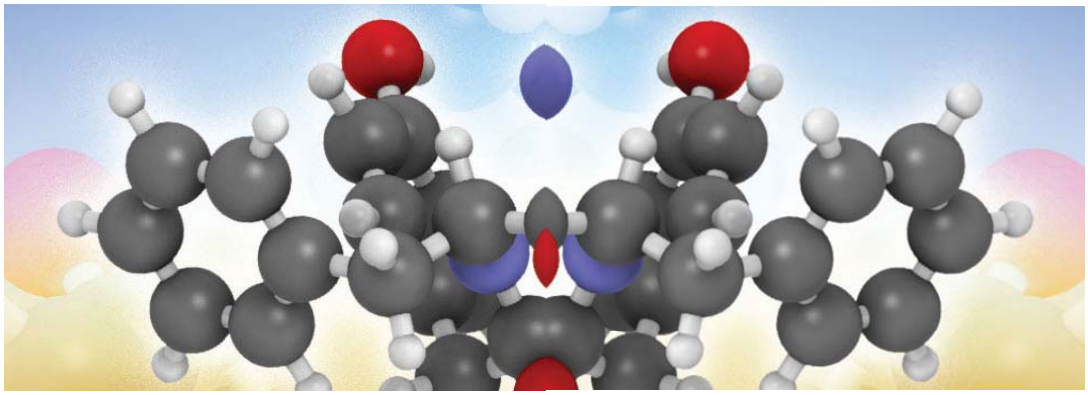


5th USP Workshop on Therapeutic Peptides: Regulations, Standards and Quality

November 5-6, 2018

Speaker Biographies & Abstracts (listed alphabetically)

Fouad Atouf, Ph.D.
Vice President, Science-Global Biologics
U.S. Pharmacopeia
Rockville, Maryland

Fouad Atouf is Vice President, Science—Global Biologics, for USP. He leads all scientific activities related to the development and maintenance of documentary and reference standards for biologics and antibiotics, and oversees the biologics laboratories in USP–U.S. and USP–India. His department supports the work of the associated USP Expert Committees. Dr. Atouf has been at USP for over 10 years and served in a variety of scientific leadership roles including being the regional champion for the Middle East and North Africa Region, where he helped facilitate programs designed to enhance the understanding of the role of regulations and standards in the registration of medicinal products. Dr. Atouf has strong background and experience in the development and regulation of *cellular and tissue-based products*. Prior to joining USP in 2006, his research at the U.S. National Institutes of Health focused on developing methods for the *in vitro* generation of cell-based therapies for diabetes. Dr. Atouf is the author of numerous publications in peer-reviewed journals and a frequent speaker at national and international scientific conferences. Dr. Atouf earned his Master's degree in Biochemistry and his Ph.D. in Cell Biology from the Pierre & Marie Curie University, Paris, France.

Presentation
USP Welcome
Monday, November 5, 2018, 8:30 – 8:40 a.m.

Michael Berger
Director Quality Control I
Bachem AG
Bubendorf, Switzerland

Michael Berger received his education in analytical chemistry at the University of Applied Sciences in Burgdorf, Switzerland in 1993. After 5 years in different roles in method development, project management and QA at an analytical contract laboratory, he joined Bachem in 1998 as a QC laboratory head. In the meantime and in various roles, he managed all kinds of challenges in the field of analytical peptide chemistry. In his current position Michael is running Bachem's department for analytical project management including the development, implementation and validation of analytical methods as well as the introduction of new analytical technologies.

Presentation
Quantitative HPLC determination of D-His-Glucagon with Proteolytic Sample Preparation
Monday, November 5, 2018, 2:55 – 3:15 p.m.

Although epimerization of amino acids is generally one of the challenges of peptide synthesis and characterization, only few amino acids remain notorious problem makers even with modern techniques. One of them is histidine that may epimerize post-synthesis in the finished peptide at certain conditions. Moreover, impurities with epimerized histidine frequently co-elute with the target peptide in RP-HPLC. Special methods such as IEX-HPLC or chiral GC amino acid analysis must be applied in such cases. An alternative method for the quantitative determination of D-His-Glucagon in Glucagon will be presented. The method comprises a proteolytic digest of the Glucagon sample followed by HPLC quantitation of the histidine-containing peptide fragment. The method can be validated for routine release analysis and represents an example for a general application with histidine-containing peptides. The approach has already been applied successfully for several other peptides with histidine isomers that were difficult to separate otherwise.

Jordan Chill, Ph.D.
Associate Professor
Bar Ilan University
Ramat Gan, Israel

Dr. Jordan Chill is a returning scientist from the National Institutes of Health (NIH) and Senior Lecturer in Bar Ilan University's Department of Chemistry.

During his PhD studies (with Prof. Jacob Anglister, Weizmann Institute) Dr. Chill studied the structure of the cellular receptor for interferon (IFN) in humans, resulting in the first available structure of the IFN receptor, as well as a map of hydrophobic and electrostatic interactions by which the receptor recognizes its ligand and begins the IFN signaling pathway. These findings can now be utilized by pharmaceutical companies to search for more effective IFN-based therapies. During his post-doctoral studies (with Dr. Ad Bax, NIDDK/NIH, USA) Dr, Chill focused on membrane-associated proteins (MPs), hydrophobic proteins which are embedded in the cellular membrane and are involved in transport, recognition and membrane structure. At the NIH Chill learned and designed new NMR methods sufficiently sensitive to obtain structural information for a 68-kDa ion channel, an incredible size for an NMR study.

Dr. Chill arrived at Bar-Ilan University in October 2007 and formed the bio-NMR lab. His research group applies NMR methods to study the structure, dynamics and function of proteins with an emphasis on MPs, and with possible applications to health and disease. In June 2008 the Ultra-shielded 700-MHz Bruker spectrometer was successfully installed, including a cryogenic probe optimized for 13C detection. This experimental setup allows the group to run state-of-the-art experiments for studying proteins. The group includes a research assistant and six graduate students. Since milligram quantities of proteins are required for acquisition of NMR data, the group invests significant efforts in optimization of protein overexpression in bacterial systems, and purification using analytical and biochemical methods so that sufficiently pure protein samples can be prepared. NMR measurements conducted on these samples offer structural and dynamic information which uncovers the structural basis of the functions observed for proteins.

Presentation
Just What the Doctor Ordered: How NMR Can Address Challenging Cases of Peptide Drug Characterization
Monday, November 5, 2018, 2:35 – 2:55 p.m.

Nuclear magnetic resonance (NMR) spectroscopy offers molecular insights into the composition, structure and folding of peptides and proteins. While other analytical methods such as mass spectrometry and LC-MS are routinely available to synthetic and quality control labs, advanced NMR techniques required for larger peptides remain less accessible. This accounts for the under-utilization of NMR in analytical characterization of bioactive peptides despite its unique capabilities and the considerable increase in submitted peptide drug applications. This presentation will briefly review how NMR can address complex structural questions in polypeptides, and focus on two case studies in which NMR was instrumental in providing the information necessary for accurate characterization of peptide drugs. Introducing pharma and synthetic chemistry teams to the rich world of peptide NMR will hopefully add new analytical tools to their arsenal of approaches for characterization of polypeptide APIs and solve sticky ‘sameness’ questions in an effective manner.

Michael De Felippis, Ph.D.
USP Affiliation: *Chair, USP BIO1 – Peptides and Insulins Expert Committee*

Distinguished Research Fellow
Eli Lilly and Company
Indianapolis, Indiana

Michael R. De Felippis joined The Lilly Research Laboratories of Eli Lilly and Company in 1990 after obtaining his doctorate in biochemistry from The Ohio State University. He is currently a Distinguished Research Fellow in the Bioproduct Research and Development division. His work focuses on commercializing biopharmaceutical products with particular emphasis on characterizing physicochemical properties, devising control strategies, and preparing CMC-related documentation to support product licensure in global markets. Dr. DeFelippis has published manuscripts, review articles and book chapters on the subjects of protein and peptide structural characterization and formulation design/delivery strategies.

Presentation
Workshop Overview
Monday, November 5, 2018, 8:40 – 8:50 a.m.

Workshop Wrap-up
Tuesday, November 6, 2018, 2:25 – 2:40 p.m.

Jesse Dong, Ph.D.
Vice President, Peptide Chemistry
Neon Therapeutics
Cambridge, Massachusetts

Jesse Z. Dong, Ph.D., is Vice President, Peptide Chemistry at Neon Therapeutics. At Neon he is leading the peptide chemistry activities of developing neoantigen cancer vaccines, process development and tech support for cGMP manufacturing. Prior to joining Neon, Jesse worked at Ipsen as Vice President of Compound Discovery, heading global Peptide Chemistry Division and leading peptide-based R&D programs. He is the inventor of TYMLOS™ (Abaloparatide), Setmelanotide, Relamorelin and Taspoglutide. Jesse is named inventor or co-inventor in 68 issued US patents and over 80 US patent applications. He is a co-author of 149 publications and abstracts.

Presentation
Development of Personal Cancer Vaccine NEO-PV-01
Tuesday, November 6, 2018, 1:05 – 1:25 p.m.

Neon Therapeutics, a clinical-stage immuno-oncology company developing neoantigen-based therapeutics, has pioneered a proprietary neoantigen platform to develop a personal cancer vaccine, NEO-PV-01. The neoantigen-targeting peptides in the vaccine are intended to engage the immune system to precisely and selectively attack tumors. Our objective is to create and deepen anti-tumor immune responses and broaden the range of cancers treatable via immuno-oncology approaches.

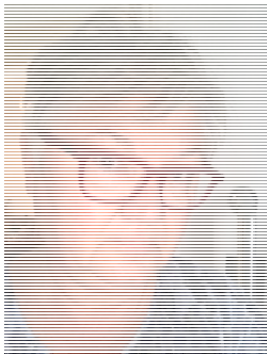
The manufacturing schematic of NEO-PV-01 will be discussed as well, which includes the automated and scalable peptide manufacturing processes that we believe provide advantages in both turnaround times and manufacturing capacities.

Scott Frank, Ph.D.
Senior Research Advisor
Eli Lilly and Company
Indianapolis, Indiana

Scott received his B.S. in chemistry from Illinois State University and his doctorate in organic chemistry from Indiana University in 2000. Scott joined Eli Lilly and Company as a Senior Organic Chemist in 2001 in Discovery Chemistry Research and Technology. In 2004, he transitioned to Chemical Product Research and Development. As a member of that organization, Scott has had a number of scientific roles supporting both early and late phase molecule development. Additionally, he has served in a role as director until 2017, at which time he returned to the research path as a Senior Research Advisor. In his current position, Scott is responsible for commercialization activities and strategies for both small molecule and synthetic peptide assets, encompassing early phase integration and late phase interface with commercial manufacturing. Scott is an author or co-author on multiple publications and an inventor on several patents. His interests include continuous manufacturing as well as phase appropriate analytical and control strategy development, and leveraging these approaches to reduce CMC costs and overall cycle times.

Presentation
Bioassay and a Phase Appropriate Control Strategy for Synthetic Therapeutic Peptides APIs
Tuesday, November 6, 2018, 9:25 – 9:45 a.m.

Biological Cell Based Assays are a required specification test to determine the potency of biopharmaceutical products. Regulatory agencies require this information to approve biologic pharmaceuticals even for early phases of clinical development. However, the regulatory opinion around synthetic peptides is ambiguous. These molecules vary in terms of molecular size and complexity as well as route of manufacture. Moreover, they do not fit well into guidance documents related to pharmaceuticals or biopharmaceuticals. This talk will discuss the purpose of cell based bioassays with respect to higher order structure, when bioassay development is important as well as the use of alternate and complimentary analytical techniques to structurally characterize synthetic peptide therapeutics.



Gyöngyi Gratzl, Ph.D.
USP Affiliation: *Member, USP BIO1 – Peptides and Insulins Committee*

Group Leader, Senior Scientist
Hikma Pharmaceuticals
Bedford, Ohio

Gyöngyi Gratzl has over 25 years pharmaceutical experience in developing analytical methods and parenteral formulations for peptides, proteins and glycoproteins in academia (Univeristy of Utah, Cleveland Clinic etc.) and industrial settings like Boehringer-Ingelheim. She has a passion for peptide, glycoprotein characterization with wide range of bioanalytical techniques and bioassay development. Her specialties are spectroscopic, light scattering and biological assay development. Currently, she is leading the biological formulation research and development group at Hikma. Her focus is on lyophilization cycle development and stable peptide liquid formulation development for medical devices.

Presentation
Therapeutic Peptide Aggregation Studies with Orthogonal Techniques
Tuesday, November 6, 2018, 10:45 – 11:05 a.m.

Peptide aggregation can occur through chemical or physical degradation and is dependent on the thermodynamic stability of the peptide's native state. The driving force behind peptide aggregation is the reduction in free surface energy by the removal of hydrophobic residues from contact with the solvent. Peptide aggregation can be reversible or irreversible and the aggregates formed can be soluble/insoluble, covalent/non-covalent and native/non-native. Peptide aggregation is a nucleation/growth phenomenon. A lag phase exists at the initial state since there is an energy barrier to nucleation, which specifically is the free energy necessary to create a new solid–liquid interface. The energy barrier is highest when reaching a critical size for the new phase, when nucleus growth can proceed. Insoluble aggregates form when the aggregates are large enough to exceed their solubility. The further growth of these aggregates will occur in the direction that creates an orientation with the lowest free energy to assemble, which can result in an ordered morphology e.g. fibrils. Peptide aggregates can show a large variety of sizes from dimers or or several nanometers to hundreds of micro-meters. Nucleation is considered to be the initiating stage for most peptide aggregation process in solution. It is therefore beneficial to reduce all soluble aggregates in the bulk drug product to aid long-term stability. This presentation will discuss orthogonal aggregation measurement techniques with case studies to cover the wide size range (1 nm to 100 µm) and different type of aggregates focusing on each technique's advantages and limitations:

1. Chromatographic techniques (reversed phase and size exclusion chromatography)
2. Sedimentation velocity analytical ultracentrifuge
3. Ion mobility mass spectrometry
4. Static and dynamic light scattering
5. Field-flow fractionation
6. Imaging techniques

Peptide aggregation can be initiated by a number of factors, including temperature (e.g. freeze-thaw), ionic strength and interfacial exposure (solid–liquid, liquid–liquid, gas–liquid). These factors interact with the engineering environment of the production process which dictates the micro-environment the peptide product encounters, e.g. mixing rate, temperature during compounding, filling etc. Examples will be shown, how process parameters can effect peptide aggregation.

Norbert Hilf, Ph.D.
Vice President, Translational Development
immatics biotechnologies GmbH
Tuebingen, Germany

Norbert Hilf, Ph.D., is Vice President Translational Development of Immatics biotechnologies GmbH, a biotech company located in Germany and Texas dedicated to developing T-cell based immunotherapies against cancer. Dr. Hilf studied biochemistry, having received his doctoral degree in Biochemistry / Immunology from the University of Tuebingen, Germany working in the Department of Immunology headed by Hans-Georg Rammensee. Dr. Hilf joint Immatics biotechnologies when the company was founded in 2004. Initially, his work focused on the development of multi-peptide cancers vaccines and on the transition of such vaccines into early phase clinical trials. More recently, Dr. Hilf's department is also involved in the translation of Immatics' other treatment modalities into clinical development, including adoptive cellular therapies and bispecific T-cell receptors.

Presentation
The GAPVAC Project: Active Personalization of Peptide Vaccines for Patients with Newly Diagnosed Glioblastoma
Tuesday, November 6, 2018, 1:25 – 1:45 p.m.

The need for treatment personalization in cancer therapy is evident as every tumor is molecularly unique. Especially immunotherapy should, for optimal efficacy, be customized to the highly individual antigenic landscape of every tumor. Glioblastoma (GB) are immunologically regarded as resistant and "cold" with an average of 30-50 mutations. This tumor type can thus be considered poor in addressable neoantigens. To fully exploit all available antigens in GB, mutation-derived neoantigens as well as non-mutated antigens that are over-presented in the individual tumor should be addressed.
Methods:
The GAPVAC Consortium realized an immunotherapy, in which patients with newly diagnosed glioblastoma (N=16) were offered two complementary peptide-based actively personalized vaccines (APVAC) based on the mutational landscape, transcriptome and immunopeptidome of the individual tumors. For APVAC1, up to 7 non-mutated human leukocyte antigen (HLA) A*02:01- or A*24:02-restricted, GB-associated antigens were selected from a pre-manufactured warehouse of synthetic peptides allowing fast 'off-the-shelf' formulation. APVAC1 vaccines were completed by addition of 2 HLA class II restricted peptides and a viral marker peptide. APVAC2 contained 2 *de novo* manufactured peptides per patient, preferentially neo-epitopes targeting private tumor mutations. Non-GMP pre-synthesis was implemented to assess manufacturability before entering GMP manufacturing. APVAC vaccinations (i.d.) with GM-CSF and poly-ICLC were applied concomitant to standard therapy. Regulatory approval in five European countries was achieved based on a standardized APVAC selection and core manufacturing process with variable, patient-tailored drug products as outcome.
Results:
Design and manufacturing of personalized APVACs was successful for all patients demonstrating the feasibility of the complex personalization approach. Manufacturing issues, occurring during the APVAC1 as well as the APVAC2 production process, could in all cases be successfully handled. For APVAC2, analyses revealed between 19 and 84 somatic, non-synonymous mutations in the patients' tumors. None of these could be confirmed in the actual immunopeptidome of the patient's tumor by mass spectrometry and there is growing evidence that this is at least in part caused by biological attrition from the mutation to HLA-presented mutated peptides. Thus, for APVAC2, mutated antigens (19mer peptides) were mainly selected

based on predicted HLA class I epitopes.
Short, non-mutated APVAC1 antigens induced sustained $CD8^+$ T-cell responses. 51% of vaccinated APVAC1 class I peptides were immunogenic. 85% of the mutated APVAC2 peptides induced predominantly multi-functional $CD4^+$ T-cell responses of favorable T_H1 type; 45% of APVAC2 peptides induced also $CD8^+$ T-cell responses. Median OS was 29 months from diagnosis for patients that received APVAC vaccinations (N = 15). The safety profile of vaccinations was favorable and consistent with the mechanism of action of the vaccinations.

Conclusions:

The GAPVAC approach demonstrated safety and feasibility of peptide-based personalized vaccinations combining a warehouse-based and *de novo* manufacturing concept. For targeting of neo-epitopes, the choice of the relevant (i.e. HLA presented) mutations and peptides is challenging. For targeting of non-mutated cancer antigens, a warehouse concept of synthetic peptides is ideally suited. Possibly, the GAPVAC concept can be extrapolated to future developments of personalized vaccines.

S. Rafat Husain, Ph.D.
Senior Research Scientist
U.S. Food & Drug Administration
Silver Spring, Maryland

Dr. Husain is a Senior Staff Scientist at the Tumor Vaccines and Biotechnology Branch, Division of Cellular and Gene Therapies, Office of Tissues and Advanced Therapies, CBER, FDA. He has been working at the CBER, FDA for the past 22 years. He is a scientific expert on regulatory issues for products related to the clinical use of cancer vaccines, immunotherapeutic products and plasmid gene transfer for cancer therapy. His research projects involve the understanding of tumor biology and identification of potential tumor-associated antigens that can be used to establish identity and potency of cancer vaccines. Dr. Husain has published more than 70 research and regulatory articles in peer-reviewed journals and as book chapters. He is actively engaged in outreach activities to assist stakeholders to bring investigational products to the market.

Presentation
Current Regulatory Perspectives on Therapeutic Peptide Vaccines
Tuesday, November 6, 2018, 1:45 – 2:05 p.m.

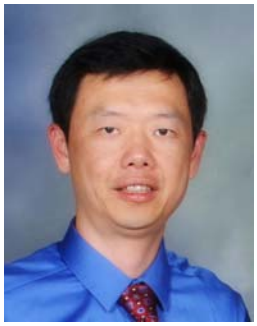
Recent advances in cancer vaccines and immunotherapies promise a number of innovative treatments for cancer patients. Peptide-based cancer vaccines are an attractive approach that relies on the usage of short peptide fragments to elicit peptide-specific T cell responses in the peripheral blood of cancer patients. The encouraging results from first-generation short peptide-based cancer vaccines prompted exploration of next generation vaccines using synthetic long peptides 20-35 amino acids in length. More recently, personalized vaccines tailored to match a patient's cancer mutations are also under development. More than 150 active clinical trials using peptide-based therapeutic vaccines are being reviewed by the Office of Tissues and Advanced Therapies (OTAT). Most of them are intended to be used as cancer vaccines. The quality attributes of these vaccine products can be complex, and often difficult to characterize. This presentation will discuss the type of products reviewed by OTAT and the manufacturing challenges of peptide-based cancer vaccines.

Jan Jezek, Ph.D.
Chief Scientific Officer
Arecor
Essex, United Kingdom

Dr. Jezek is the Chief Scientific Officer at Arecor Ltd. He has been trained as a biophysical chemist, and was the principal scientist at Insense Ltd, leading the development of a range of novel medical devices from the proof-of-concept all the way to market. During his time at Insense, he and his team developed a novel formulation platform to achieve superior stability of proteins and peptides. His inventions related to protein stabilisation led to inception of Arecor Ltd as a separate company focusing on commercialisation and further development of the stabilisation platform. Dr. Jezek is responsible for scientific development of Arecor's technology as well as its commercial application and associated intellectual property. He is the author of several papers and a number of patents which underpin Arecor's technology.

Presentation
Development of Differentiated Peptide Therapeutic Products using an Innovative Formulation Technology
Monday, November 5, 2018, 11:55 a.m. – 12:15 p.m.

The competition in the peptide therapeutic market is increasing and successful product development requires a number of good decisions to be made with respect to the target product profile, formulation, delivery device and intellectual property. Convenience of administration and consequent patient adherence have become a major driving force toward improved products, both for new peptide therapeutic entities and for life cycle management of existing ones. This talk will present several case studies demonstrating how innovative formulation of selected peptide therapeutics can achieve superior product profiles, enabling products with improved storage stability, convenience of use and desirable in vivo properties. The case studies will focus on peptides used in the treatment of diabetes as well as other conditions.



Xiaohui (Jeff) Jiang, Ph.D.
Deputy Division Director
U.S. Food & Drug Administration
Silver Spring, Maryland

Xiaohui (Jeff) Jiang received his Ph.D. in chemistry from the University of California, San Diego. Currently he is the Deputy Director of the Division of Therapeutic Performance in the Office of Research and Standards, under the Office of Generic Drugs. His work at the FDA is focused on the complex generic products to develop and implement novel scientific approaches in evaluations of active ingredient sameness, pharmaceutical equivalence and bioequivalence. During GDUFA I, he contributed to several complex generic approvals including Glatiramer Acetate injection, Sevelamer and Colesevelam Suspension and Tablets. Prior joining the FDA, Dr. Jiang worked in biopharmaceutical industry and government agencies.

Presentation
Follow up Discussion on FDA Guidance after Public Comments
Monday, November 5, 2018, 9:55 – 10:15 a.m.

In October 2017, FDA published a draft guidance for industry, “ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin”. It is intended to assist potential applicants in determining when an application for a synthetic peptide drug product (synthetic peptide) that refers to a previously approved peptide drug product of rDNA origin (peptide of rDNA origin) should be submitted as an abbreviated new drug application (ANDA). During the public comment period, the Agency received a total of 22 comments that covered different topics including peptide policy, API and product characterization, peptide-related impurity characterization and control, and risk mitigation strategies. In the presentation, sample comments from each topic area will be discussed.

Edwin Kellenbach, Ph.D.
Principal Scientist
Aspen Oss
Noord-Brabant, Netherlands

October 1986: M. Sc. (cum laude) in organic chemistry (Leiden University) and in-vivo NMR (Max Planck Institute Dortmund).
November 1991: Thesis: “DNA-binding by the Glucocorticoid Receptor”, Utrecht University.
November 1991-April 1992: post-doc at the Department of Molecular Physics, Wageningen University. May 1992-April 1994: NMR specialist within the Structure Analysis section, Solvay-Pharma, Weesp.
May 1994-October 2001: Section Leader of the Structure Analysis section, Organon, Oss, the Netherlands. November 2000-October 2002: Section Head Analytical Chemistry, Organon, Riom, France.
November 2002-September 2011: Senior Director Analytical Development, MSD, Oss. September 2011-October 2013: Section Lead GTO Biochemistry (15 persons). November 2013- April 2016: Program Manager Biochemistry.
May 2016-present: Principal Scientist Biochemistry.
Member of European Directorate for the Quality of Medicine (EDQM) expert group 6 (biologicals). Member of the USP expert panel on synthetic peptides.
Coauthor of over 30 articles on proteins and protein-DNA interaction, analytical chemistry and physicochemical characterization in peer reviewed journals.

Research interests
Spectroscopy, peptides and proteins, heparins and heparinoids, physicochemical and extended characterization of biopharmaceuticals, chirality, polymorphism, structural biology, structure-activity relations.

Presentation
Synthetic Therapeutic Peptide Structure Elucidation and Purity Analysis by NMR
Monday, November 5, 2018, 2:15 – 2:35 p.m.

Introduction
Besides identity and content analysis NMR is a strong tool for peptide structure elucidation/confirmation and purity analysis.

Structure Elucidation
In the recent decades, multidimensional, heteronuclear NMR has become a strong tool in protein structure determination. The techniques and methodologies developed can be applied for the structure elucidation/confirmation of peptides and (peptide related) impurities as well. Amino acids can be readily identified by their characteristic spin systems and chemical shifts. Unambiguous determination of the amino acid sequence can be performed by the long range coupling over the amide bonds using long range heteronuclear correlation techniques. Although the theory behind multidimensional, heteronuclear NMR is complex, no fundamental knowledge is required to be able to apply these techniques and interpret the results. NMR can be run unsupervised 24/7 using sample changers/automation and does not require extensive method development. Information on (proline) rotamer distribution and higher order structure (folding) may also be obtained. The upper limit in terms of peptide size exceeds the size of synthetic peptides by far, even at moderate (400 MHz) field strength). In the presentation, several examples will be shown to demonstrate

Purity Analysis

NMR is *not* the method of choice for routine impurity analysis of peptides because of the large number of similar, related impurities at similar, low levels potentially present. However, NMR *is* a powerful, technique to detect and identify unrelated and maybe unforeseen impurities such as process related impurities not easily detected by HPLC analyses in peptides. Protonated impurities such as coupling agents and scavengers used in deprotection can be sensitively detected by NMR because of the overestimation of these these small molecules relative to the larger peptide molecules. NMR can also be used to elucidate the structure of isolated peptide impurities in conjunction with mass spectrometry. Furthermore, peptide modifications undetectable by MS, may be elucidated by NMR because of its nondestructive nature. NMR is therefore an excellent technique for root cause analysis and troubleshooting rather than routine analysis.

Conclusion

Multidimensional, heteronuclear NMR is a strong tool for structure elucidation/conformation of synthetic, therapeutic peptide yielding also information on higher order structure/folding.

For purity determination, NMR is especially suited as an exploratory trouble shooting technique for the detection of unforeseen/unrelated impurities in synthetic therapeutic peptides.

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Maura Kibbey, Ph.D.
Director, Global Biologics
U.S. Pharmacopeia
Rockville, Maryland

Dr. Maura Kibbey is a Director of Science & Standards in USP's Global Biologics Department. Maura and her team work with the five USP Expert Committees and multiple Expert Panels for biologics and antibiotics to develop documentary standards (chapters and monographs) and Reference Standards that support biopharmaceutical quality assessment. Before joining USP, Dr. Kibbey worked for several biotechnology and diagnostic companies in the Washington DC area as well as at the National Institutes of Health. Her scientific expertise includes development and validation of many different assay types for measurement of individual molecules, their activities, or binding interactions. She has published over 40 peer-reviewed articles and has been an invited speaker or workshop organizer for numerous scientific conferences.

Presentation
Cell Based Bioassays in Compendial Standards
Tuesday, November 6, 2018, 9:05 – 9:25 a.m.

USP, regulators, and manufacturers share a common goal of reducing *in vivo* testing yet replacing animal assays with suitable *in vitro* assays may be challenging. This presentation will highlight USP's current efforts to include modern bioassays in the *USP-NF* as well as bridging expectations for revision sponsors who would like to propose a modern assay for the compendium. Case studies will include bioassays ensuring potency of therapeutic peptides.

Norbert Nagel, Ph.D.
Head of Biophysical and Physical Characterization
Sanofi
Frankfurt, Germany

Norbert Nagel received a Ph.D. from Frankfurt University in 1998. Afterwards he joined Hoechst-Marion-Roussel as post-Doc, held several lab head positions at Aventis and presently heads the Biophysical and Physical Characterization Unit within the R&D organization of Sanofi Frankfurt.

Presentation
Peptide Physical Stability and Non-Covalent Aggregation: Challenges and Solution
Tuesday, November 6, 2018, 10:25 – 10:45 a.m.

Peptides can be more prone to physical instability and aggregation than large proteins. Small variations of the primary sequence and different formulations sometimes have a strong effect on physical stability. Different types of physical aggregates and aggregation mechanisms are briefly introduced. An example of a marketed peptide therapeutic is presented, where the physical instability caused a significant delay in development. Approaches to avoid comparable physical stability issues during development will be outlined together with selected analytical methods to rank physical stability and to detect physical instability and early signs of aggregation

Bradley Pentelute, Ph.D.
Associate Professor of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts

Bradley L. Pentelute, Associate Professor of Chemistry. He is currently an tenured Associate Professor at MIT Department of Chemistry, an Associate Member, Broad Institute of Harvard and MIT, an Extramural Member of the MIT Koch Cancer Institute, and Member, Center for Environmental Health Sciences MIT. Since starting his own research group at MIT in 2011 he has been awarded the Eli Lilly Award in Biological Chemistry (2018), Bristol Myers Squibb Award in Organic Chemistry (2017), Amgen Young Scientist Award (2016), Novartis Award in Organic Chemistry (2016), Alfred P. Sloan Fellowship (2015), NSF CAREER Award (2014), Sontag Distinguished Scientist Award (2013), Young Chemical Biologist Award, International Chemical Biology Society (2013), Deshpande Innovation Grant (2013), and the Damon Runyon-Rachleff Innovation Award (2013). He received his undergraduate degree in Psychology and Chemistry from the University of Southern California, and his M.S and Ph.D. in Organic Chemistry from the University of Chicago with Prof. Steve Kent. He was a postdoctoral fellow in the laboratory of Dr. R. John Collier at Harvard Medical School, Microbiology.

Presentation
High-Fidelity Flow Synthesis of Peptides and Proteins
Monday, November 5, 2018, 11:15 – 11:35 a.m.

Here we describe a rapid flow solid phase peptide synthesis methodology that enables incorporation of an amino acid residue in 40 seconds with amide-bond formation taking only 7 seconds. To demonstrate the broad applicability of this method, it was employed to synthesize hundreds of peptides and proteins.

Jean-Marc Poudrel, Ph.D.
Program Manager
PolyPeptide Group
Brussels, Belgium

Jean-Marc Poudrel is Customer Program Manager at PolyPeptide SA near Brussels (Belgium) where he currently leads and coordinates multidisciplinary teams developing manufacturing processes and control strategies to successfully bring peptide APIs from toxicological and clinical phases to commercialization. In this role since 2011 he is responsible for establishment of project scope, budget and timeline as well as for project execution with cross-functional oversight. He received his Ph.D. in Organic and Medicinal Chemistry from the University of Montpellier (France) in 1997. After a 3-year post-doctoral fellowship in Sydney (Australia), he joined the peptide CMO industry at UCB-Bioproducts in 2001 as Head of the Analytical Services. In this function he set-up a state-of-the-art mass spectrometry laboratory to support characterization of peptides intermediates and products, and was responsible for method validation and stability studies. As part of Lonza in 2006 he became Head of Analytical Development with oversight on both in-process control and analytical development laboratories, focusing on the development and validation of analytical methods for starting materials, process intermediates and active pharmaceutical ingredients, as well as setting of release specifications.

Presentation
Setting of Peptide API Specifications
Monday, November 5, 2018, 9:15 – 9:35 a.m.

Regulatory specifications are a key requirement for any product registration that must be agreed between the peptide CMO and the sponsor as well as carefully justified to regulatory authorities. Within the PolyPeptide Group, the API registered specifications are not only based on process capabilities but also developed from a thorough process understanding and a comprehensive process and peptide characterization that goes beyond routine testing methods. API specifications are tightened and fine-tuned as clinical phases progress and manufacturing process matures. The approach followed and methodologies used will be further described and exemplified.

Anuja Rane, Ph.D.
Associate Scientist
Teva Pharmaceuticals
West Chester, Pennsylvania

Anuja Rane is currently working as an Associate Scientist with Teva Pharmaceuticals in West Chester, PA. Her primary research focus is on separations technologies (using chromatography and capillary-based platforms) and higher order structure analysis of monoclonal antibodies, complex proteins and peptides. Anuja has close to 4 years of industry experience in analytical method development, method transfer, and qualification. She obtained her Ph.D. in Pharmaceutical Sciences from the University of the Sciences, Philadelphia (Philadelphia College of Pharmacy) in 2014. In her leisure time, she enjoys traveling, dancing and practicing yoga.

Presentation
Charge Variant Analysis of Therapeutic Peptides
Monday, November 5, 2018, 1:55 – 2:15 p.m.

Charge heterogeneity is commonly observed in therapeutic proteins which can affect their efficacy and safety. For large proteins, charge heterogeneity occurs during production due to post-translational modifications (e.g. glycosylation), purification process and also during storage. In synthetic peptides, charge variation can take place due to chemical degradation (e.g. oxidation, deamination, etc.) during synthesis, purification and storage. Depending on the nature of modification, the resultant charge variant species can be more acidic or basic than the native main peptide molecule. In this study, we explored the feasibility of using capillary electrophoresis based isoelectric focusing method, which is widely used for large proteins, to characterize the charge heterogeneity of therapeutic peptides with >30 amino acids. Moreover this technique can be used for comparability between generic and innovator product; and to monitor batch-to-batch consistency of charge distribution in drug product. This presentation highlights the capabilities and limitations of this assay to characterize medium size peptides along with examples of comparability studies.

Jon Rasmussen, Ph.D.
Director, Global Development
PolyPeptide Group
Skaane, Sweden

Jon H. Rasmussen currently leads global development in the Polypeptide Group. He completed his undergraduate studies at Danmarks Tekniske Universitet (DTU) and got his Ph.D. from the same institution supplemented with studies at Universitá di Roma “La Sapienza”, Italy. Peptides, peptidomimetics and related peptidic motifs became his focus with positions at Pantheco and the PolyPeptide Group. With the PolyPeptide Group he has held positions within Project Management, Process Development and Technical Operations.

Presentation
Synthetic Peptide API Manufacturing: A Mini Review
Monday, November 5, 2018, 10:55 – 11:15 a.m.

Synthetic peptide manufacturing is a maturing yet expanding technology. Increasing complexity of the target products combined with increasing requirements on quality, cost and timelines as well as a large variation in scale create interesting challenges. This presentation will give a short overview of the status of the current manufacturing technologies and how they link to the target product requirements. In addition, some key points on where the manufacturing technology is going in the future are reviewed.

Kevin Seibert, Ph.D.
Senior Research Advisor
Eli Lilly and Company
Indianapolis, Indiana

Kevin earned his BS, MS, and PhD in Chemical Engineering and has over 20 years' experience working in small molecule synthesis for both Merck and more recently with Eli Lilly. Kevin was Area Head of Merck's Natural Products Isolation pilot plant as well as technical lead in the engineering development organization. He has worked on the process development and optimization of many early as well as late phase products and led the technology transfer, validation, and launch of several marketed compounds. Kevin has also led initiatives for developing enhanced filings in support of the ICH Q8, Q9, Q10 and Q11 guidelines. Most recently, Kevin is responsible for the engineering design and implementation of Lilly's synthetic peptide development facility. He has worked closely with an expert team to implement a strategy for synthesizing peptides using a standardized manufacturing platform and applying the strategy to Lilly's growing peptide portfolio. Kevin also leads the engineering group responsible for the commercialization of Lilly's latest phase peptide assets. Kevin has co-authored many refereed publications and conference presentations in the area of criticality assessment, design space mapping and implementation of Quality by Design principles.

Presentation
Convergent Peptide Syntheses: A Platform for Commercial Peptide Manufacturing
Monday, November 5, 2018, 11:35 – 11:55 a.m.

Solid Phase Peptide Synthesis (SPPS) is the primary approach used in manufacturing to produce synthetic peptides. SPPS provides certain advantages over full solution phase chemistry approaches as the peptide on resin can be synthesized more rapidly and isolated with a higher purity. However, as a peptide chain grows longer challenges with increased levels of analog impurities can lead to marked increases in costs associated with purification, largely due to decreasing coupling efficiency related to mass transfer resistances and steric hindrance. Convergent peptide synthesis can be a very effective alternative to SPPS alone, when synthesizing long synthetic peptides. The method combines SPPS and the solution phase chemistry, where the fragments of a peptide chain are first synthesized linearly on resin, and then coupled in solution. The synthesis of short peptide fragments reduces the risk of single deletion and double addition impurities in the synthesis. Coupling fragments in solution also may significantly reduce the solvent use, resulting in greener synthetic approaches. Additionally, convergent approaches to peptide synthesis are far more amenable to alternative reactor designs such as flow infrastructure given the low concentration, high potency and high value of the peptide assets. Control strategies for convergent chemistry approaches can also be significantly simplified given that peptides are routinely terminally purified through chromatographic means. Synthesis impurities that are markedly different in molecular weight are often more effectively separated in preparative chromatographic systems due to the differences in retention time. Synthesis impurities resulting from full linear builds are often characterized by single deletion impurities, with very similar amino acid sequence and therefore much more challenging to separate without sacrificing significant yield. The focus of this presentation will be on our efforts to develop a platform for peptide synthesis focused on linear fragment builds, convergent fragment couplings, and alternative unit operations allowing for improved manufacturability in a typical small molecule synthesis setting.

Daniel Studelska, Ph.D.
Senior Principal Analytical Chemist
Mallinckrodt Pharmaceuticals
Hazelwood, Missouri

Dr. Studelska's training is in Psychology (BA University of Minnesota, Morris), Physiological Psychology (MS in Experimental Psychology NDSU) and Pharmacology (PhD Mayo Graduate School of Medicine). Postdoctoral training was at Washington University School of Medicine in the Department of Anatomy and Neurobiology with Karen O'Malley studying neuronal expression of mRNA of tyrosine hydroxylase and in the Department of Cell Biology with David E. James, studying glucose transporters. He subsequently worked for nine years under Jacob Schaefer in a large solid-state NMR research group at the Dansforth Campus of the University as a Staff Research Associate. He joined Lijuan Zhang's glycobiology lab with a focus on glycosaminoglycans in the Department of Pathology and Immunology, back at the Medical School, as a Staff Scientist for three years before he started his career at Mallinckrodt Pharmaceuticals. He has been working with peptides here for 12 years, starting in a quality lab before moving to R&D.

Presentation
One-Fell-Swoop Chromatography for In-Process Assay of Linaclotide
Monday, November 5, 2018, 1:35 – 1:55 p.m.

Orthogonal modes, size exclusion (SEC) and reverse phase (RP) are used simultaneously ingradient elution. The method enables estimation of soluble product multimers and product purity in one run, to replace unsuitable final product analytical methods with a method that can be used for in process analysis to monitor multimer impurities when there is an opportunity to make adjustments to the process, saving time and money. Because salt is not employed in the mobile phases the method is compatible with LC-MS applications. Details of the mechanism thought to be involved in this separation will be presented.

René Thürmer, Ph.D.
Deputy Head Pharmaceutical Biotechnology
BfArM, Federal Institute for Drugs and Medical Devices, Germany
Bonn, Germany

Dr. René Thürmer received his diploma in chemistry and his Ph.D. in biochemistry from the University of Tübingen. He joined the BfArM (Federal Institute for Drugs and Medical Devices, Bonn, Germany) in 2000. He currently serves as a CMC reviewer and is Deputy Head of the Unit Pharmaceutical Biotechnology. His experience is in the field of formulation, manufacture and control of medicinal products, in particular in the field of oligonucleotides, peptides, proteins, liposomes, sustained release polymer drug products, depot formulations, polymer-conjugated drug products, natural and synthetic surfactants, nanomedicine and others.

Presentation
European Regulatory Update on CMC Requirements for Synthetic Peptides
Monday, November 5, 2018, 9:35 – 9:55 a.m.

Many synthetic peptides are currently worldwide approved as drugs. Nevertheless, identification of critical quality attributes (CQAs), analytical challenges and characterization issues are still discussed in the community. This presentation will also focus on new advances concerning synthetic peptides developed as generics to a drug substance manufactured by recombinant origin. Differences between biologicals and synthetic peptides will be highlighted.

Daniela Verthely, Ph.D.
Chief, Lab of Immunology
U.S. Food & Drug Administration
Silver Spring, Maryland

Dr. Verthelyi received her MD from the University of Buenos Aires and a PhD from the Virginia Tech in USA, and then completed a fellowship training in Immunology at the Section in Retroviral Immunology in the Center for Biologics Evaluation and Research of the FDA before joining the Office of Biotechnology Products in CDER, FDA. She is now Chief of the Laboratory of Immunology and chairs CDER's newly formed Center for Excellence in Infectious Diseases and Inflammation. She has authored over 70 peer reviewed articles and several patents, and directs a lab focused on developing tools to monitor and control innate immune and inflammatory responses including potential impurities in therapeutic products that may foster unwanted immune responses therapeutic proteins reducing their life-saving potential. She currently serves as Chair of the Center for Excellence in Infectious Diseases and Inflammation, Chairs the FDA-NIH Immunology Interest Group and serves on the Advisory Boards for the NIH-FDA Cytokine Interest Group and the NIH Human Immunology, and has received FDA's and CDER's "Excellence in Laboratory Sciences" awards, among other honors.

Presentation
Immunogenicity and Impurities
Tuesday, November 6, 2018, 11:05 – 11:25 a.m.

Improved bioanalytical techniques may enable a determination of immunogenicity risk paving the way for a new generic pathway for a select group of low risk peptides. This talk will discuss some of the scientific considerations regarding the immunogenicity risk assessment described in the FDA Guidance for the Submission of Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin.

Allison Wolf, Ph.D.
Principal Research Scientist
Eli Lilly and Company
Indianapolis, Indiana

Allison Wolf is a Principal Research Scientist in Global Regulatory Affairs CMC at Eli Lilly in Indianapolis, Indiana. She has been a regulatory scientist for 17 years and has worked on small molecules, peptides, oligonucleotides, therapeutic proteins, and monoclonal antibodies. Her experience spans clinical development, commercialization, and post approval. Allison started her career as a medicinal chemist at Pharmacia and Upjohn after graduating from the University of Notre Dame with a M.S. degree in organic chemistry. In 2001, she moved into Regulatory CMC at Pharmacia and later joined Lilly as a regulatory scientist in 2003. In her current role, she leads a group of regulatory scientists responsible for the development and implementation of CMC regulatory strategies for therapeutic peptides, proteins, and monoclonal antibodies in all phases of clinical development and commercialization.

Presentation
Integrating Approaches from Different Product Modalities to Create Advanced Regulatory Strategies for Peptides
Monday, November 5, 2018, 8:55 – 9:15 a.m.

Regulatory guidance and precedent for small molecules and biologics provide direction and perspectives to help guide drug development and commercialization. However, many of the available guidance documents specifically exclude synthetic peptides from scope. This presentation will share how a combination of approaches used for small and large molecules can be leveraged to build a robust control strategy for a therapeutic peptide that is based on enhanced product and process knowledge. This approach, when applied to a synthetic peptide, can alleviate some of the common regulatory challenges faced by peptide manufacturers. Developing and implementing a product-specific control strategy can lead to improvements in product quality and supply chain robustness, which is good for industry, health authorities, and the patients.