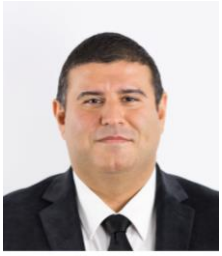
Workshop on Nanomedicines: Technical and Regulatory Perspectives
March 20–22, 2017

Speaker Biographies & Abstracts (listed alphabetically)



Ecevit Bilgili, Ph.D.
Assoc. Professor & Assoc. Chair, Chemical, Biological, & Pharmaceutical Engineering Dept.
New Jersey Institute of Technology (NJIT)
Newark, NJ

Dr. Ecevit Bilgili is an associate professor and associate chair of the Chemical, Biological, and Pharmaceutical Engineering Department at New Jersey Institute of Technology (NJIT), Newark, NJ. His Particle Engineering & Pharmaceutical Nanotechnology Laboratory conducts research in formulations and processes for high-value-added products with enhanced functionalities. His research interests currently include bioavailability enhancement of BCS Class II drugs, preparation and characterization of drug nanoparticles, nanocomposites, and amorphous solid dispersions as well as mathematical modeling of the associated manufacturing processes such as nanomilling, spray drying, fluidized bed granulation, and nanoextrusion. Besides experimentation, his research group uses population balance modeling, discrete element modeling, and microhydrodynamic modeling for elucidating complex physical transformations such as particle breakage, aggregation, agglomeration, and growth in the aforementioned processes. Few highlights from his recent research include preparation of concentrated sub-100 nm drug suspensions for sterile filtration, fast-dissolving surfactant-free drug nanocomposites with colloidal superdisintegrants for bioavailability enhancement of BCS Class II drugs, and a nanoextrusion platform for assessing nanocomposites vs. amorphous solid dispersions. Dr. Bilgili authored 65 peer-reviewed journal articles, 3 U.S. patents, 2 provisional patents, and several invention disclosures. He delivered 85 national/international conference presentations and 24 invited talks/seminars and served as session chair/co-chair in 12 conferences. He is currently the leader of Project A1: Particle Formation within the NSF ERC for C-SOPS. Dr. Bilgili is one of the U.S. editors of the Elsevier journal *Advanced Powder Technology* and has served as a reviewer for 18 leading pharmaceutics, chemical engineering, and powder technology journals. Dr. Bilgili also served as an elected Executive Committee Member of the Particle Technology Forum of AIChE and the Chair of AIChE Area3a: Particle Production and Characterization. He received the Best PhD Thesis in Particle Technology Award from AIChE and NJIT's Excellence in Teaching Award. Dr. Bilgili's research has been funded by NSF, FDA, IFF, Nisso, and several pharmaceutical companies such as Boehringer-Ingelheim and Catalent.

Presentation
Impact of Drug Nanocrystal Aggregation in Oral Dosage Forms
Wednesday, March 22, 2017, 10:20 – 10:50 a.m.

Incorporation of BCS Class II drug nanoparticles, which are usually prepared by wet stirred media milling, into solid dosage forms entails drying of the nanosuspensions for the production of nanocomposite microparticles (NCMPs) as an intermediate step. Unfortunately, formation of drug nanoparticle aggregates and particle growth during either the wet-milling/storage, drying, or redispersion in liquids can lead to reduction of drug surface area. Ensuing slow and incomplete nanoparticle recovery during dissolution may lead to unexpectedly poor bioavailability although drugs have been milled to nano-sizes. Typically, soluble polymers, surfactants, and sugars are used as dispersants to minimize drug nanoparticle clustering and facilitate recovery of drug nanoparticles during aqueous redispersion/ dissolution.

Redispersion of NCMPs incorporating drug nanoparticles and superdisintegrants was investigated in order to elucidate the impact of drug nanoparticle aggregation/nanoparticle recovery and relate redispersion to dissolution response.

Susanne Bremer-Hoffman, Ph.D.
Senior Scientific Officer
European Commission
Ispra, Italy

Susanne Bremer-Hoffman, Dr. rer nat, holds a Ph.D. degree in Biology obtained from the Charite University Hospital Berlin in Germany for her work on the development of immunotherapies against leukemia. After post-doctoral research at the Federal Institute for Risk Assessment in Germany, Susanne Bremer-Hoffman jointed the JRC (Joint Research Centre) of the European Commission and became a team member of ECVAM (European Centre for the Validation of Alternative Methods) in 1995. She was involved in formal validation studies of toxicological in vitro tests detecting embryotoxicity and endocrine disruption as well as the regulatory acceptance of successfully validated tests at the OECD. Furthermore, she collaborated in several publically funded projects including the public/privat partnership initiative "SEURAT-1"and contributed to more than 80 peer-reviewed scientific paper.

Susanne Bremer-Hoffman is member of the European Nanomedicine Characterisation Laboratory (EU-NCL) which has started in 2015. In this project, she is responsible for the liaison of the EU-NCL with stakeholders in particular with regulatory bodies.

Presentation
Perspectives on the Start-Up of EU-NCL
Monday, March 20, 2017, 10:50 – 11:20 a.m.

The manufacturing process of nanomedicines is often complex and requires a careful monitoring of inconsistencies between batches and changes in the manufacturing process before clinical applications can be considered. Furthermore, safety concerns related to the use of nanomaterial must be addressed as early as possible during product development. The recently established European Nanomedicine Characterisation Laboratory (EU-NCL) offers a service free of charge to product developer in order to address such needs and to support the translation of promising nanomedicines towards clinical applications. Six laboratories have virtually merged their state-of-the-art infrastructure and a team of multidisciplinary expertise offers a detailed and confidential characterisation of emerging nanomedicines in order to support product developer in their decision making for the next steps in product development.

The EU-NCL is closely interacting with the working group "nanomedicine" of the international pharmaceutical regulators forum ensuring the establishment of a regulatory relevant testing cascade. Within a first survey, ten regulatory bodies shared their experiences with the regulation of nanomedicines.

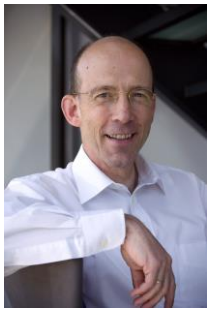
The establishment of the EU-NCL benefits to a large extend from experiences of U.S. NCI NCL which is a partner of the EU-NCL. This collaboration will be of particular importance for further harmonisation of information requirements and test methods supporting the mutual acceptance of data both sides of the Atlantic.

Detailed information on the EU-NCL infrastructure, its services and the application procedure can be found at http://www.euncl.eu. The EU-NCL project is funded by the European Union's Horizon 2020 research and innovation programme under grant agreement No 654190.

Sudnhir Chakravarthi, Ph.D.
Research Investigator II
Bristol-Myers Squibb
New Brunswick, NJ

Dr. Chakravarthi graduated with a PhD in Pharmaceutical Sciences at the University of Nebraska Medical Center. The focus of this research was primarily on polymeric (PLGA) nanoparticles and microparticles as drug delivery/sustained release vehicles. Dr. Chakravarthi also has extensive academic experience in mechanistic evaluation of cellular uptake and intracellular disposition of nanoparticles. Following his graduation, Dr. Chakravarthi worked in a wide range of roles with increasing levels of responsibility. He spent his formative years in the pharmaceutical industry working as a formulation scientist straddling the discovery-exploratory pharmaceutics interface where, in addition to developing fit-for-purpose formulations of NCEs, Dr. Chakravarthi had to explore and develop novel formulation platform approaches for poorly soluble drugs. He evaluated nanosuspensions and lipidic drug delivery platforms for supporting early phase clinical trials of NCEs.
Later, Dr. Chakravarthi undertook the responsibility of product development for generic drugs (both oral and parenteral products), with a primary focus on specialty products. Dr. Chakravarthi was instrumental in establishing scalable platform technology for commercial development of a sustained release polymeric dosage form. Dr. Chakravarthi's contributions were instrumental to several regulatory filings. His related development efforts in the life-cycle management of peptide drugs established Dr. Chakravarthi as an expert in specialty product development. At Bristol-Myers Squibb, Dr. Chakravarthi is responsible for commercial development of both biologic and small molecule parenterals.
Dr. Chakravarthi has three published manuscripts and has authored three book chapters in the field of polymeric drug delivery. Dr. Chakravarthi has over 20 presentations to his credit and is actively involved in drug delivery-focused scientific community.

Presentation
Biomaterials for Polymeric Particulate Delivery Systems: Technical and Regulatory Considerations
Wednesday, March 22, 2017, 9:00 – 9:30 a.m.



Daan Crommelin, Ph.D.
Emeritus Professor, Department of Pharmaceutics
Utrecht University
Utrecht, the Netherlands

Prof. Daan Crommelin is professor emeritus from the Department of Pharmaceutics at Utrecht University. Until December 2011 he was scientific director of the Dutch Top Institute Pharma in Leiden. He is adjunct professor at the Department of Pharmaceutics and Pharmaceutical Chemistry at the University of Utah. Crommelin is co-founder of OctoPlus, a Leiden based company specialized in the development of pharmaceutical (mainly protein based) product formulations and advanced drug delivery systems. He published extensively and edited a number of books/journals. He is Editor-in-Chief of the AAPS book series 'Advances in the Pharmaceutical Sciences'. He advises venture capital groups and acts as a consultant for several big pharma companies and SME's. He chaired the Board of the UCAB Foundation: the Utrecht Center of Excellence for Affordable Biotherapeutics, a WHO supported initiative and the Board of Pharmaceutical Sciences of the International Pharmaceutical Federation (F.I.P.). He was chair of the organizing committee of the Pharmaceutical Sciences World Conference 2007 in Amsterdam. He is past president of the European Federation of Pharmaceutical Sciences (EUFEPS) and past vice-chair of the scientific advisory board of the European Innovative Medicines Initiative (IMI).

Presentations

Non-Biological Complex Drugs: Regulatory Challenges
Monday, March 20, 2017, 9:00 – 9:30 a.m.

Non-biological complex drugs (NBCDs), including many nanomedicines, are a class of medicinal products that cannot be fully quantitated and characterized by physico-chemical analytical means. They share that characteristic with other complex drugs belonging to the class of biologics. Examples of NBCD products are glatiramoids, iron-carbohydrate complexes, polymeric micelles, complex ocular emulsions and liposomes. The complex nature of NBCD products means that slight variations in the manufacturing process can substantially change the composition of final products and their profile. Currently regulators mainly use the generic drug approval pathway to process applications for follow on NBCDs. Are these existing regulatory approaches indeed able to assess equivalence of these NBCD products or should a nano-similar approach (cf. biosimilars) be pursued? As patents of the first generation of "complex drugs have expired and authorized follow-on versions in Europe and Asia have demonstrated (through publications in the public domain) non-comparability in clinical studies, the importance of appropriate science-based approval standards is evident.

Characterization of Liposomes
Tuesday, March 21, 2017, 3:15 – 3:45 p.m.

Several liposomal formulations have been successfully developed and reached the market place. Examples are doxorubicin, daunorubicin and amphothericin containing liposomes. A number of other liposomal products are presently under development both for parenteral and non-parenteral use. All these formulations have to meet the high quality criteria as defined for pharmaceutical products. To ensure proper liposome performance, batch to batch reproducibility and stability of the liposome dispersions have to be established. This requires definition of the characteristics of liposome dispersions in the preformulation stage, clinical test stage and final production stage. As patents expire generic versions of liposomes containing bioactives are now under development. Worldwide the regulatory status of these generic versions of liposomes is not clear. The FDA has issued draft Guidances for liposome products in general and for generic versions of doxorubicin containing liposomes. The EMA has issued a Reflection Paper for 'intravenous liposome products with reference to an innovator liposomal product'.
In this lecture I will discuss liposome characterization techniques and present some thoughts regarding regulatory strategies.

Marina Dobrovolskaia, Ph.D., MBA, PMP
Head, Immunology Section, Nanotechnology Characterization Lab
Frederick National Lab for Cancer Research
Frederick, MD

Dr. Dobrovolskaia is a Senior Principal Scientist and Head of the Immunology Section at the Nanotechnology Characterization Laboratory (NCL). Dr. Dobrovolskaia joined the NCL in February 2005 to establish the immunology assay cascade and build a preclinical framework to conduct an immunological safety assessment of nanoparticle platforms and nanotechnology-formulated drugs and imaging agents. She currently directs characterization related to nanomaterials' interactions with components of the immune system.
Dr. Dobrovolskaia is a member of several working groups on Nanomedicine, Oligonucleotide Safety, and Endotoxin Detection. She has published more than 45 peer-reviewed papers regarding nanomaterial interactions with the immune system, and prepared and edited two editions of the “Handbook of Immunological Properties of Engineered Nanomaterials”, which has received international recognition. Dr. Dobrovolskaia is an invited speaker at numerous national and international nanotechnology-related conferences. She has served a 4-year term as a Special Associate Editor in Immunology for the “Nanomedicine: Nanotechnology, Biology and Medicine” Journal published by Elsevier and is currently an editorial board member for the Journal of Nanotoxicology and Nanomedicine by IGI Global.

Before joining the NCL, Dr. Dobrovolskaia worked as a Research Scientist in a GLP laboratory at PPD Development, Inc. in Richmond, VA. She received her M.S. degree from Kazan State University in Russia, her Ph.D. from N.N. Blokhin Cancer Research Center of the Russian Academy of Medical Sciences in Moscow, Russia, MBA degree from Hood College in Frederick, MD, and completed two postdoctoral trainings at the National Cancer Institute in Frederick, MD and the University of Maryland in Baltimore, MD. She is also a member of Project Management Institute and a certified Project Management Professional. Her areas of expertise include cell signaling, innate immunity, immunotoxicity of complex drug formulations, bioanalytical methodology, and endotoxin detection and quantification.

Presentation
Immunological Characterization of Nanotechnology-Based Formulations: Challenges and Considerations
Monday, March 20, 2017, 1:10 – 1:40 p.m.

Martin Fritts, Ph.D.
Research Associate, Nanomechanical Properties Group
National Institute of Standards and Technology/NCI
Gaithersburg, MD

Presentation
Characterization of Nanomaterials-Best Practices and Databases
Tuesday, March 21, 2017, 10:20 – 10:50 a.m.

Alexis Guillot, Ph.D.
Senior Scientist
PHAST GmbH
Homburg, Germany

Alexis Guillot is senior scientist in the company PHAST GmbH in Homburg, Germany. He received in 2010 a certification as pharmacist at the University of Auvergne, in Clermont-Ferrand, France and a Master degree in nanopharmaceutical formulation at the University of Angers, France and at the INSERM U1066 MNT, Micro- et Nanomédecines biomimétiques in Angers. He started his career as scientist at PHAST GmbH in 2010 and obtained a PhD degree in 2015 at the University of Saarland and the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) in Saarbrücken, Germany. His PhD thesis dealt with the development of characterization methods and *in vitro* drug release testing methods for nanopharmaceuticals.

Presentation
In Situ Spectroscopy with Nanoparticles
Tuesday, March 21, 2017, 1:45 – 2:15 p.m.

Characterization techniques for nanoparticles generally focused on the size, shape and zeta-potential. However, *in vitro* drug release tests and quantification of entrapped and free drug remain a challenge for nanoparticles. Aim of this study was to evaluate the combination of fiber optics with derivative spectrophotometry (DSP) in a compendial dissolution apparatus for two model-drugs, cyclosporine A (CSA) and budesonide (BUD), and for two particulate systems: soft lipid nanoparticles (Lipidot®) and poly(lactic-co-glycolic acid) (PLGA) microparticles (MPs) and nanoparticles (NPs). Moreover, solid phase extraction (SPE), an accurate, repeatable, fast and automatable technique, was successfully tested and validated to thoroughly quantitate free and entrapped drug.

Anthony Hickey, Ph.D.
USP Affiliation:
Chair, JS – Nanotechnology Expert Subcommittee

Distinguished RTI Fellow
Research Triangle Institute
Research Triangle Park, NC

Dr. Hickey is Distinguished RTI Fellow, at the Research Triangle Institute, Emeritus Professor of Molecular Pharmaceutics of the Eshelman School of Pharmacy (2010-present, Professor 1993-2010), and Adjunct Professor Biomedical Engineering in the School of Medicine, at the University of North Carolina at Chapel Hill. He obtained Ph.D. (1984) and D.Sc. (2003) degrees in pharmaceutical sciences from Aston University, Birmingham, UK. Following postdoctoral positions, at the University of Kentucky (1984-1988) Dr. Hickey joined the faculty at the University of Illinois at Chicago (1988-1993). In 1990 he received the AAPS Young Investigator Award in Pharmaceutics and Pharmaceutical Technology. He is a Fellow of the Royal Society of Biology (2000), the American Association of Pharmaceutical Scientists (2003) and the American Association for the Advancement of Science (2005). He received the Research Achievement Award of the Particulate Presentations and Design Division of the Powder Technology Society of Japan (2012), the Distinguished Scientist Award of the American Association of Indian Pharmaceutical Scientists (2013) and the David W Grant Award in Physical Pharmacy of the American Association of Pharmaceutical Scientists (2015). He has published numerous papers and chapters in the pharmaceutical and biomedical literature, one of which received the AAPS Meritorious Manuscript Award in 2001. He has edited five texts on pharmaceutical inhalation aerosols and co-authored three others on 'Pharmaceutical Process Engineering', pharmaceutical particulate science and 'Pharmaco-complexity'. He is founder (1997, and formerly President and CEO, 1997-2013) of Cirrus Pharmaceuticals, Inc., which was acquired by Kemwell Pharma in 2013; founder (2001, and formerly CSO, 2002-2007) of Oriel Therapeutics, Inc, which was acquired by Sandoz in 2010 and founder and CEO of Astartein, Inc. (2013-present); member of the Pharmaceutical Dosage Forms Expert Committee of the United States Pharmacopeia (USP, 2010–2015, Chair of the sub-committee on Aerosols) and formerly Chair of the Aerosols Expert Committee of the USP (2005-2010). Dr. Hickey conducts a multidisciplinary research program in the field of pulmonary drug and vaccine delivery for treatment and prevention of a variety of diseases.

Presentation
USP Perspectives for Drug Products Containing Nanomaterials
Monday, March 20, 2017, 11:20 – 11:50 a.m.

The USP has commissioned a joint subcommittee of members from several expert committees (Dosage Forms, Chemical Analysis, Physical Analysis and Excipients) to address current and future references to formulations and methods related to nanomaterials. The subcommittee has reviewed US FDA publications and the scientific literature to identify major nanomaterials, notably liposomes, polymeric and inorganic nanoparticles, included in formulations. In addition, the key physico-chemical properties of these formulations, methods of analysis and products, of which they are components, have been identified. Gaps in the current descriptions of these formulations, physico-chemical characteristics and specific methods, including dynamic light scattering and zeta potential measurement, were identified with the recommendation that the relevant expert committee add these items to their workplan for general chapter expansion or development.

Mario Hubert, Ph.D.
USP Affiliation:
Member, General Chapters-Physical Analysis 2015 Expert Committee

Principal Scientist
Bristol-Myers Squibb
New Brunswick, NJ

Mario Hubert, Ph.D. received both his MSc and Ph.D. from Slovak University of Technology in Slovakia researching powder agglomeration by roll compaction. He continued the academic path as postdoctoral fellow at Ben Gurion University of Negev in Israel and The University of Florida in USA focusing on powder/particle characterization, pneumatic conveying, powder mixing, caking and sampling.

Upon completion of the postdoctoral fellowships, Mario worked for Mettler Toledo as application consultant for PAT (process analytical technology) tools. He joined Bristol Myers Squibb (BMS) in 2006 where he lead solid state analysis group primarily responsible for development, validation and transfer of analytical methods for both small and large molecules. The methods include crystal form, particle size, surface area, subvisible particles, rheology etc.

Presentation
Particle Size and Shape Characterization: Current and Emerging Techniques
Wednesday, March 22, 2017, 9:30 – 10:00 a.m.

The presentation focuses on a number of analytical techniques for particle size, shape and concentration measurements. Application and sensitivity of traditional techniques (static and dynamic light scattering, surface area by BET, SEM) as well as emerging techniques (Nanosight, Mass resonance measurement, TEM) are discussed. A portion of the presentation focuses on application of novel In Situ TEM - Poseidon™Technology to studying and understanding of aggregation in therapeutic proteins. Advantage of the Poseidon technology is that it allows imaging of fully hydrated samples directly within TEM in static or dynamic environment.

Fred Klaessig, Ph.D.
Manager
Pennsylvania Bio Nano Systems, LLC
Doylestown, PA

Fred Klaessig is currently with Pennsylvania Bio Nano Systems, a consulting firm. Once the Technical Director for Aerosil & Silanes and later the Business Director for the Aerosil product line at Evonik Degussa Corp., his responsibilities included commercial overview, customer support, new product introduction and regulatory interactions. AEROSIL® fumed silica and AEROXIDE® P25, titania, and Alu C, alumina, have many industrial uses in reinforcement, rheology control, abrasion and UV absorption. The great interest in nanotechnology raised safety and chemical registration concerns about this class of materials, which led to his on-going interest in standardization & informatics (ASTM E56, ISOTC-229). He has worked on stakeholder involvement for the University of California's Center for the Environmental Implications of Nanotechnology and is an Advisory Board member for NanoFASE.

Fred received a B.S. in Chemistry from the University of California, Berkeley and a Ph.D. in Physical Chemistry from Rensselaer Polytechnic Institute. Prior industrial experience included R&D at Betz Laboratories, now a division of GE Water Services, and QC at Bio-Rad Laboratories.

Presentation
Nanotechnology – Common Language for Nomenclature, Standards (ISO, ASTM) and Data Reporting
Monday, March 20, 2017, 8:30 – 9:00 a.m.

Nanotechnology terminology will be examined from the standpoint of the influence chemical registration activities ('new' TSCA and REACh) may have when pursuing FDA-regulated topics. Examples will be provided of recent controversies, or perhaps better expressed as unresolved testing challenges, that primarily involve inorganic materials used as inert carriers, excipients, adjuvants or additives. The underlying driving forces will be discussed and on-going nanoinformatics efforts outlined. The terminology developed at ISO TC-229 and the informatics efforts at ASTM represent communications tools when responding to regulator inquiries.

Aaron Krueger, Ph.D.
Scientist II, Particle Characterization Core Facility
KBI Biopharma, Inc.
Boulder, CO

Aaron received his Ph.D. in Structural Biology and Biochemistry from the Department of Biochemistry at the University of Colorado, Anschutz Medical Campus. His projects focused on identification and characterization of small molecule enzyme inhibitors using High Throughput Screening and structure-based drug design, with an emphasis on x-ray crystallography. Aaron also holds a Bachelors of Science in Chemistry from North Dakota State University. Aaron currently holds the position of Scientist II at KBI BioPharma in the Particle Characterization Core and focuses on subvisible particle identification and characterization and biophysical characterization. Prior to KBI, Aaron was a postdoctoral fellow for Dr. John Carpenter at the University of Colorado, Anschutz Medical Campus where he worked on method development and applications for subvisible particle analysis, development of methods to assess biophysical stability of commercial biopharmaceutical products, container compatibility studies, and assessment of particles originating from primary packaging materials. He has over 14 years of biomedical research experience, across a wide range of projects, including liposomal drug delivery systems, small molecule and peptide drug design, structure-based design strategies, protein purification, formulation and stability strategy, protein biophysical characterization, and subvisible particle analysis. His current focuses are the development of novel methods for nanoparticle tracking analysis and resonant mass measurement and stability assessment of biomolecules using differential scanning calorimetry.

Presentation
Complementary Technologies for Characterization of Particles in the Nano/Colloidal Range
Tuesday, March 21, 2017, 11:35 a.m. – 12:05 p.m.

Andrew Latham, Ph.D.
Principal Scientist, Pharmaceutical Sciences and Clinical Supply
Merck & Co., Inc.
West Point, PA

Andrew Latham received his B.S. in Chemistry from Salem State College in Salem, Massachusetts in 2003. Studying under Professor Mary Beth Williams in the Chemistry Department at The Pennsylvania State University, his Ph.D. work was focused on the synthesis, characterization and applications of magnetic nanomaterials. In 2008, Andrew began his industrial career with Merck & Co. in their Analytical Sciences group where the majority of his work was focused on the development of delivery systems for siRNA therapeutics. He has since worked in both Preformulation and Sterile Formulation groups, most recently working on lipid nanoparticles for the delivery of oligonucleotides. Currently, Andrew is a Principal Scientist in Merck's Discovery Pharmaceutical Sciences group.

Presentation
Oligonucleotide Lipid Nanoparticles: Development, Process Optimization and Specification Setting
Tuesday, March 21, 2017, 3:45 – 4:15 p.m.

Lipid nanoparticles (LNPs) are currently a leading delivery platform for a range of oligonucleotides used in both therapeutics and vaccines including the delivery of siRNA and mRNA. Optimization of LNPs as therapeutic products is enabled by the development of structure-activity relationships linking LNP physiochemical and macromolecular properties to bioperformance. During LNP development it is critical to control the oligonucleotide-LNP drug product assembly process to ensure reproducibility and to enable the correlation of drug product properties with efficacy and/or toxicity. Methods by which product properties can be rationally manipulated are thus critical enablers of this fundamental knowledge build. The siRNA LNPs presented herein are composed of ionizable amino lipids, neutral lipids and poly(ethylene glycol) (PEG) lipids with each component contributing to specific physiochemical properties and, therefore, bioperformance. Full characterization of the LNP drug product is critical to the establishment of clinically relevant specifications. Building an understanding of how product physiochemical and macromolecular properties are linked to in-vivo performance is necessary to develop an effective and safe LNP released against specifications that are meaningful. This presentation is focused on the LNP assembly process, efforts aimed at optimizing this process and the characterization tools used to probe the interdependency between lipid chemical diversity, assembly process, formulation composition and formulation ratios. Developing strong analytical and pharmacological understanding is accomplished through well controlled experimentation in order to vary particle attributes. In addition, the correlation between particle properties to gene silencing and toxicology will also be presented. Furthermore, analytical characterization of the oligonucleotide-LNP drug product offers unique challenges and techniques which are not typically encountered in more traditional drug development. Along with more typical analyses, less common techniques are those such as UHPLC with Charged Aerosol Detection (CAD), Ion Exchange Chromatography (IEX), Encapsulation Efficiency (EE), Dynamic Light Scattering (DLS), and Capillary Electrophoresis (CE). These techniques are used for high throughput analysis for in process testing and screening as well as to monitor stability of the drug product and its constituents. Explained herein are the applications of these techniques as they relate to LNP and siRNA characterization and specification setting. In summary, how understanding the LNP assembly process and efforts to optimize this process combined with the analytical characterization tools developed result in the establishment of relevant specifications for clinical candidates will be discussed.

Tao Lu Lowe, Ph.D.
Associate Professor, Biomedical Engineering
University of Tennessee Health Science Center
Memphis, TN

Presentation
Current and Emerging Techniques
Wednesday, March 22, 2017, 10:50 – 11:20 a.m.

Margareth Marques, Ph.D.
Principal Scientific Liaison
U.S. Pharmacopeia

Principal scientific liaison at the Science Department at the United States Pharmacopeia. Scientific liaison to the USP Expert Committee on Dosage Forms working on general chapters for performance tests (dissolution/drug release), and for some pharmaceutical dosage forms (products applied to the skin, ophthalmic products, etc.), responsible for the USP general chapters on osmolality, titrimetry, and UV/Vis spectrophotometry. Dr. Marques is also responsible for developing specifications for reagents, test solutions, buffer solutions, etc., used in USP – NF monographs. She manages the USP database on chromatographic columns, the USP database on dissolution methods and the USP web site on column equivalency. She has a B.Sc. and an M. Sc. both in Pharmacy by the University of Sao Paulo, Brazil. She has a Ph. D. in Analytical Chemistry by the State University of Campinas, Brazil. She managed analytical laboratories at Ciba-Geigy, Sandoz, and Astra.

Workshop Report/Closing Remarks
Wednesday, March 22, 2017, 12:50 – 1:05 p.m.

Scott McNeil, Ph.D.
Director, Nanotechnology Characterization Laboratory (NCL)
Frederick National Lab for Cancer Research
Frederick, MD

Dr. McNeil serves as the Director of the Nanotechnology Characterization Laboratory (NCL) for Leidos Biomedical Research at the Frederick National Laboratory for Cancer Research, where he coordinates preclinical characterization of nanotech cancer therapeutics and diagnostics. At the NCL, Dr. McNeil leads a team of scientists responsible for testing candidate nanotech drugs and diagnostics, evaluating safety and efficacy, and assisting with product development--from discovery ‐ level, through scale ‐ upand into clinical trials. NCL has assisted in characterization and evaluation of over 300 nanotechnology products, several of which are now in human clinical trials.
Dr. McNeil is a member of several working groups on nanomedicine, environmental health and safety, and other nanotechnology issues. He is an invited speaker to numerous nanotechnology-related conferences and has several patents pending related to nanotechnology and biotechnology. He is also a Vice President of Leidos Biomedical Research. Prior to establishing the NCL, he served as a Senior Scientist in the Nanotech Initiatives Division at SAIC-Frederick where he transitioned basic nanotechnology research to government and commercial markets. He advises industry, State and US Governments on the development of nanotechnology and is a member of several governmental and industrial working groups related to nanotechnology policy, standardization and commercialization. Dr. McNeil's professional career includes tenure as an Army Officer, with tours as Chief of Biochemistry at Tripler Army Medical Center, and as a Combat Arms officer during the Gulf War. He received his bachelor's degree in chemistry from Portland State University and his doctorate in cell biology from Oregon Health Sciences University.

Presentation
Analytical Aspects
Monday, March 20, 2017, 3:30 – 4:00 p.m.

The Nanotechnology Characterization Laboratory (NCL) at the U.S. Frederick National Lab for Cancer Research (FNL) conducts preclinical characterization and toxicity testing of nanoparticles intended for cancer therapeutics and diagnostics. The NCL is a partnership among the National Cancer Institute (NCI), the U.S. Food and Drug Administration (FDA) and the National Institute of Standards and Technology (NIST). As part of its assay cascade, NCL characterizes nanoparticles' physicochemical attributes, their in vitro biological properties, and their in vivo compatibility using animal models. The NCL also looks at trends across nanoparticle platforms, parameters that are critical to nanoparticle biocompatibility, and develops assays for preclinical characterization of nanoparticles. The NCL has developed more than 40 protocols that rigorously characterize nanoparticle physicochemical properties, as well as in vitro immunological and cytotoxic characteristics and ADME/Tox profiles in animal models. NCL’s many collaborations with nanotech investigators and expertise with a variety of nanoparticle drug delivery platforms have allowed us to elucidate trends relating physicochemical properties such as size and surface chemistry to nanoparticle behavior in biological systems, biodistribution, safety, and efficacy. This presentation reviews analytical and physicochemical experiments that have proven useful in providing “go/no-go” decision-making data for nanomedicines, with a focus on challenges that differ from those in the development of traditional small molecule therapeutics.

Ajit Narang, Ph.D.
Senior Scientist, SMPS
Genentech, Inc.
San Francisco, CA

Ajit Narang works for Genentech, Inc., in South San Francisco, CA as a Sr. Scientist responsible for the pharmaceutics and biopharmaceutics of small molecules in preclinical and early clinical development of various dosage forms. He also serves as Adjunct Faculty at the Universities of Tennessee and Phoenix; Industrial Advisory Board member of Western Michigan University; a panel member of the Biopharmaceutics Technical Committee (BTC) of the Pharmaceutical Quality Research Institute (PQRI) in Arlington, VA; a panel member of the International Pharmaceutics Excipient Council (IPEC) committees; vice-Chair of the Formulation Design and Delivery (FDD) section of the American Association of Pharmaceutical Scientists (AAPS), and committee member of a Master's Student at Campbell University, North Carolina.

Ajit earned his Ph.D. from the University of Tennessee in Memphis, Masters in Pharmaceutics from the Banaras Hindu University in India, and Bachelors in Pharmaceutical Sciences from the University of Delhi in India.

He has over 15 years of drug product development experience working for Bristol-Myers Squibb, Co. (BMS) in New Jersey, Wockhardt Pharmaceuticals (ex-Morton Grove Pharmaceuticals) in Illinois, and Ranbaxy Research Labs in India in different capacities.

Ajit has contributed to several preclinical, clinical, and commercialized drug products including NDAs, ANDAs, and 505B2s. He is credited with over 40 peer-reviewed articles; 2 books; 7 patent applications; 20 invited talks; and 60 presentations at various scientific meetings.

His current research interests are translation from preclinical to clinical and commercial drug product design; incorporation of QbD elements in drug product development; and mechanistic understanding of the role of material properties on product performance.

Presentation
Development of In vitro Release Procedure for Small Molecules and Biologics
Tuesday, March 21, 2017, 8:30 – 9:00 a.m.

James Nolan
Director, Nanomedicine Development & Manufacturing
Pfizer, Inc.
Cambridge, MA

Mr. Nolan is a director within Pfizer's Pharmaceutical Sciences group which is responsible for the development, characterization and manufacture of novel nanoparticle drug products. Prior to Pfizer, Jim led the process and analytical development efforts related to the research and clinical stage nanoparticle programs at BIND Therapeutics. Prior to joining BIND Therapeutics, Jim spent over 10 years in various roles within EMD Serono's Bioprocess development organization, including leading units responsible for process analytics and downstream process development. Jim has 15 years of experience in pharmaceutical development and analytical characterization of clinical stage therapeutics, including monoclonal antibodies, immune-cytokines, Fc-fusion and PEGylated proteins as well as most recently nanoparticle drug products. Mr. Nolan holds a BS in Biology and Biotechnology from Worcester Polytechnic Institute, a MS in Biological Sciences from the University of Massachusetts- Lowell and a MBA from Worcester Polytechnic Institute

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Presentation
Characterization of Nanomedicine Drug Product Critical Quality Attributes
Tuesday, March 21, 2017, 9:30 – 10:00 a.m.

Targeted nanomedicines improve the biodistribution and therapeutic index of therapeutic agents. The biological performance of nanomedicines is often associated with a number of quality attributes. This correlation can be established though a combination of biological studies and rigorous physiochemical characterization. Nanomedicines possess attributes beyond those of the active drug component and include characteristics more closely associated with the particle and/or an active targeting moiety. This presentation reviews the identification and characterization of certain nanoparticle quality attributes and the impact to both the efficacy and safety of clinical stage nanomedicines.

Donald Parsons, Ph.D.
USP Affiliation:
Member, Chemical Medicines Monographs 3 Expert Committee

Head, Drug Product Process Science
Moderna Therapeutics
Cambridge, MA

Don Parsons is Head of Drug Product Process Sciences for Moderna Therapeutics, where he directs early clinical stage formulation and process development for Moderna's lipid nanoparticle drug delivery platform for messenger RNA therapeutics. Prior to joining Moderna, Don served as Vice President of Pharmaceutical Development at BIND Therapeutics. At BIND, Don supervised analytical, formulation, and process development for the company's targeted nanoparticle drug delivery platform known as Accurins, helping to bring two products into the clinic. Don has over 25 years of experience in pharmaceutical product development. His research interests include materials science, drug delivery, and the application of quality by design principles to the development of innovative and complex drug products.

Presentation
Industrial Perspective on Nanomedicine Characterization Strategies
Tuesday, March 21, 2017, 2:25 – 2:55 p.m.

Alan Rawle, Ph.D.
Applications Manager
Malvern Instruments
Westborough, MA

Alan Rawle has more than 30 years' experience in various aspects of science and technology. Alan has a degree in industrial chemistry and a Ph.D in supported alloy catalysts both acquired at Brunel University, London, UK. After a career in liquid crystal displays engineering he moved onto technology transfer, and thence on to electro-optics, lasers, signal processing, and ultimately materials characterization techniques.
Since 1990, Alan has been with Malvern Instruments as the Applications Manager based in Westborough, MA, USA. Dr Rawle has spent many years working on the ISO TC24/SC4 (Particle Characterization) standardization committee assisting the writing of documentary standards in light scattering, small angle x-ray scattering, image analysis, zeta potential, and dispersion as well as his own interest in the theory and practice of sampling. He has delivered short courses on a regular basis at Pittcon on particle sizing techniques and sampling. Dr. Rawle is CoChair of E 56.02, the Characterization SubCommittee of the ASTM E56 Committee on Nanotechnology and is also a member of 6 other ASTM committees.

Presentation
The Use of Zeta Potential for the Characterization of Nanomaterials
Tuesday, March 21, 2017, 1:25 – 1:55 p.m.

In the characterization of nanoparticulate matter, surface is one of the 4 defining '4S' parameters (the others being size, shape, and solubility). The surface defines how the material interacts with its environment and is thus crucial in defining the holistic properties of a nanoparticulate system. The surface area and composition plus the corona play a large role in understanding the behavior of a material (liquid or solid) in liquid suspension but the charge plays a crucial part in the thermodynamic stability of any multiphase system. As pharmaceutical formulations contain smaller and smaller materials in an attempt to overcome solubility (and thus drug delivery) issues, the issue of particle-particle interactions becomes crucial in understanding and attempting to control product stability. A charged surface will be covered with charges of the opposite magnitude and this charge falls off as the distance from the particle moves into the dispersant phase. When a particle moves it takes with it a stream of counter-charged ions and interacts with its environment via what Is called the 'slipping plane'. The magnitude of charge (the zeta potential) at this slipping place has implications for particle stability in the medium it resides. If this charge is of insufficient magnitude, then van der Waals attraction will draw particles together with resulting agglomeration and potential precipitation and sedimentation.

The zeta potential is especially sensitive to small changes in immediate environment – pH, concentration and nature of external ions, especially polyvalent ions. As an example, small concentrations of calcium ions in the ppm level can destabilize intralipid soya bean emulsions causing microembolism. For systems considerably smaller than a micron, especially in the nano (1 – 100 nm) range, then magnitudes of zeta potential greater than the oft-quoted 30 mV are necessary to confer stability on systems. Typically for 300 nm systems something of the order of 60 mV may be needed and this must be substantially increased (> 100 mV?) for material in the nano region.

This talk provides an overview to the measurement of zeta potential in nanomaterial characterization and its use in predicting formulation stability.

Christie Sayes, Ph.D.
Associate Professor of Environmental Science
Baylor University
Waco, TX

Presentations

Characterization of Nanomaterials
Tuesday, March 21, 2017, 10:50 – 11:35 a.m.

End of Life for Nanomedicines
Wednesday, March 22, 2017, 11:20 – 11:50 a.m.

Zhigang Sun, Ph.D.
USP Affiliation:
USP Government Liaison, General Chapters-Physical Analysis 2015 Expert Committee

Branch Chief (Acting), Office of Process and Facilities, OPQ, CDER
U.S. Food & Drug Administration
Silver Spring, MD

Dr. Zhigang Sun is currently acting as the Branch Chief at Division of Process Assessment II, Office of Process and Facilities (OPF), OPQ, CDER, FDA. He joined FDA in 2006 and has served as Chemistry Reviewer, Senior Chemistry Reviewer, and Team Leader at Office of Generic Drugs (OGD) as well as Team Leader at Office of Pharmaceutical Science (OPS). In addition to review work, Dr. Sun participated in several working groups and committees in OGD, OPS, and OPQ and he is the Agency Expert in the areas of particle characterization and particle specifications. He has frequently been invited as a speaker and/or an organizer/session chair/moderator for many conferences such as AAPS Annual Meeting, AIChE Annual meeting, IFPAC Annual Meeting, and PQRI workshop. He served as the Assistant Country Director - Drugs (Acting) at FDA China Office from November 2016 to January 2017. He has also served as a FDA liaison for 2015-2020 USP General Chapters – Physical Analysis Expert Committee as well as USP Expert Panel (2015-2020) on Analytical Methodologies Based on the Light Scattering Phenomena. Dr. Sun received his Ph.D. in Chemical Engineering from Purdue University. He has over 60 patents, book chapters, papers, and presentations.

Presentation
Scientific and Regulatory Considerations on Particle Size Analysis of Nanomaterials
Wednesday, March 22, 2017, 11:50 a.m. – 12:20 p.m.

Incorporation of nanomaterials in drug product formulation has many advantages such as improved solubility, decreased degradation or physiologic clearance rates, decreased systemic toxicity, and improved clinical efficacy. Accurate determination of particle size distribution of nanomaterials is crucial for developing nanomaterial drug products due to significant impact of nano-particle sizes on drug performance and/or quality. Although numerous commercially available instruments have been used extensively for particle size analysis of nanomaterial drug products, how to select suitable particle sizing methods and establish appropriate particle size specifications for nanomaterial drug products is still a big challenge for quality control of nanomaterial drug products manufactured at large commercial scales.

This presentation will give an overview of particle sizing techniques submitted in various drug applications for quality control of nanomaterial drug products, with more focus on scientific and regulatory considerations on particle size analysis of nanomaterial drug products. It will also include a discussion of regulatory submission expectations with respect to control of particle size distribution of nano-particles based on commonly seen deficiencies in new drug applications (NDAs), abbreviated new drug applications (ANDAs), and investigational new drug applications (INDs). The objective of this presentation is to illustrate how to develop particle sizing methods as well as establish particle size specifications for nanomaterial drug products to ensure reproducible commercial manufacturing for consistent drug product quality.

René Thürmer, Ph.D.
USP Affiliation:
Member, Glatiramer Expert Panel

Deputy Head-Unit Pharmaceutical Biotechnology
BfArM - Federal Institute for Drugs and Medical Devices
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
Quality Considerations and regulatory Perspectives for Drug Products Containing Nanomaterials: European Perspective
Monday, March 20, 2017, 10:20 – 10:50 a.m.

The presentation will describe how the EU promotes the development of new nanomedicines by publishing guidance, providing scientific advice and engaging with multiple regions for the convergence of scientific requirements to support the quality, safety and efficacy of nanomedicines. Regulatory challenges deriving from the use of an innovative technology that crosses different platforms will be highlighted.

Donald Tomalia, Ph.D.
CEO/Founder
NanoSynthons, LLC, National Dendrimer & Nanotechnology Center
Mt. Pleasant, MI

Dr. Tomalia is the CEO/Founder of NanoSynthons LLC and National Dendrimer & Nanotechnology Center, Distinguished Visiting Professor (Chemistry Department) Columbia University, NY; Adjunct Professor (Department of Chemistry) University of Pennsylvania, PA and Affiliate Professor (Department of Physics) Virginia Commonwealth University, VA. He received his B.A. in Chemistry from the University of Michigan and Ph.D. in Physical–Organic Chemistry from Michigan State University while working at The Dow Chemical Company (1962-1990). He has founded three dendrimer-based nanotechnology companies; namely: NanoSynthons LLC (2010), Dendritic Nanotechnologies, Inc. (2001) and Dendritech, Inc. (1992). Other positions currently held by Tomalia include: Advisory Board CLINAM, European Foundation for Clinical Nanomedicine; Sr. Scientific Advisor to the European Union CosmoPHOS Nano Project (2012-present). Dr. Tomalia also serves as Faculty Member, *Faculty 1000 Biology*; Associate Editor, *Journal of Nanoparticle Research* (Springer); Editorial Advisory Board, *Nanomedicine* (Elsevier) and *Current Bionanotechnology.*

He is the pioneering scientist/inventor credited with the discovery of poly(oxazolines) (Industrial Research-100 Awards in 1978 & 1986) and dendrimers. His 1979 discovery of dendrimers (dendritic polymer architecture) led to a third R&D-100 Award in 1991 and the Leonardo da Vinci Award (Paris, France) in 1996. He received the International Award of The Society of Polymer Science Japan (SPSJ) (2003) which recognized his discovery of the fourth major macromolecular architectural class; namely, *dendritic polymers*. He was the invited "Linus Pauling Memorial Lecturer" (2010) Portland, OR and recipient of the Wallace H. Carothers Award (American Chemical Society) (2012). *American Advancement Association of Science* (AAAS) Elected Fellow (2016).

Presentation
Systematic Engineering of Critical Nanoparticle Design Parameters as a Strategy for Developing Predictive Nanoscale-QSAR for Nanomedicines
Tuesday, March 21, 2017, 9:00 – 9:30 a.m.

All well-defined hard/soft nanoparticles (NPs) used in nanomedicine applications exhibit at least six important physico-chemical features. These features referred to as *critical nanoscale design parameters* (CNDPs) include: *size, shape, surface chemistry, flexibility/rigidity, architecture and interior composition*. It is now widely recognized that these CNDPs dramatically influence important nanoparticle properties desired for nano-therapy/drug delivery such as nano-toxicity, excretion modality, pharmacokinetics, biodistribution, complement activation, drug/intrinsic NP targeting, NP-protein interactions, etc. to mention a few.

It is now widely recognized by both chemists/physicists that CNDPs exhibited by all well-defined, hard/soft NPs define important and highly predictive nanoperiodic property patterns. This lecture will overview predictive, nanoperiodic property patterns that may be used for guiding the systematic design/synthesis (i.e., *quantitative nanostructure activity relationships* (QNARs)) to produce desired and optimized NP properties for specific applications.

Katherine Tyner, Ph.D.
USP Affiliation:
USP Government Liaison, JS – Nanotechnology Expert Subcommittee

Associate Director of Science (acting)
Office of Pharmaceutical Quality ScienceI can, CDER
U.S. Food and Drug Administration
Silver Spring, MD

Dr. Katherine Tyner is the Associate Director of Science (acting) in the immediate office of the Office of Pharmaceutical Quality, CDER/FDA. As Associate Director, Dr. Tyner leads the OPQ Science Staff in coordinating the intersection between science, review and policy in OPQ as well as facilitating interactions between other CDER offices and FDA Centers. She received her PhD in Chemistry from Cornell University and joined the Food and Drug Administration in 2007 as a chemist specializing in nanotechnology. While at the FDA, Dr. Tyner has investigated the quality, safety, and efficacy of drug products containing nanomaterials, and she currently leads the CDER nanotechnology working group and is active in other CDER and FDA nanotechnology initiatives. Dr. Tyner is the author of multiple book chapters and journal articles concerning the appropriate characterization and biological impact of nanoparticle therapeutics.

Presentation
Quality Considerations and Regulatory Perspectives for Drug Products Containing Nanomaterials: FDA Perspective
Monday, March 20, 2017, 9:30 – 10:00 a.m.

In recent years there has been an increased focus on developing drug products containing nanomaterials. With this increased focus, there has been a corresponding increase in applications for drug products containing nanomaterials to the United States Food and Drug Administration (FDA) submitted for Agency review. Although subject to the same rigorous regulatory standards as any other drug product, unique properties that arise from the small size and large surface area of nanomaterials may lead to additional scientific considerations when following current FDA guidelines and practices. Such considerations may extend to determining the correct analytical techniques to characterize and control the drug product. This presentation will discuss these scientific considerations and present current regulatory perspectives for drug products containing nanomaterials.

Matthias Wacker, Ph.D.
Head of Department, Pharmaceutical Technology and Nanosciences
Fraunhofer-Institute for Molecular Biology and Applied Ecology
Frankfurt, Germany

Dr. Matthias G. Wacker received his PhD in Pharmaceutical Technology in 2010 and started a scientific career at Goethe University in Frankfurt. His research is focusing industrial nanotechnology with emphasis on the optimization of manufacturing processes for nanocarrier devices as well as methodology for assessing the release of drugs and drug candidates from nanoscaled dosage forms.

He is a member of the Center for Drug Research Development and Safety (ZAFES) and joined the Fraunhofer-Institute for Molecular Biology and Applied Ecology (IME) in 2013. There he is heading the Department of Pharmaceutical Technology and Nanosciences.

Since 2015 his department is also part of the LOEWE research center Translational Medicine and Pharmacology (TMP). Additionally, he holds a position at Goethe University and is involved in several research and teaching activities including guest lectures at the State University of Maringá (Brazil) and the University of Namibia (Namibia).

Presentation
Challenges in the Release Testing of Next-Generation Nanomedicines
Monday, March 20, 2017, 2:30 – 3:00 p.m.

Despite all advances in drug delivery, the limitations of the analytical technologies involved in the characterization of nanomedicines are still impeding further progress of an emerging market. Discriminating between different formulations and batches, drug release is one of the most important quality criteria in development and quality control of pharmaceutics. Unfortunately, there are only few methods available to sensitively measure this important parameter for nanosized carriers. The wide range of materials and formulations used in drug therapy also requires different approaches for various types of formulations. Currently, there are several methods established for the release testing of orally administered nanocrystal formulations. However, for more sensitive dosage forms such as liposomes or polymeric particles, there is no ‘gold standard’ at hand. With the development of the dispersion releaser (DR) technology, a novel dialysis-based technique will come into market. In future, it may be used to support formulation development with a more reliable methodology to improve future products.

Sylvia Wagner, Ph.D.
Head of Department, Bioprocessing & Bioanalytics
Fraunhofer Institute for Biomedical Engineering
Sulzbach, Germany

Sylvia Wagner studied chemistry at the University Karlsruhe. She did her PhD thesis in the group of Prof. Dr. H. v. Briesen at the IBMT. From 2008-2016 she was group manager at the IBMT and since 2015 she is head of department “Bioprocessing & Bioanalytics”. Her main research topics are focused on nanobiotechnology and development of preclinical *in vitro/ex vivo* models in the field of nanotoxicology as well as nanomedicine. Nanoparticulate formulations for the specific drug targeting as well as for crossing of biological barriers were preclinically tested in different *in vitro* and *ex vivo* cell culture models. Her department has established e.g., several blood-brain barrier cell culture models, a gastrointestinal barrier model, a lung model and a dermal barrier model for permeation studies. Her department was and still is involved in several joint research projects in the field of drug delivery systems based on nanotechnologies which were and are funded by EU and BMBF (“NanoDrug”; “NanoCancer”; “NanoBrain”; “BioTrap for CCC”) as well as projects supported by the German Federal Armed Forces and the private industry. One of her actual projects called “GITCare” is focused on the oral delivery of nanoparticulate packaged drugs for tumor therapy. Furthermore, several projects based on nanoparticle risk assessment coming more and more into focus, e.g., the BMBF funded projects “MINAC” and “NanoUmwelt” and the EU funded project “HISENTS”.

Presentation
Biocompatible Nanoparticles for Targeted Delivery
Wednesday, March 22, 2017, 8:30 – 9:00 a.m.

Since many centuries there have been huge challenges in medicine.
For example, evolution gave birth to an extremely useful structure: The blood-brain barrier (BBB) that protects our central nervous system homeostasis by shielding off toxic substances and pathogens. But biologically valuable does not always mean pharmacologically welcome. The BBB does not distinguish between friend and foe and causes many potentially effective brain therapeutics to fail *in vivo* - not because of a lack of potency, but because they cannot pass this barrier. This dilemma especially comes into focus for the rapidly growing numbers of neurodegenerative disorders.
Another example comes from tumor therapy. The main disadvantages of conventional chemotherapy are modest tumor response and dose limiting side effects because of non-specific action of drugs to all fast proliferating tissues.
Both described scenarios are still two of many unsolved problems in modern medicine.
However today, we can use the elegant approach of molecular Trojan Horses: the fast-emerging field of nanotechnology offers the possibility to enlarge the pool of substances by packing promising drugs into nanoparticles. Nanoparticles are a promising approach to achieve the special requirements to a drug delivery system. With them the long pursued goal of the pharmaceutical research, the specific „drug targeting“ and the „controlled release” of the drug thus minimizing side effects seems to get into reach. Nanoparticles as drug carriers can be prepared by different well established methods e.g., desolvation or evaporation techniques based on well-known biodegradable polymers such as human serum albumin (HSA), poly(lactic acid) (PLA) or copolymers like poly(lactic-co-glycolic acid (PLGA). The drug can be incorporated during the nanoparticle synthesis or adsorbed on the particle surface. Furthermore, the surface of these nanoparticles can be modified with ligands recognizing the corresponding receptor e.g. at the BBB or on cancer cells. Nanoparticles show a high drug loading efficiency with minor drug leakage as well as the ability to circumvent multidrug resistance paired with good storage stability. By this, we can mask the original physicochemical properties of substances. The advantages are tempting: Apart from reducing peripheral doses and consequently side effects, drugs can be delivered directly to target structures.
This talk will give you a short overview how and where we can use nanoparticles. The research on nanoparticles is on the starting blocks to go into clinical trials and further go on the market. However some analytical hurdles are to be taken and some regulatory recommendations are urgently needed.

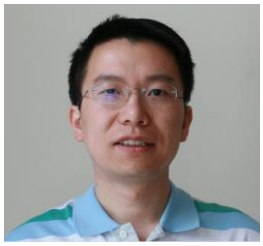
William Zamboni, Pahrm.D., Ph.D.
Associate Professor, UNC Eshelman School of Pharmacy
UNC Lineberger Comprehensive Cancer Center
University of North Carolina, Chapel Hill, NC

William Zamboni received his Bachelor of Science, Doctor of Pharmacy and Doctor of Philosophy degrees from the University of Pittsburgh School of Pharmacy, in Pittsburgh, PA. He completed his Oncology Residency at the Warren G. Magnuson Clinical Center, National Institutes of Health, in Bethesda, MD and his Research Fellowship at the Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, in Memphis, TN. Currently, he is an Associate Professor in the School of Pharmacy and UNC Lineberger Comprehensive Cancer Center. Dr. Zamboni's research program is part of the Division of Pharmacotherapy and Experimental Therapeutics in the UNC Eshelman School of Pharmacy and Molecular Therapeutics in the UNC Lineberger Comprehensive Cancer Center. He is the Director of UNC GLP Bioanalytical Facility and the Director of the Translational Oncology and Nanoparticle Drug Development Initiative ($TOND_2I$) Lab at the University of North Carolina in Chapel Hill.

He has been involved in translational studies of anticancer agents for several years. His research interests focus on the application of pharmacokinetic, pharmacodynamic, and pharmacogenetic principles in the optimization of the chemotherapeutic treatment of cancer. A second focus of his research is on the development of carrier-mediated agents (CMAs), such as nanoparticles, liposomes, conjugates and antibody drug conjugates (ADC). He has focused on evaluating the relationship between the disposition of these agents and the mononuclear phagocyte system and the factors that affecting the delivery of these agents to tumors and tissues, including the brain. He has developed methods and technologies to differentiate between the inactive-encapsulate/conjugated and active-release forms of the drugs in plasma, tissues and tumors. He also is developed phenotypic probes of the MPS that predict the pharmacokinetic and pharmacodynamic disposition of CMAs.

Presentation
Use of Mononuclear Phagocyte Platforms to Characterize Nanomaterials, Nanoparticles and Colloids
Monday, March 20, 2017, 3:00 – 3:30 p.m.

Studies have shown that nanoparticles (NPs), nanomaterials and other substances are recognized, taken up and cleared through the mononuclear phagocyte system (MPS). Thus, we developed *ex vivo* MPS screening platforms to characterize nanomaterials, NPs and colloids and to predict the *in vivo* disposition of these agents in animal models and patients. Pharmacokinetic studies of Doxil, DaunoXome, micellar doxorubicin (SP1049C) and small molecule (SM) doxorubicin were performed in SCID mice, Sprague-Dawley rats, beagle dogs and patients with cancer. An *ex vivo* MPS profiling platform was used to evaluate the interaction between the same agents, as well as colloid-forming and non-colloid forming SM drugs. In all species, the systemic clearance was highest for SP1049C and lowest for Doxil. With the exception of dog blood, the MPS screening results of mouse and rat blood showed that the greatest reduction in phagocytosis occurred after the *ex vivo* addition of SM-doxorubicin > SP1049C > DaunoXome > Doxil. The MPS profiling platform in rats, but not dogs, could differentiate between colloid forming and non-colloid forming drugs. The results of the MPS profiling platform were consistent with *in vivo* clearance rates of NP and SM anticancer drugs in mice, rats, dogs and patients. This study suggests the MPS profiling platform is an effective method to screen and differentiate the important characteristics of NPs and colloid-forming drugs that affect their *in vivo* clearance. Implications of these findings on preclinical prediction of human clearance will be discussed.



Jingtao Zhang, Ph.D.
Department of Pharmaceutical Sciences, Merck Research Laboratories
Merck & Co., Inc.
West Point, PA

Dr. Jingtao Zhang is a principal scientist in the Department of Pharmaceutical Sciences of Merck Research Laboratories at West Point, Pennsylvania. Over the 10 years' industrial tenure, he has extensive experiences in diverse modalities including synthetic peptides, small molecules, nanomedicine, and oligonucleotides. His current role is in the preformulation and drug delivery research supporting the development of synthetic peptides and small molecule therapeutics. His past roles were in the formulation, biophysical characterization, and analytical testing of siRNA drug delivery systems to advance the clinical development of siRNA therapeutics. Prior to Merck, he received his Ph.D. in Chemical Engineering from the University of Wisconsin-Madison in 2007. He published more than 20 articles in peer-reviewed journals and presented extensively in industrial and academic conferences.

Presentation
The Importance of Multi-Dimensional Characterization in the Pharmaceutical Development and Control of siRNA Nanoparticle Drug Product
Tuesday, March 21, 2017, 4:15 – 4:45 p.m.

Nanoassemblies such as Lipid nanoparticles (LNP) have been a critical enabling technology during the development of small interfering RNA (siRNA) therapeutics. Despite the compelling therapeutic opportunity offered by siRNA, its poor physiochemical and pharmaceutical properties frequently result in the failue during in vivo translation. LNPs have been proven to be a highly effective approach to overcome this challenge and is currently expanding its application to other emerging new modalities (e.g. mRNA vaccine, CRISPR-CAS9 gene editing). It should be borne in mind that LNP based siRNA drug delivery system is a highly complex drug product and its pharmaceutical development can be challenging. In-depth and multi-dimentional characterization to ensure the consistency and quality is one of the critical actitivty required for the development of this product.

This presentation will focus on the advanced understanding in the structure and heterogeneity distribution of siRNA based lipid nanoparticles achieved during the pharmaeceutical devleopment process. Results from the characterization by Cryo-TEM, SAXS, multi-angle light scattering will be presented. In addition, size-based separation as well as different fractionation methods that permit the study of size, composition, and bioperformance polydispersity in LNPs will be presented. LNPs with similar bulk properties were evaluated in-depth using the above methods and profound differences in batch polydispersity were observed between them. The present results suggest that LNP drug products are highly complex and diverse in nature and care should be taken in examining and understanding them to ensure quality and consistency. The methods described here can not only serve as a method for understanding LNP product property, permitting control on product quality, but also could serve as a potential manufacturing method for product purification. Understandings obtained in this work can help to facilitate the development of LNPs as a well-defined pharmaceutical product.

Ye Zhang, Ph.D.
Drug Product Quality Reviewer, CDER
U.S. Food and Drug Administration
Silver Spring, MD

Ye Zhang is a drug product quality reviewer at Center for Drug Evaluation and Research, U.S. Food & Drug Administration (FDA). Since joining FDA in 2014, Ye has been worked on risk based Chemistry, Manufacturing and Control (CMC) review for immediate release, modified release and liquid based drug products. Prior to FDA, Ye was a Principal Scientist at Merck for seven years working on biophysical and chemical method development, formulation development, and cGMP batch release and stability to support preclinical and clinical development of siRNA drugs including lipid nanoparticles (LNP), antibody conjugates and peptide conjugates. Ye had worked on designing and developing nanoparticle formulations for liver, lung, tumor and skin delivery of siRNA while at SiRNA Therapeutics from 2004 to 2006. Ye received her M.D. from Beijing Medical University and Ph.D. in Pharmaceutical Sciences from University of Colorado.

Presentation
Development of In vitro Release Procedure for Complex Nanotechnology Products
Monday, March 20, 2017, 1:40 – 2:10 p.m.

Since the discovery of RNA interference (RNAi) by Fire and Mello in 1998 and the demonstration of synthetic small interfering RNA (siRNA) mediated RNAi by Tuschl and colleagues in 2001, therapeutic development of siRNA drugs to silence disease genes has been pursued extensively. Efficient delivery of siRNA to target cells and tissues with minimal toxicity is the major challenge for the successful development of siRNA based therapeutics. For systemic delivery of siRNA, one of the most advanced delivery technologies is lipid nanoparticles (LNPs). In order to rapidly screen and select lead candidates for in vivo evaluation of LNPs for systemic siRNA delivery, an in vitro assay is developed. The strategy is to mimic the in vivo experience of LNPs after systemic administration, such as interactions with serum components, exposure to endosomal pH environments, and interactions with endosomal membrane lipids. It is postulated that the amount of siRNA released from LNPs after going through these treatments can be used as a screening tool to rank order the effectiveness of siRNA delivery by lipid nanoparticles in vivo. LNPs were incubated with 50% serum from different species (i.e. mouse, rat, or rhesus) at 37°C. The resulting samples were then reacted with anionic, endosomal-mimicking lipids at different pHs. The amount of siRNA released from LNPs was determined using spectrophotometry employing the fluorescent indicator SYBR Gold. Our results indicated that the amount of siRNA liberated was highly dependent upon the species of serum used and the pH to which it was exposed. A good correlation between the amount of siRNA released and the in vivo efficacy was observed. In conclusion, an in vitro siRNA release assay was developed to screen and rank order LNPs for in vivo evaluation.