

FOCUS: MASS SPECTROMETRY-BASED STRATEGIES
FOR NEUROPROTEOMICS AND PEPTIDOMICS: EDITORIAL

Focus on Mass Spectrometry-Based Strategies for Neuroproteomics and Peptidomics, Honoring Dr. Lingjun Li, Recipient of the 2014 ASMS Biemann Medal

This special Focus Issue of the *Journal of the American Society for Mass Spectrometry* celebrates the accomplishments of Dr. Lingjun Li, the recipient of the 2014 ASMS Biemann Medal. Lingjun is the Vilas Distinguished Achievement Professor and Professor of Pharmaceutical Sciences and Chemistry at the University of Wisconsin-Madison (UW-Madison).

She received her B.E. degree in Environmental Analytical Chemistry from Beijing University of Technology, China, and her Ph.D. degree in Analytical Chemistry/Biomolecular Chemistry from the University of Illinois at Urbana-Champaign (UIUC) in 2000 under the supervision of Professor Jonathan Sweedler. She then did postdoctoral research at the Pacific Northwest National Laboratory (with Dr. Richard Smith) and Brandeis University (with Professor Eve Marder) before starting her independent career at UW-Madison in December 2002.

In addition to receiving the Biemann Medal, she has been recognized with numerous other awards, including an NSF CAREER Award, a Sloan Research Fellowship, the ASMS Research Award in 2004, and the 2011 Pittsburgh Conference Achievement Award. Dr. Li has been active with the Chinese American Society for Mass Spectrometry (CASMS), serving as President and a member of the Executive Team.

Dr. Li and her team have created several multi-faceted and integrated MS-based platforms that include high resolution in-situ peptide mapping, tissue imaging, in vivo microdialysis, high sensitivity micro-separation techniques coupled with tandem MS de novo sequencing, new isotopic and isobaric labeling strategies for comparative and quantitative proteomics and peptidomics strategies, and improved bioinformatics tools to allow large-scale discovery and functional analysis of novel neuropeptides. More recently, the Li group also employed a novel use of ion mobility MS to address several remaining technical challenges associated with peptidomics research. They developed a novel site-specific strategy to rapidly and precisely localize peptide epimers, and new strategies to probe peptide sequence scrambling and peptide misidentification and to improve isobaric tandem mass tag quantification in quadrupole time-of-flight (QTOF) based instrumentation.



Lingjun Li (left) and ASMS President Sue Weintraub at the 2014 ASMS Conference (Baltimore, MD)

Many of these integrated platforms and multifaceted approaches have been used by Lingjun's group to address a variety of applications, including the discovery of protein biomarkers in neurodegenerative diseases. However, she is perhaps best known for her contributions to the field of peptidomics. For example, Professor Li and her group discovered more than 300 novel neuropeptides in crustacean model organisms whose genomic sequences are currently unavailable. These findings significantly expanded our knowledge about neuropeptides in these important model organisms and transformed current understanding of neuropeptide family organization and functional consequences of neuropeptide multiplicity.

The subject of this Focus Issue is to highlight MS-based strategies for neuroscience and neuroproteomics applications, with special emphasis on neuropeptides and peptidomics. In an excellent review article by one of the contributors to this Focus Issue, *peptidomics* has been defined as “the comprehensive characterization of peptides present in a biological sample...



Lingjun Li with her former postdoctoral mentor, Dick Smith (left), at the 2014 ASMS Conference (Baltimore, MD). (Photo courtesy of Rong Wang, Icahn School of Medicine at Mount Sinai)

Peptidomics is a specific subdiscipline of proteomics, the characterization of proteins in a biological sample.”[1] “Endogenous, native peptides cover a multitude of biological functions without which life would not exist.” One might consider peptidomics to be far less complex and *easier* than proteomics because sample digestion is not required typically, and the smaller size of peptides compared with proteins. However, “endogenous peptides range considerably in size and properties, and MS/MS sequence determination from 5+ to 10+ charge states is not a trivial task,” and de novo peptide sequencing is still challenging.

But mass spectrometry is a key enabling technology for the growing field of peptidomics. This special Focus Issue that honors Lingjun Li’s Biemann Medal and reflects Lingjun’s interests and accomplishments contains papers devoted to the development and application of mass spectrometry for neuroproteomics and peptidomics. All of the invited authors were suggested by Lingjun herself. Vivian Hook (University of California, San Diego) comments on the accomplishments and the future promise of neuroproteomics and peptidomics to provide solutions to human diseases. The limitations of approaches for quantitative peptidomics and peptide identifications and the issues to be aware of to properly interpret results are discussed by Lloyd Fricker (Albert Einstein College of Medicine). Lingjun Li’s group (University of Wisconsin-Madison) combined high resolution MALDI Orbitrap-based imaging mass spectrometry with data-dependent acquisition (DDA) tandem MS analysis and gas-phase fractionation for in situ characterization of the crustacean neuropeptidome with improved chemical information. An optimized informatics pipeline that includes database searching with approaches for identification and label-free quantification for high throughput, quantitative peptidomics analysis is proposed in the paper by Dick Smith’s group (Pacific Northwest National Laboratory). The role of neuropeptides in nematode *Ascaris suum* behavior

was explored by MALDI-TOF mass spectrometry-based peptidomics and is described in the paper by Antony Stretton (University of Wisconsin-Madison). A report by Boris Van Hiel of the Functional Genomics and Proteomics group at KU Leuven (Belgium; headed by Liliane Schoofs) discussed the use of LC-MS/MS to identify putative bioactive neuropeptides from the medically and economically important tsetse fly. Peter Verhaert (Delft University of Technology, The Netherlands; now at Lund University, Sweden and Antwerp University, Belgium) and coworkers describe a protocol for targeted de novo sequencing for the identification of several novel inter- and intra-molecular disulfide bond containing peptides from amphibian skin defensive secretions. Jonathan Sweedler’s group (University of Illinois at Urbana-Champaign) used MS-based strategies to characterize peptides contained within and secreted from dorsal root ganglion nerve cell bodies to aid the understanding of the chemical composition of the mammalian peripheral sensory-motor system. LC-MS/MS and electrophoresis were used (Xianquan Zhan, Central South University, China) to identify nitrotyrosine-modified proteins in human astrocytoma tissue and to provide insights on the potential role of tyrosine nitration in the pathogenesis of astrocytoma formation and brain cancer.

- (1) “Neuropeptidomics Mass Spectrometry Reveals Signaling Networks Generated by Distinct Protease Pathways in Human Systems” by Vivian Hook and Nuno Bandeira
- (2) “Limitations of Mass Spectrometry-Based Peptidomic Approaches” by Lloyd D. Fricker
- (3) “High Throughput in situ DDA Analysis of Neuropeptides by Coupling Novel Multiplex Mass Spectrometric Imaging (MSI) with Gas Phase Fractionation” by Chuanzi OuYang, Bingming Chen, and Lingjun Li
- (4) “An Optimized Informatics Pipeline for Mass Spectrometry-Based Peptidomics” by Chaochao Wu, Matthew E. Monroe, Zhe Xu, Gordon W. Slys, Samuel H. Payne, Karin D. Rodland, Tao Liu, and Richard D. Smith
- (5) “Mass Spectrometry of Single GABAergic Somatic Motoneurons Identifies a Novel Inhibitory Peptide, As-NLP-22, in the Nematode *Ascaris suum*” by Christopher J. Konop, Jennifer J. Knickelbine, Molly S. Sygulla, Colin D. Wruck, Martha M. Vestling, and Antony O. W. Stretton
- (6) “Peptidomics of Neuropeptidergic Tissues of the Tsetse Fly *Glossina morsitans morsitans*” by Jelle Caers, Kurt Boonen, Jan Van Den Abbeele, Liesbeth Van Rompay, Liliane Schoofs, and Matthias B. Van Hiel
- (7) “Screening Method for the Discovery of Potential Bioactive Cysteine-Containing Peptides using 3D Mass Mapping” by Luuk N. van Oosten, Mervin Pieterse, Martijn W. H. Pinkse, and Peter D. E. M. Verhaert
- (8) “Peptidomics and Secretomics of the Mammalian Peripheral Sensory-Motor System” by Emily G. Tillmaand, Ning Yang, Callie A. C. Kindt, Elena V. Romanova, Stanislav S. Rubakhin, and Jonathan V. Sweedler

- (9) “Nitroproteins in Human Astrocytomas Discovered by Gel Electrophoresis and Tandem Mass Spectrometry” by Fang Peng, Jianglin Li, Tianyao Guo, Haiyan Yang, Maoyu Li, Shushan Sang, Xuejun Li, Dominic M. Desiderio, and Xianquan Zhan

Given Professor Klaus Biemann’s long interest and pioneering contributions to peptide MS, it is very appropriate for Lingjun Li to have received the Biemann Medal. On behalf of the editors at *JASMS* and Lingjun’s friends and former and present colleagues, I congratulate Lingjun for her much-deserved award.

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References

1. Schrader, M., Schulz-Knappe, P., Fricker, L.D.: Historical perspective of peptidomics. *EuPA Open Proteomics* **3**, 171–182 (2014)