

Chris was so full of great advice that until I sat down to write this eulogy, I never realized all the things he taught me. He taught me to give students and post-docs room to be creative if you wanted to see their best work. He said that Masahiro, Randy Hampton, myself, Stephen Trent, Andy Zoeller, Olivier Morand and Matt Anderson — just to name a few — all made their best discoveries ignoring his advice.

And, he put science into perspective in ways I had never considered. One day, I complained to Chris about a paper in the literature published by a big famous LPS guy that was, in a word, malarkey. I said, isn't it amazing what this guy can publish, and it's mostly wrong! That triggered my most memorable Raetz line ever. Chris said, "Doug, 99% of what is published is wrong. Get used to that. " There was another pause. Chris was not shy and had no false modesty. He continued, "You know, only 95% of what I publish is wrong. That is what makes me better than most people". And, he had a good laugh. This, of course, was an exaggeration, but the crystal of truth was there, pure and purely Raetz.

The summer before last, I was travelling in South America when Chris called. He told me all was well- he had just had a JBC paper and a new RO1. After some discussion of the latest lipid A miracle someone in his lab had performed, he said, "of course, health wise, things aren't going that well. It looks like the cancer is taking over, and I am just going to try and enjoy my summer." He said it so calmly, rationally and thanked me for my medical advice – the little I had given him- and my friendship. And then he hung up. It was a good bye call of course. I have missed Chris ever since, but his words, his wisdom, his positive view about science and discovery, and his unfailing friendship changed my life forever and for this I thank him.

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Chris Raetz

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And now a remembrance from Russell Bishop.

I interviewed with Chris to become a post-doc in his lab on the same day Bill Clinton was re-elected for his second term. The large majority of Chris' lab members at that time were women, which I was told could be attributed to Kathryn Brozek, who had positively influenced grad student recruiting when Chris was setting up his lab at Duke. Chris warned me that I had to win approval from his existing contingent of trainees before I could ever be recruited to his lab as a post doc. Fortunately, I was later informed that I could join the lab if I could manage to secure a fellowship. In the Spring of 1998, I arrived at the lab newly married with a 4 month old daughter, a newly minted PhD in biochemistry from the University of Alberta, and with support from the Alberta Heritage Foundation for Medical Research. Chris' first act of generosity toward me was to pay the bill of moving my belongings over the 4000 km journey from Edmonton to Durham. I could never have afforded to pay that cost myself.

I didn't know anything about Chris except that I liked the papers he was publishing (mostly in JBC) as I was gearing up to write my PhD thesis. The project I eventually inherited was forged previously by the work of Masahiro Nishijima, and later, by Kathryn Brozek. It soon became obvious to me that Chris' lab was a special place. Everybody's particular enzyme required that they knew how to prepare its substrate, but the product of that enzyme would be the substrate for the next person's enzyme - so everybody depended on the success of everyone else. Chris oversaw all this at Monday morning group meeting, which started at 8:30AM and usually ended around 11AM with Chris having reviewed everybody's notes from the previous week. He would notice little things, like an apparent contaminant in a TLC plate that he recalled having seen before 6 months ago and wondered if it was really a contaminant or something more important. His memory was incredible.

For a department Chairman, Chris was visible in the lab far more than I imagined he would be. I assumed he must work extensively after hours to do all the other things he had to do, but the one time I stayed at his house we (he and Madeline and I) watched an episode of Seinfeld together and all retired for the evening at a reasonable time. It soon became clear to me that Chris Raetz had to have some special gifts to be able to do all the things he was constantly doing. If only I could ever be that organized!

I will always remember Chris for his generosity, but I should also mention something about his child-like enthusiasm for the process of discovery. He had just uncovered in a Blast search that some of the enzymes of lipid A biosynthesis appeared to be conserved in plants. Charlie Sweet had pulled out the old mortar and pestle and was grinding up Arabidopsis extracts to screen for various enzymes, but the experiments seemed a bit beyond the expertise of this bunch of E. coli aficionados. Then, I walked into Chris' office after he had just gotten off the phone and he informed me that a core facility in Wisconsin could make targeted mutants in Arabidopsis for a nominal fee. Chris was literally jumping for joy. I will never forget his excitement at that moment. Chris genuinely loved discovery and he genuinely cared when experiments didn't work. He seemed ever present in the lab because he really cared to know what was going on.

When I was looking for faculty positions, Chris encouraged me to take my PagP project with me. I was recruited to the University of Toronto in 2000. Since Chris had a vested interest in my work, I wasn't surprised when he invited himself for a visit. I think he genuinely wanted to find out if I had been given all the resources I needed to be successful. Chris gave a dynamite seminar outlining Bill Doerrler's recent results with MsbA mutants and proceeded to meet my colleagues. I arranged for Chris to meet Lewis Kay and Chris soon convinced Lewis that he and I should start collaborating on PagP. The outcome of that collaboration had a lot to do with me being awarded tenure in 2005.

I soon learned that I wasn't the only Raetz survivor to benefit from Chris' influence after they had left the Raetz lab. His phone calls were consistent - about once every 4-6 months - for the 11 years after I left his lab. I'm certain that I was invited to speak at several prestigious meetings because Chris had suggested my name. I'm probably on the editorial board of the JBC for the same reason.

After I was recruited to McMaster University in 2006, I invited Chris up for a seminar to save him the trouble of having to invite himself. My students had heard so much about Chris Raetz and they were all excited to meet him. Not long before, I had driven my eldest daughter (then 8) to reconnect with the Raetz Survivors in Worcester for Chris' fictitious Danforth lecture (really just an excuse to surprise Chris for his 60th birthday). You have to be pretty special to have your trainees do something like that for you. Chris' visit to McMaster was the last time I saw him before he informed me that he had to have his thyroid removed. I was so relieved to learn that he was still working and in remission. In October 2010, Chris invited me to give a talk at Duke - 10 years after I had left (and my first time back). He was doing great. The last time we talked he asked me to provide a review for a manuscript on lipid A in plants that he was submitting to PNAS. He mentioned he was planning to stay at Bill Dowhan's place in Houston to undergo a procedure that, in his words, probably wouldn't work. It didn't sound ominous to me at the time, but I was worried by his insistence that I should be identified as a potential supervisor for some of his trainees, as a part of what he called his "contingency plan". On Thursday August 11, I felt the compulsion to send Chris an e-mail to ask him how he was doing. On Friday I got a reply - he said he decided not to go to Houston after all and that although things were pretty tough, so far there were no major complications. You can imagine my shock when I learned he was gone on Tuesday. Chris shone bright, like a soaring meteor. I miss him now, but I am grateful to have known him.

REMEMBERING, cont'd.

Anne-Marie Staub

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published together including two papers in Nature. Thanks to her German colleagues, she identified for the first time tyvelose as a component of O-antigen {09} of Salmonella typhi: (Tyvelose-1-3-Mannose-1)n-6-Mannose, and characterized the O-antigen {12} as : Rhamnose-1-6-Glucose-1-Galactose. She achieved immunochemical characterization of many other O-antigens (S. gallinarum, S. paratyphi, S. typhimurium, S. newport, S. adelaïde, S. senftenberg, S. johannesburg, S. zuerich, S. strasbourg, S. cholerae suis). Léon Le Minor, offered her the opportunity to study the consequences of bacterial conversion by bacteriophage, and the modifications of the O-antigens. In 1967 she became the head of the Bacterial Antigen Unit and was appointed Professor in 1970. In addition to her scientific career, she was also co-director of the General Immunology Course of Institut Pasteur from 1960 to 1974. She retired in 1977.

In 1969, A-M. Staub was awarded with Drs Hiroshi Nikaido (Boston) and Winifred M. Watkins (London), the Paul Ehrlich and Ludwig Darmstaedter prize, the most prestigious international prize in Medicine and Biology awarded in Germany. In 1973, she was distinguished as Knight of the Legion of Honor. In 1993 she was nominated and elected "Honorary Life member" of the International Endotoxin and Innate Immunity Society.

All those who had the privilege of working with A-M. Staub remember a boss who had found the proper balance between authority and humanity, between firmness and kindness. All appreciated her rigor, her generosity, her honesty, and her great culture. As stated by Ernst Rietschel: "She was a remarkable scientist, personality and woman and I always admired her openness, willingness to share her data, and respect of younger researchers, as I was at the time. She was a scientific giant without making us feel her superior intellectual and experimental capabilities. Anne-Marie will remain for us a silent superstar of immunochemistry and a human being who served as a prototype of scientific originality, human behavior and collegial relationship." ▲

Malcolm B. Perry

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O157:H7, Brucella abortus, Bordetella parapertussis and B. bronchiseptica, Vibrio cholera and Yersinia pestis. He developed many LPS O-chain glycoconjugates as vaccines against some of these bacteria and many others.

A mentor for many, he was unassuming, modest, and generous. He was a Fellow of the Royal Society of Canada, of the British Royal Institute of Chemistry and received the Canadian Society for Microbiology Gold Medal. He was nominated and elected Honorary Life Member of the IEIIS in 2000.

Malcolm Perry passed away in June 2012. He was a great scientist, a pioneer in our field, and such a discrete person that many scientists do not know his name, but they know his work, which will continue to inspire our research for long. In addition, his friends will remember, the cheerful man, his humor, his passion for literature, music and photography as well as, in his later years, his renewed enjoyment of flying a small twin-seater plane. ▲

Drs. Szabo (*left*) and Perry (*right*) in laboratory at Université de Paris Sud, Orsay, 1979

Ladislas Szabo

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for analyzing different other members of the genus started. Dr. Szabo initiated collaboration with physicists in Orsay, opening new perspectives for LPS analysis and mass spectrometry being still fruitful in the group.

Ladislas Szabo passed away on the 27th of January, 2013. Jean-Marc Cavaillon from the Pasteur Institute, his wife Nicole Haeffner-Cavaillon from INSERM, and I from CNRS, head of the actual Orsay group, are grateful to this erudite scientist, sportive man and music lover, to have introduced us to the fascinating world of endotoxin research when we were students. ▲

A Novel Therapeutic Opportunity for Eritoran?

by Jerrold Weiss, Stefanie Vogel, and Kari Ann Shirey

Eritoran (E5564), a product of Eisai Inc. with demonstrated potent TLR4 antagonist properties *in vitro* and *in vivo*, has been instrumental in comparative structural biology studies in demonstrating the structural and functional differences between endotoxin and endotoxin-like TLR4 agonists and antagonists. However, despite multiple encouraging preclinical experiments, demonstration of a clear and compelling clinical niche for its therapeutic use has been difficult to achieve.

The findings of IEIIS members **Kari Ann Shirey** and **Stefanie Vogel**, published last spring as a letter in Nature (see full reference below)[1], have provided new hope for an important therapeutic application for Eritoran. Their studies were prompted by the novel observations and insights of Imai et al.[2] and the subsequent observations of Vogel and colleagues[3] showing that TLR4$^{-/-}$ mice were resistant to doses of a mouse-adapted strain of H1N1 influenza virus that were lethal in wild-type mice. These combined observations led Shirey *et al.* to hypothesize that blocking TLR4 signaling, even after initiation of potentially lethal influenza infection, could be protective.

The findings reported by Shirey KA *et al* bear out this prediction and support a model of influenza pathogenesis that includes ROS-induced formation of oxidized host phospholipids that can act as TLR4 agonists and help instigate and perpetuate a cytokine storm contributing to acute lung injury and lethality. The protective effects of Eritoran are manifest even when treatment of infected mice is delayed for 6 days and are CD14- and TLR2-dependent, reflecting CD14-dependent delivery of Eritoran to MD-2/TLR4 and the possible role of TLR2-containing receptors as targets of Eritoran. The CD14- and TLR2-independence of influenza mortality by contrast, is consistent with the selective TLR4 agonist properties of at least certain oxidized phospholipids and their ability to engage, albeit with lower affinity than Eritoran, MD-2/TLR4 in a CD14-independent fashion. The findings of this study suggest novel therapeutic potential of Eritoran that should be further explored given its well-documented safety profile. The original findings of Imai *et al.* raise the possibility that this therapeutic approach can be applied in an array of settings of acute lung injury resulting from a variety of sterile or infectious causes. Studies are ongoing in the Vogel lab to determine the efficacy of Eritoran in other infectious models of acute lung injury and to move this product forward in animal models that respond to non-adapted strains of human influenza as well.

[1] Shirey KA, Lai W, Scott AJ, Lipsky M, Mistry P, Pletneva LM, Karp CL, McAlees J, Gioannini TL, Weiss J, Chen WH, Ernst RK, Rossignol DP, Gusovsky F, Blanco JC, Vogel SN. The TLR4 antagonist Eritoran protects mice from lethal influenza infection. Nature. 2013 May 23;497(7450):498-502.

[2] Imai Y, Kuba K, Neely GG, Yaghubian-Malhami R, Perkmann T, van Loo G, Ermolaeva M, Veldhuizen R, Leung YH, Wang H, Liu H, Sun Y, Pasparakis M, Kopf M, Mech C, Bavari S, Peiris JS, Slutsky AS, Akira S, Hultqvist M, Holmdahl R, Nicholls J, Jiang C, Binder CJ, Penninger JM. Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. Cell. 2008 Apr 18;133(2):235-49.

[3] Nhu QM, Shirey K, Teijaro JR, Farber DL, Netzel-Arnett S, Antalis TM, Fasano A, Vogel SN. Novel signaling interactions between proteinase-activated receptor 2 and Toll-like receptors in vitro and in vivo. Mucosal Immunol. 2010 Jan;3(1):29-39.

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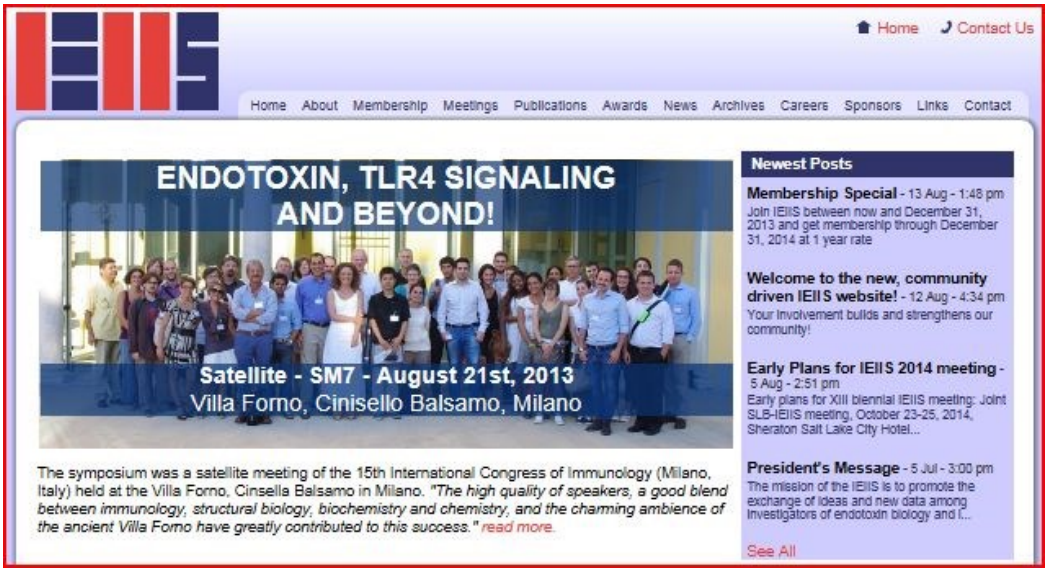

IN THEIR OWN WORDS …
2012 IEIIS YOUNG INVESTIGATOR AWARDEES

Brittany Needham

The primary focus of my research is the study of the Gram-negative bacterial surface, which is covered with a complex molecule called lipo-polysaccharide (LPS) that provides a barrier against the often-hostile environment encountered by a bacterial cell. The bioactive portion of LPS that anchors the molecule into the cell surface is lipid A (endotoxin). In its natural, unmodified form, lipid A can over-stimulate the human immune system, leading to severe inflammation and toxic shock. This is a problem in vaccines and can lead to adverse side effects. However, if lipid A is appropriately altered in structure, the immune response can be optimized and can be quite beneficial as the required adjuvant in vaccines. Lipid A variants have broader potential than many current adjuvants, which have a limited scope and do not necessarily stimulate the optimal immune response for many kinds of infections.

We have worked to modify lipid A by exploiting diverse lipid A modification mechanisms that bacteria have evolved as a means of survival in the environment and during infection. These diverse modification mechanisms applied in combination lead to many unique lipid A structures, many not found in nature. Through such manipulation of lipid A modification strategies, we genetically engineered 61 different *Escherichia coli* strains that produce an extensive range of lipid A surface profiles, characterized by thin-layer chromatography and mass spectrometry. The customized bacteria that produce modified lipid A, as well as the purified LPS and lipid A, were found to vary the activation level of TLR4 and effectively modulate the amplitude and nature of the cytokine response produced by human macrophages. Furthermore, testing these samples in mice indicated that they could be effective as adjuvants in activating the immune response for vaccines.

Recent publications

Modulating the innate immune response by combinatorial engineering of endotoxin.

Needham BD, Carroll SM, Giles DK, Georgiou G, Whiteley M, Trent MS.
Proc Natl Acad Sci U S A. 2013 Jan 22;110(4):1464-9.

Fortifying the barrier: the impact of **lipid A** remodelling on bacterial pathogenesis.
Needham BD, Trent MS.
Nat Rev Microbiol. 2013 Jul;11(7):467-81.

Rebecca Coll

The department of Biochemistry and Immunology at Trinity College Dublin where I completed my undergraduate degree has a strong emphasis on research in the area of innate immunity. I did my dissertation project in Andrew Bowie's lab on the role of the TLR adapter SARM in regulating MAPK activity. As I really enjoyed my project, I was keen to continue my research in the area of innate immune receptor signalling and started my Ph.D. with Luke O'Neill in 2008.

Initially, my Ph.D. research focused on the inflammasomes and IL-1b production. I characterised a novel small molecule inhibitor of the NLRP3 and AIM2 inflammasomes called Bayer-31. More recently, we have also been analysing the mechanism of action of a highly specific NLRP3 inhibitor called CRID3 and are testing this *in vivo* as a potentially very exciting treatment for NLRP3 associated diseases such as diabetes. During my Ph.D. I also became interested in the role of the glutathione-*S*-transferase, GSTO1, in TLR signalling. Knockdown of GSTO1 in a macrophage cell line resulted in a profound defect in both TLR4 and TLR1/2 stimulated responses. These and other results suggest that glutathionylation is a key regulatory mechanism involved in specific TLR signalling pathways.

I am currently doing my first post-doctoral fellowship in Luke O'Neill's lab where we are investigating the role of glutathionylation as a post-translational regulatory mechanism in innate immune signalling. In May, I will be doing a short visiting fellowship in Phil Board's lab at the Australian National University in Canberra and in the future I hope to work towards developing novel therapeutics that target components of the innate immune system.

Recent publications

Modulatory mechanisms controlling the NLRP3 inflammasome in inflammation: recent developments.
Haneklaus M, O'Neill LA, Coll RC.
Curr Opin Immunol. 2013 Feb;25(1):40-5.

The cytokine release inhibitory drug CRID3 targets ASC oligomerisation in the NLRP3 and AIM2 inflammasomes.
Coll RC, O'Neill LA.
PLoS One. 2011;6(12):e29539.

Awards from the 12th Biennial IEIIS Meeting Tokyo, Japan, October 2012

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with testing in animal models and then in the clinic, and back. Dr. Cavaillon has also made numerous contributions to the IES and IEIIS, including service as President of the IES from 1998-2000.

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 award is generously supported in perpetuity by an endowment from the Trustees of the Stanley Watson Foundation.*

The award honors Frederick B. Bang (1916-1981), a remarkable biomedical investigator of John Hopkins University School of Medicine. In his endeavors, Dr. Bang often made use of marine organisms to gain insights to biological phenomenon of clinical significance including endoxemia. In addition to his interest in bacterial endotoxins, Dr. Bang had broad research interests in other areas of host defense including hepatitis and parasitic diseases.

Shizuo Akira, M.D., Ph.D.: Professor in Department of Host Defense, Osaka University, Japan. Prof. Akira has made many ground-breaking discoveries in the field of Immunology, most significantly concerning innate immune host defense mechanisms. Among his greatest contributions have included characterization of an array of Pattern Recognition Receptors (e.g., Toll-Like Receptors, RNA helicases) and downstream signal/transducing elements (e.g., MyD88) that play essential roles in innate immune recognition and responses. His discoveries have helped transform earlier notions of "non-specific" innate immune recognition to that of molecules that have the intrinsic capacity to recognize molecular motifs that are expressed uniquely by broad classes of microbes or by the host under perturbed conditions. His numerous highly influential publications have made Prof. Akira the world's most cited scientist.

HONORARY LIFETIME MEMBERSHIPS: *Awarded to investigators for outstanding career contributions to knowledge of bacterial endotoxins and innate immunity. Recipients are granted a permanent exemption from dues and meeting registration fees. Nominations are reviewed by a group of past, current, and future IEIIS presidents.*

Ulrich Seydel joined the Borstel Research Center in 1979 where he subsequently became the first to characterize the structure of free lipid A and became head of the Division of Biophysics. A major focus of his work was characterization of the biophysical basis of endotoxin recognition by the immune system, including the role of the three-dimensional arrangement of assemblies/aggregates of endotoxin molecules. To better simulate the topological arrangement of endotoxin molecules in the outer membrane of Gram-negative bacteria, Uli and his colleagues developed novel asymmetric planar membranes with LPS occupying just one of the two leaflets of these synthetic membranes as in the Gram-negative bacterial outer membrane. These asymmetric membranes were used as a test system to better characterize the action of complement and of specific antimicrobial peptides. Uli was an active member and leader of the IEIIS and served as Editor-in-Chief of the Journal of Endotoxin Research from 2004-2006.

Barnet Sultzer described in 1968 the C3H/HeJ mouse strain which showed a defect in leukocyte responses to LPS. These findings represented a seminal contribution to early endotoxin research, providing an early clue that the bioactivity and toxicity of endotoxin were dependent on specific host-encoded targets. This mouse strain was exploited to map the gene alteration responsible for the deficient LPS response and, as a result, the key role of TLR4 in host response to LPS. The C3H/HeJ mice also provided experimental observations that demonstrated for the first time that the failure to respond to LPS was associated with increased susceptibility to Gram-negative bacterial infection. This strain also provided a key test system to distinguish host responses to LPS vs. that induced by a contaminant of certain LPS preparations and made possible the identification of "endotoxin protein" (EP) that had B cell mitogen, polyclonal B cell activator, and adjuvant properties independent of LPS. Among numerous additional important observations of Dr. Sultzer were early studies showing distinct signaling pathways activated by LPS vs. EP in lymphocytes and macrophages, B cell mitogen properties of PPD-tuberculin, early evidence for an immunologic role of cholera and pertussis toxins, and ability of BCG to act as a T-independent antigen. The studies on PPD-tuberculin also provided an early experimental setting in which to distinguish B cells from T cells.

Sadaaki Iwanaga, Professor Emeritus, Department of Biology, Kyushu University, Fukuoka, Japan. He and his colleagues spear-headed seminal studies on the innate immune system of an invertebrate animal, the horseshoe crab. This included detailed description of both endotoxin- and β-glucan-triggered hemolymph coagulation cascade. The molecular dissection of the endotoxin- and β-glucan-sensitive elements of this cascade contributed significantly to the development of an ultrasensitive, highly specific second generation of the *Limulus* assay. These studies were instrumental in definition of key role of PAMP/MAMP-recognition in regulated triggering of the coagulation protease cascade. The studies in this invertebrate immune system provided a model for the Toll-activating cascade in Drosophila. Studies in the horseshoe crab led also to discovery of other important molecules in invertebrate innate immunity, including lectins, serpins, and antimicrobial proteins. ▲

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Welcome to our newest members from 2010 to present.

We look forward to your continued participation in our Society and invite you, along with our current membership, to share your studies on our website, in our newsletter, and at our 2014 biennial meeting.

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