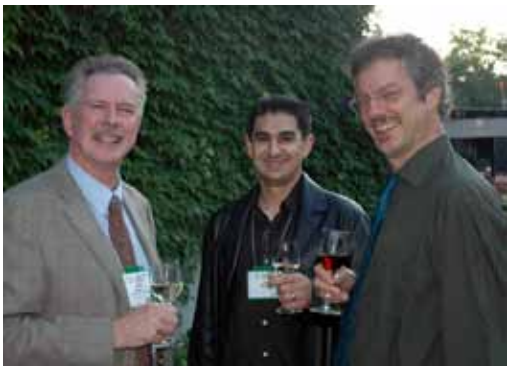
AMERICAN PEPTIDE SOCIETY NEWSLETTER

Volume 7, Number 1 Spring 2010

Also In This Issue:

Morten P. Meldal, 2009 Ralph F. Hirschmann Awardee, Follows in Hirschmann's Footsteps



From left: Morten Meldal, Les Miranda, John Wade

The official journal of the American Peptide Society (APS), *Biopolymers: Peptide Science,* has recently dedicated a special issue in honor of Morten P. Meldal, who was the 2009 recipient of the American Chemical Society's Ralph F. Hirschmann Award in Peptide Chemistry, sponsored by Merck Research Laboratories. The inscription of the award reads: "For greatly advancing solid-phase combinatorial chemistry through enabling and screening techniques, bio-compatible resins, organic transformations of peptides and glycopeptides, CuAAC 'click' chemistry, and peptide catalyst development." Much of the content of the issue came from the award session in Meldal's honor, which came in the shadow of the passing of Hirschmann in June of 2009. A detailed obituary about Hirschmann was penned by Roger M. Freidinger and Daniel F. Veber and published in Journal of Peptide Science 15, 2009, 796-797.

Like Hirschmann, Meldal has pursued academic and industrial careers, perceived peptides as synthetic targets, and contributed innovative technology and practical solutions, which have enabled general scientific problems to be addressed. Both can be credited with giving our community new insight and theory; however, their common interest in producing products of contemporary value has particularly driven their science to creating patentable inventions, which have impacted greatly on our quality of life. In the case of Meldal, these innovations include the concept of polyethyleneglycol (PEG) based resins with unprecedented swelling behavior, physical methods for studying functionalized polymer beads, chemical technologies for making glycopeptides, real-time on-resin spectrophotometric monitoring techniques, multiple column synthesis for assembly and analysis of large split mix libraries, as well as optical encoding of beaded solid supports for high-rate tracking of chemical identity during synthesis and screening. It is also important to mention that Meldal originated the highly cited, widely used Cu- catalyzed cycloaddition of acetylenes and azides (CuAAC) to form triazoles, which he presented at the APS Meeting in San Diego in 2001.

Like Hirschmann, Meldal has also actively served to ensure the perpetuity of our field. Meldal founded the Society of Combinatorial Sciences in 1999, chaired the Eurocombi 2 symposium in 2003, and is currently co-chairman of the 31st

(Continued on Page 2)

Morten P. Meldal

(Continued from Page 1)

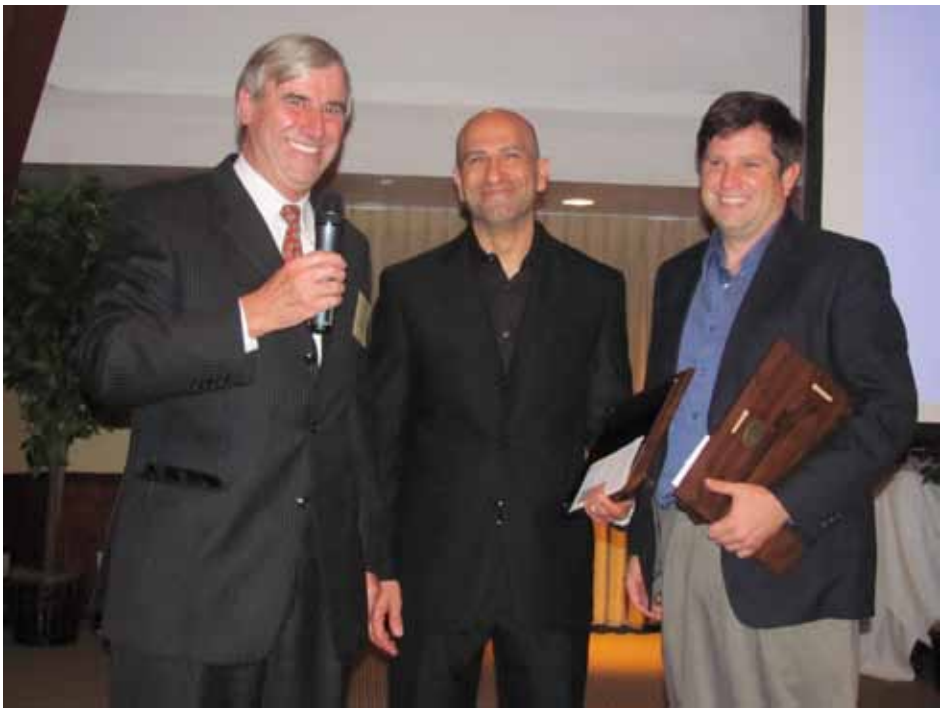
Daniel H. Rich and Ralph Hirschmann

European Peptide Society (EPS) Meeting to be held in Copenhagen, Denmark, on September 5 to 9, 2010. Looking forward to the 31st EPS meeting in Copenhagen, as well as the next APS meeting, when it returns to San Diego in 2011, I enjoy memories speaking with both Hirshmann and Meldal at past peptide meetings. To get us all in the mood for the upcoming peptide society events, I share pictures of these giants of our field, enjoying a meeting with good colleagues: Hirschmann with Daniel H. Rich; Meldal with John Wade and Les Miranda. Hope to see you at the poster sessions.

William D. Lubell
Professeur Titulaire
Département de Chimie
Université de Montréal

2010 Gordon Research Conference on the Chemistry and Biology of Peptides Ventura, CA, USA

The meeting was held from February 28 to March 5; co-chairs were Mark Spaller (Dartmouth) and Sam Gellman (Wisconsin). The meeting reached its attendance limit (~175) and featured a diverse set of lectures in topic areas including "Pushing the boundaries of peptide science," "Peptide assembly," "Antimicrobial peptides," "Peptide-based medicinal chemistry," "Peptides and synthesis," "Peptides in membranes and physical analysis," "Biological applications" and "Peptide engineering." The final lectures were delivered by the winners of the 2010 Vincent du Vigneaud Awards, Phil Dawson and Reza Ghadiri. Nearly 100 posters were presented. Vice-chairs Maria Bednarek (MedImmune) and Fred Naider (College of Staten Island, CUNY) have taken the helm for the 2012 GRC; Les Miranda (Amgen) and Dek Woolfson (Bristol) were elected to serve as vice-chairs at this meeting and co-chairs in 2014. The American Peptide Society held its biannual council meeting/teleconference during one of the free afternoons.

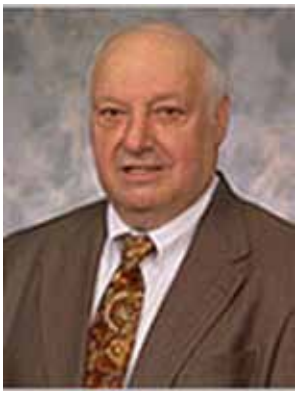


From left: Bachem President Philip Ottiger, Vincent du Vigneaud Award winners M. Reza Ghadiri and Phil Dawson

2010 Vincent du Vigneaud Award Winners

The American Peptide Society's Vincent du Vigneaud Awards were presented to Phil Dawson and M. Reza Ghadiri (both of Scripps Research Institute) on March 4, 2010 as part of the Gordon Research Conference. These prestigious awards, generously sponsored by Bachem, recognize outstanding achievements in peptide research.

Waleed Danho Receives North Jersey ACS Section 2009 Lifetime Achievement Award



Dr. Waleed Danho

Dr. Waleed Danho of Hoffmann-La Roche has a well deserved world-wide reputation as a leader and innovator in the field of peptide chemistry and the application of peptide chemistry to pharmaceutical discovery. Within Roche, he leads a peptide synthesis group that serves as a center of excellence for the entire global Roche organization. His style is characterized by openness, honesty, and a willingness to take the time to listen to others seeking advice. His drive and enthusiasm for science and success are exemplary and, amazingly, seem to intensify as his career progresses. He serves as a role model for medicinal chemists and has expanded his influence greatly through his mentorship of younger chemists.

Waleed completed his Ph.D. degree in the laboratories of Prof. H. Zahn at the RWTH University of Aachen in Germany in 1967. During his graduate career, he developed a new synthesis of the A- chain of insulin leading to the first crystalline semi-synthetic insulin. After a postdoctoral fellowship at the University of California, San Francisco, with Professor C. H. Li on the synthesis of human growth hormone, he joined the faculty of the University of Baghdad, College of Medicine as an assistant professor of Biochemistry. His research on pancreatic and pituitary hormones of camels led to the critical discovery that lipotropin is a pro-hormone of endorphin.

In 1976 he returned to the University of Aachen, as a group leader in the Department of Insulin Research to continue his ground breaking work on the synthesis of insulin. His efforts on the synthesis of pro-insulin led to the preparation of a 45-amino acid fragment of proinsulin and represented the largest fragment synthesized at that time by solution phase peptide synthesis. His research group went on to establish a structure-activity-relationship for insulin in an attempt to discover the core pharmacophore as documented in numerous publications.

In 1980 Waleed joined Hoffmann-La Roche Inc. as a Research Group Chief in the Chemical Research Department. Since that time he has risen to the rank of Distinguished Research Leader. His Roche career has been marked by a focus on peptides as drugs as well as tools for biological proof of concept. Waleed's drive and ability to cultivate strong and extensive collaborations with medicinal and structural chemists have been critical to his success and ability to achieve his goals. The scope of these activities is documented in over 200 publications, 16 patents, and a number of presentations at national and international peptide symposia. Some of the key contributions to Roche and peptide chemistry are highlighted in the paragraphs below.

Waleed's early work at Roche involved the isolation, characterization and synthesis of thymic hormones, in particular thymosin alpha-1. His work led to the discovery that thymosin alpha exists as a precursor and the hormone itself is a "by-product" or artifact of the purification step. In the beginning of 1983, with advent of the "genetic revolution," peptides became powerful tools for the quest for protein therapeutics. Waleed and his team led a number of efforts in the generation of antibodies and active site determination for proteins of therapeutic interest such as IL-1, Il-2 and Ig-E. This body of work was achieved through the synthesis of large numbers of linear and conformationally constrained peptides as a "protein mimic" and represented the first step in the design of small molecule peptide mimics as drugs.

In 1985 Waleed in collaboration with medicinal and structural chemists co-led an effort to effectively develop peptides mimetics as small molecule drugs. The satiety peptide Cholecystokinin (CCK-7) was chosen as the target. Waleed systematically investigated the contribution of each of the amino acids as well as the conformational

(Continued on page 4)

Waleed Danho

(Continued from page 3)

requirement of each of the side chains of the amino acids by synthesizing linear and cyclic peptides of CCK-7, leading to the design of potent cyclic peptide mimetics. He also carried out key studies that led to the discovery of small molecule antagonists of IL-2 and the IL-2 receptor. Taken together, these efforts clearly demonstrated the complexity and challenges associated with using peptide and protein structures as the starting point for small molecule design and provided important guidance for future endeavors.

From 1994 to 1996 Waleed joined the anti-sense research group and was intimately involved in developing strategies for the automated ligation of peptide nucleic acids (PNA) which led to a Roche patented anti-sense technologies platform.

In 1996 Waleed assumed the leadership of a peptide metanocortin-4 (MC-4) receptor agonist program for the treatment of obesity. Waleed's group embarked on establishing the structure-activity-relationship of MC-4 receptor agonists through conformational analysis and synthesis of a large number of linear and cyclic peptides. This led to the discovery of a highly specific and potent cyclic peptide MC-4 receptor agonist, which is currently being evaluated as an anti-obesity agent. During the same period, it was recognized that the melanocortins, specifically the MC-4 subtype, have an effect on erectile function. Under Waleed's leadership an opportunistic program was initiated to identify and develop an MC- 4 agonist for the treatment of male erectile dysfunction, and rapidly led to the discovery of a potent and selective peptide that has entered Phase 2 clinical trials.

Through his pioneering work on the melanocortins, and other GPCR ligands, Waleed developed a strategy to determine the chemical tractability of large peptide ligand GPCRs as targets. More recently, Waleed was involved in the synthesis and design of peptides related to obesity and diabetes, in particular peptide YY. This led to the discovery of truncated, highly selective PYY3-36 (Y2R) agonists as well as strategies for their delivery and extending their duration of action.

Waleed's scientific career has been marked by this unquenchable thirst for success. His enthusiasm and positive thinking is contagious and has been a great asset for the younger chemists who often seek him as an advisor, mentor, and coach. He is a deep and broad thinker and a most honest yet strongly optimism-inspiring debater, with an endless love for science. In addition to outstanding synthetic and analytical skills, he has an unmatched sense of structure and conformation concerning cyclic peptides in particular; computer modeling usually confirms his design and predictions. His academic peers rank him among the world leaders of drug-discovery oriented peptide research. Thus his visibility is highly international and extends over both academia and the pharmaceutical industry.

Also in 2009 Waleed was awarded the Meienhoffer Award at the Roche Colorado Corporation Peptide Symposium (RCCPS09) In Boulder Colorado, for his contribution to "peptide as drugs." Upon learning that he received the Meienhofer Award Waleed proclaimed "It is a tremendous honor to receive such acknowledgement from my colleagues. RCCPS brings together so many innovative minds in the peptide field. I appreciate the effort all of us are making to bring the therapeutic benefits of peptides to the market."

Peptides versus Non-Peptides

Submitted by Maurice Manning

Maurice Manning

The peptide field has been under siege for over two decades by the illusionary promise of non-peptides. It is high time for the peptide community to break this siege by dispelling; once and for all, the myth that non-peptides are superior to peptides as therapeutic agents.

To this end, I and my colleagues have addressed this issue for the vasopressin/oxytocin field in a recent review entitled: "Peptide and non-peptide agonists and antagonists for the vasopressin and oxytocin V_{1a}, V_{1b}, V_2 and OT receptors: research tools and potential therapeutic agents," Manning, M., Stoev, S., Chini, B., Durroux, T., Mouillac, B., Guillon, G., *Prog. Brain Res.* 2008; **170**:473–512. If this review cannot be accessed via PubMed, email me for a pdf (maurice.manning@utoledo.edu).

The review, the first of its kind, deals with both peptide and non-peptide agonists and antagonists of oxytocin and vasopressin. It was written as an attempt to set the record straight with regard to the supposed superiority of non-peptides over peptides in this field, as both pharmacological research tools and as potential therapeutic agents. As this review reveals, the record of non-peptides in the oxytocin/vasopressin field is not all it is cracked up to be. Of the many non-peptide vasopressin V_{1a}, V_{1b}, V_2 and V_{1a}/V_2 receptor antagonists, the numerous oxytocin receptor antagonists and the small number of non-peptide oxytocin and vasopressin agonists listed in Tables 21-24 in this review, only two have been approved by the FDA: Conivaptan (Vaprisol), a V_2/V_{1a} antagonist, and SAMSCA (Tolvaptan), a V_2 antagonist. Conivaptan must be given i.v. in a hospital setting (see pages 494–495). It thus clearly offers no advantage over a peptide V_2/V_{1a} antagonist. Only time will tell whether the very recently approved SAMSCA offers any advantages over Conivaptan.

At the Neuropeptide Conference in Chicago, October 14–16, 2009, it was reported that two additional non-peptides can be added to the list of failed non-peptides in Tables 21–24. One is the Sanofi non-peptide vasopressin V_{1b} antagonist SSR149415, which was reported to be ineffective in a clinical trial for depression, and the other is the Wyeth (now Pfizer) non-peptide oxytocin agonist WAY 267464, which will not be evaluated in a clinical trial.

To dispel the long-held myth that non-peptides are superior to peptides as therapeutic agents, we in the peptide community need to do two things:

1. Carry out an objective assessment of the record of therapeutic successes in the clinic for all non-peptides reported to date. These assessments should be reported in reviews, such as the review mentioned here.
2. Be informed and inform others, especially members of grant review panels and study sections, about the remarkable recent progress in the development of peptide therapeutics.

In this regard, the Peptide Therapeutics Foundation (PTF) Website provides a link to a 2008 Summary Report entitled: "Development trends for Peptide Therapeutics." This very impressive Summary Report provides an up-to-date resume of the truly astonishing progress being made in the development of therapeutically effective peptides. This is exciting reading for peptide chemists. The full 2008 PTF report is expected to be available at an affordable price early in 2010.

In this vein also, a very recent related comprehensive review entitled: "Synthetic therapeutic peptides: science and the market" by Vlieghe, P., Lisowski, V., Martinez, J. and Khrestchatisky, M. in *Drug Discovery Today* (in press) is a must read for all peptide chemists. This timely review clearly shows that the peptide field is undergoing a very exciting renaissance.

Finally, to ensure the continued vitality of the peptide field, our peptide organizations need to be at the forefront of efforts to help the peptide field get its share of research funds; by requesting that peptide chemists be members of Study Sections and grant review panels which review peptide chemistry grants.

FASEB Report on NIH Research Funding Trends Highlights Need for Sustained Funding in FY2011

The Federation of American Societies for Experimental Biology (FASEB) has released an updated compilation of data on research funding at the National Institutes of Health (NIH), as well as a statement about how current trends could affect biomedical research in FY2011. "Based on projections from the President's budget summary, we will see a significant decline in the number of grants in FY2011 at the proposed funding level," said Howard Garrison, Ph.D., Director of FASEB's Office of Public Affairs and author of the data resource. "This represents a reduction of research capacity and the potential delay or interruption of promising new efforts to find treatments and cures for life-threatening diseases."

"While it is clear the President recognized the importance of investing in biomedical research, based on the 3.2 percent increase he proposed in his FY2011 budget, the supplemental appropriations the agency received in FY2010 has created a wealth of emerging opportunities that cannot be ignored," stated Mark O. Lively, Ph.D., FASEB President. "We want to ensure that policymakers understand that our progress against devastating conditions like cancer and Alzheimer's disease depends on sustaining the momentum of our current enterprise. This is more than just a trend in data; it is symbolic of a diminishment of hope."

FASEB hopes the series of graphs and analyses, which provides information on expenditures for research grants, grant numbers, success rates, and average award sizes, will help policymakers understand the case for sustained funding for biomedical research. To that end, FASEB has recommended that Congress appropriate $37 billion for NIH in FY2011.

To view the FASEB NIH data resource, please visit:

http://www.faseb.org/Policy-and-Government-Affairs/Data-Compilations/NIH-Research-Funding-Trends.aspx.

FASEB is composed of 23 societies with more than 90,000 members, making it the largest coalition of biomedical research associations in the United States. FASEB enhances the ability of scientists and engineers to improve – through their research – the health, well-being, and productivity of all people. Our mission is to advance health and welfare by promoting progress and education in biological and biomedical sciences through service to our member societies and collaborative advocacy.

American Peptide Society Member Benefits

- A subscription to *Biopolymers – Peptide Science*
- Discounted subscription rates for the following journals:
  - *Chemical Biology & Drug Design*
  - *International Journal for Peptide Research & Therapeutics*
  - *Protein and Peptide Letters*
  - *Current Protein & Peptide Science*
  - *Current Proteomics*
- Free professional position and resume posting on the website
- Membership in the Federation of American Societies for Experimental Biology (FASEB)
- Reduced membership rates for students and postdocs
- Travel grants to symposia for qualified graduate students and postdocs.

For more information, please visit our website:

http://www.AmPepSoc.org

Please note that our mailing address has changed to:

American Peptide Society
P.O. Box 13796
Albuquerque, NM 87192

World Wide Events

2010 AAPS National Biotechnology Conference, May 16 - 19, 2010
Hilton San Francisco Union Square
San Francisco, California
For more information:
http://www.aapspharmaceutica.com/nationalbiotech

24th Annual Symposium of The Protein Society, August 1 - 5, 2010
Manchester Grand Hyatt
San Diego, California
For more information:
http://www.proteinsociety.org

31st European Peptide Symposium, September 5 - 9, 2010
Bella Center, Center Boulevard 5
2300, Copenhagen, Denmark
For more information:
http://www.31eps.dk/

14th International Biotechnology Symposium and Exhibition, September 14 - 18, 2010
Rimini, Italy
For more information:
http://www.ibs2010.org

4th Pharmaceutical Sciences World Congress (PSWC), November 14 - 18, 2010
New Orleans, Louisiana
For more information:
http://www.aapspharmaceutica.com

5th International Peptide Symposium, December 4 - 9, 2010
Kyoto International Conference Center, Kyoto, Japan
For more information:
http://www.5ips.jp/

Pacifichem 2010, December 18 - 19, 2010
Hawaii Convention Center
Honolulu, Hawaii
For more information:
http://www.pacifichem.org/

31st European Peptide Symposium Copenhagen, Denmark, September 5 – 9, 2010

The 31st European Peptide Symposium will take place September 5 – 9, 2010 at the Bella Center in Copenhagen, Denmark, and will be chaired by Morten Meldal, Knud J. Jensen and Thomas Hoeg-Jensen. The meeting venue is conveniently located near the charming and cultural Copenhagen city centre.

Please join your colleagues from around the world at this meeting, which will include cutting-edge research and fascinating developments in a broad range of topics presented by leading international experts from both industry and academia. The confirmed invited speakers are presently Bill Degrado, Stephen Kent, Tom Muir, Herbert Waldmann, Fernando Albericio, Paul Alewood, Annette Beck-Sickinger, Ernest Giralt and Horst Kessler.

The 31EPS will allow you to present your latest results and will provide ample opportunity to meet colleagues with similar or complementary research interests. To accommodate as many high-quality talks as possible, there will be a few parallel sessions in addition to the plenary sessions and a special session for young investigators. The poster sessions will take place in a large hall adjacent to the exhibition area, where the latest research tools and services will be presented by international companies. At 31EPS, an inspiring atmosphere for the exchange of ideas and for building long-lasting collaborations will be established.

Potential exhibitors and sponsors are welcome to contact the conference secretariat: 31EPS, DIS Congress Service, telephone: +45 44 92 44 92; email: 31eps@discongress.com; http://www.31eps.dk.

5th International Peptide Symposium Kyoto, Japan, December 4 – 9, 2010

It is a great pleasure and honor to host the Fifth International Peptide Symposium (5th IPS) to be held on December 4 – 9, 2010, in Kyoto, Japan. The conference is presented in conjunction with the 47th Japanese Peptide Symposium, and organized under the auspices of the Liaison Committee of international peptide societies: American Peptide Society, Australian Peptide Association, Chinese Peptide Community, European Peptide Society, Indian Peptide Society, Korean Peptide Protein Society, and Japanese Peptide Society. The 5th IPS is a cooperation of numerous academic societies in Japan, and is supported by the Ministry of Education, Culture, and Sports, Science and Technology (MEXT) of Japan.

The Symposium will cover a wide spectrum of topics related to peptide sciences. Internationally distinguished speakers will be invited to present results of their innovative research. Please join us in the 5th IPS to exchange the latest scientific information while renewing old friendships and establishing new ones.

Potential sponsors and exhibitors are welcome to contact the conference secretariat: Congress Corporation, E-mail: 5ips@congre.co.jp.

Please visit our website for the latest information: http://www.5ips.jp. We look forward to seeing you in Kyoto!

Yoshiaki Kiso, Chair
Nobutaka Fujii, Co-Chair
5th International Peptide Symposium

5th IPS Information

Special Guest Speakers:

Ada E. Yonath (Israel), Kurt Wüthrich (Switzerland)

Distinguished Speakers:

Annette Beck-Sickinger (Germany), Ettore Benedetti (Italy), Jeffrey Bode (Switzerland), Virander Chauhan (India), Ernesto Freire (USA), Samuel H. Gellman (USA), Ernest Giralt (Spain), Kyung-Soo Hahm (Korea), Itaru Hamachi (Japan), Hironobu Hojo (Japan), Ferenc Hudecz (Hungary), Yasuhiro Kajihara (Japan), Kenji Kangawa (Japan), Toru Kawakami (Japan), Stephen Kent (USA), Horst Kessler (Germany), Lei Liu (China), Dawei Ma (China), Jean Martinez (France), Morten Meldal (Denmark), Naoto Minamino (Japan), Hidehito Mukai (Japan), Kazuwa Nakao (Japan), Akira Otaka (Japan), Joel Schneider (USA), Yechiel Shai (Israel), Ian Smith (Australia), Hiroaki Suga (Japan), James P. Tam (Singapore)

Important Dates:

Final Announcement and Call for Abstracts May 2010
Abstracts Submission Deadline July 2010
Early Registration Deadline September 2010

Symposium Secretariat:

5th IPS
c/o Congress Corporation
3-6-13 Awajimachi, Chuo-ku
Osaka 541-0047
Japan
Website: http://www.5ips.jp/
E-mail: info@5ips.jp

Pacifichem 2010, Hawaii Convention Center, Honolulu, Hawaii, USA, December 18 and 19, 2010

Announcing an upcoming symposium at Pacifichem 2010 in the topic area of Biological Chemistry: Frontiers in Peptide Chemistry: Synthesis and Applications (#41)
Organized by: John C. Vederas, Steven L. Castle, Craig Hutton, Shiroh Futaki, Ian Smith, Jeff Kelly, Dawei Ma and William D. Lubell

Peptide science has grown rapidly in recent years due to interest in the synthesis of these natural products, and their utility for various applications in the fields of medicine, catalysis and nanotechnology. Focusing on recent developments in the chemistry and biology of these polyamide oligomers as well as organic molecules designed to mimic their form and function, this symposium will serve to highlight a broad variety of subjects in which peptides are synthesized and employed today. For example, peptides as therapeutics will be featured, in the light of the rapid growth of the market for peptides, which now outpaces twice as fast as the overall pharmaceutical market due to an increased number of targets and improved delivery methodologies. Similarly, the use of peptides in nanotechnology will be presented as this field has expanded rapidly in recent years because of the remarkable utility of peptides to serve as templates for the assembly of supramolecular architectures in a predetermined manner. Focus will include the synthesis of novel peptide natural products and peptide mimics possessing challenging architectures. Moreover, this symposium will reflect the impact of peptide science in cross-disciplinary research including chemistry, physics, biology, medicine and engineering.

For further information, visit the website http://www.pacifichem.org or email lubell@chimie.umontreal.ca.

American Peptide Society Newsletter

Published quarterly by the American Peptide Society, http://www.americanpeptidesociety.org.

We are always seeking items for your society's newsletter, either scientific or personal, as long as they are relevant to the field of peptide science, the Society, and its members. Please email your news items, along with any photos or graphics, to Ellen Brenner at apsnewsletter@americanpeptide-society.org. Items should be either Microsoft Word document attachments, or plain text included in the body of the email. Photos and other graphics should be high-resolution JPEG, PNG or EPS files. Please do not send photos or graphics embedded in Word documents.

Thanks to Our Sponsors:

BACHEM

PolyPeptide GROUP