Nanomedicine Virtual Workshop

DRAFT AGENDA

Advancing Measurement Technologies and Standards for Nanomedicine

14-16 June 2021

Day 1 (14 June): Application of Nanotechnology

Presenters:

- **Marianne Ashford (Keynote)** – Senior Principal Scientist, AstraZeneca
- **Scott McNeil** – Professor, Nano-pharmaceutical & Regulatory Sciences, University of Basel
- **Yvonne Perrie** – Professor in Drug Delivery, University of Strathclyde
- **Chris Tam** – Co-Founder and CEO, Integrated Nanotherapeutics
- **Adam Crowe** – Manager, Analytical Development, Precision Nanosystems
- **Qin Zou** – Group Leader and Associate Research Fellow, Pfizer

Panel Discussion:

Challenges, opportunities, emerging technologies

Day 2 (15 June): Regulatory Sciences

Presenters:

- **Anil Patri (Keynote)** – Director Nanotechnology Core Facility, US FDA
- **Rene Thürmer** – Deputy Head, BfArM Federal Inst for Drugs & Med Device
- **Xiaoming Xu** – Senior Chemist, Center for Drug Evaluation and Research, US FDA
- **Kate Arnot** – Director Regulatory CMC, AstraZeneca
- **Marina Dobrovolskaia** – Director of Operations and the Head of Immunology Section, Nanotechnology Characterization Lab, Frederick National Laboratory for Cancer Research sponsored by the National Cancer Institute
- ***TBD***

Panel Discussion:

Regulation, guidance, best practices, gaps, alignment

Day 3 (16 June): Standards & Measurement

Presenters:

- **Dean Ripple (Keynote)** – National Institute of Standards and Technologies
- **Jeffrey Clogston** – Principal Scientist and the Head of the Physicochemical Characterization Section, Nanotechnology Characterization Lab, Frederick National Laboratory for Cancer Research sponsored by the National Cancer Institute
- **Fanny Caputo** – Research Scientist, SINTEF
- **Dora Mehn** – Project Officer, European Commission's Joint Research Centre
- **Shan Zou** – Senior Research Officer, National Research Council Canada
- **Emiliana De Santis** – Senior Research Scientist, National Physical Laboratory

Panel Discussion

Measurement methods, measurement technology, reference materials, standards

Presentations overview

Presenter:

Marianne Ashford
Senior Principal Scientist

Affiliation

AstraZeneca

Presentation Title and Abstract

Design and Development of nanomedicines to enable innovative medicines

Nanomedicines can address some of the key challenges in Drug Discovery. For small molecule drug discovery; they can enable development of compounds with solubility and lack of therapeutic index; two critical properties for successful development. Nucleic acid based therapeutics have the potential to prosecute many novel targets important for treating diseases yet intracellular delivery is challenging; nanomedicines can deliver drugs intracellularly and thus are important for their exploitation.

This talk with focus on design & development of different nano-based delivery systems; it will discuss the critical factors in the design a nano delivery system for improving therapeutic index and factors important in design of a nano delivery system for intracellular delivery. It will summarise important aspects for successful clinical translation including the importance of understanding the target and disease, the need for robust formulation and manufacturing processes and for advanced analytical characterisation to ensure quality and reproducible in vivo performance.

Background

Dr. Marianne Ashford is a Senior Principal Scientist in a global role in Advanced Drug Delivery Department within Pharmaceutical Sciences at AstraZeneca. Marianne is responsible for applying drug delivery approaches which enable the progression of innovative medicines and is working to enable novel targets through intracellular delivery of new modalities such as nucleic acid-based drugs.

Marianne has been instrumental in introducing nanomedicines to improve therapeutic index into the AstraZeneca Oncology clinical portfolio. She has initiated several collaborations and the building of the internal capability in nanomedicines, drug targeting and intracellular delivery.

Marianne has published over 65 peer reviewed papers and reviews, six book chapters and holds several patents. Marianne holds Honorary Professor roles at the Universities of Nottingham and Manchester and is a Fellow of the Controlled Release Society.

Presenter:

Yvonne Perrie
Professor in Drug Delivery

Affiliation

University of Strathclyde

Presentation Title and Abstract

Delivery systems for mRNA Vaccines – the impact of formulation and route

The efficacy of RNA-based vaccines has been recently demonstrated, leading to the use of mRNA-based COVID-19 vaccines. To date, lipid nanoparticles (LNPs) based on ionizable amino-lipids are the most advanced RNA delivery systems and this technology is now being deployed in COVID-19 vaccines. Within our laboratories we have investigated the impact of the delivery system formulation and platform and the route of administration. To achieve this, we investigated the immunogenicity of a self-amplifying mRNA encoding the rabies virus glycoprotein encapsulated in 3 different non-viral delivery platforms (lipid nanoparticles, solid lipid nanoparticles and polymeric nanoparticles). Immunogenicity data in a mouse model showed that lipid nanoparticles and solid lipid nanoparticles induced similar responses and comparable potency with the commercial (non-RNA based) vaccine.

Background

Yvonne Perrie current position is Professor in Drug Delivery within the Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, Scotland. Her research is multi-disciplinary and focuses on the development of drug delivery systems to facilitate the delivery of drugs and vaccines, thus providing practical solutions for current healthcare problems.

Presenter:

Adam Crowe
Manager, Analytical Development

Affiliation

Precision Nanosystems

Presentation Title and Abstract

Characterization of Encapsulation, Extraction, and Analysis of mRNA in Lipid Nanoparticles for Drug Delivery

mRNA Lipid Nanoparticle (LNP) vaccines have proven paramount in the fight against COVID-19, however characterization of these therapeutics remains technically challenging due to their complex structure. The mRNA payload is encapsulated within a solid lipid particle suspended in an aqueous vehicle containing a range of stabilizers and excipients. Consequently, mRNA must be extracted from the LNP formulation before being characterized. Moreover, changes in the quantity, purity, or integrity of the mRNA payload must be assessed following the LNP formulation process. Herein, a general guide of methodologies and challenges for the characterization of the mRNA payload, localization with the LNP, and extraction from the LNP is presented. Overall, recommendations for industry-best-practices are discussed.

Background

Dr. Adam Michael Crowe is Manager, Analytical Development at Precision Nanosystems Inc (PNI). Adam Crowe comes with a wealth of bioanalytical experience studying enzymology, mass spectrometry, and metabolomics at the University of British Columbia (UBC). At PNI, Adam manages an analytical team focused on the development of techniques to study all characteristics of mRNA LNPs, with a focus on the mRNA payload and the structural lipids. These expertise have been employed in the development of more than 100 RNA LNP formulations from countless academic or biopharma groups through all stages of the drug development process.

Presenter:

Qin Zou
Group Leader and
Associate Research Fellow

Affiliation

Pfizer

Presentation Title and Abstract

Holistic Characterization of Nanoparticles using Advanced Analytical Tools

Engineered nanoparticles, including lipid-based nanoparticles, have become increasing important in development of medical therapeutics. In-depth understanding of these macromolecular assemblies in terms of their physicochemical properties provides solid foundation for better product quality control. Various advanced analytical techniques will be reviewed and discussed for their application in product characterization, particularly for the intact nanoparticles.

Background

Qin “Chinn” Zou is currently the group leader and associate research fellow at Pfizer Inc., responsible for product and process characterization using various biophysical and biochemical techniques. Before joining Pfizer, he was with Eli Lilly and Co. and worked on formulation development, analytical research and biophysical analysis for biotherapeutics. Qin has a PhD in physical biochemistry from University of Iowa College of Medicine, specifically on thermodynamics of protein stability, protein unfolding and protein interaction. He was also a postdoctoral fellow at Indiana University School of Medicine studying enzymology and protein crystallography.

Presenter:

Dr. René Thürmer
Deputy Head

Affiliation

BfArM (Federal Institute for Drugs and Medical Devices, Bonn, Germany)

Presentation Title and Abstract

European Regulatory Considerations on Nano-Enabled Medicinal Products

The content of the presentation will focus on recent advances in the approval of nanomedicinal products. Current regulatory considerations and requirements for pharmaceutical quality will be highlighted. It will be described how interaction with regulatory agencies early from the beginning may facilitate and promote clinical development programmes.

Background

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.

Presenter:

Dr. Xiaoming Xu
Senior Chemist

Affiliation

Center for Drug Evaluation and Research, US FDA

Presentation Title and Abstract

Supporting the Development of Drug Products Containing Nanomaterials: Guidance, Trends, and Research

Nanomaterials can appear in drug products to perform different functions, including serving as active pharmaceutical ingredients (APIs), carriers loaded with an active ingredient, or excipients. The unique properties of nanomaterials, such as small size, large surface area to mass ratio, and variable pharmacokinetic characteristics are useful to overcome some of the limitations commonly found in their larger-scale counterparts. Yet, these very properties that render nanomaterials distinct also make them challenging to control for quality and assess for bioequivalence. In this presentation, some of the common risk factors and quality considerations associated with nanomaterial containing drug products are discussed. Case studies are provided to illustrate the unique challenges associated with the characterization and quality control of nanomaterial drug products.

Background

Dr. Xiaoming Xu is a Senior Chemist in the CDER/OPQ lab. In his role as a Principle Investigator, he leads multiple research areas such as complex ophthalmics, nanomaterials, and advanced manufacturing. He also leads a particle characterization lab in CDER and provides hands-on trainings to reviewers on various topics, including concept of particle size and measurement.

Dr. Xu is a member of the FDA Nanotechnology Task Force and is co-leading the Nanotechnology Reviewer Network. As the FDA representative, Dr. Xu also participates in various international collaborations in areas relating to nanotechnologies, including standard development and International Pharmaceutical Regulator’s Program. Dr. Xu is also an editorial board member of the International Journal of Pharmaceutics.

Presenter:

Dr. Marina Dobrovolskaia
Director of Operations and the
Head of Immunology Section

Affiliation

Nanotechnology Characterization Laboratory, Frederick National Laboratory for Cancer Research sponsored by the National Cancer Institute

Presentation Title and Abstract

Biomarkers of Nanoparticle Immunotoxicity: Regulatory, Translational and Basic Research Perspective

Despite the sophistication and many therapeutic advantages, the clinical translation of nanotechnology-formulated drug products is often complicated by the immune-mediated toxicities. Cytokine storm, fever-like reactions, and complement activation are among the most common and best-studied acute dose-limiting toxicities. Immunotoxicity due to the alteration in the immune system's function, including but not limited to the immunosuppression and autoimmunity, take longer to develop and are less understood both in terms of the nanoparticle structure-activity relationship and methodologies appropriate for monitoring these toxicities. This presentation will review existing and emerging biomarkers of nanoparticle immunotoxicity, propose experimental strategies for improving our understanding of the immunological safety of nanomedicines and discuss future directions. Case studies of the role of nanoparticle physicochemical properties and their contribution to the immunotoxicity will be used to support the proposed strategy.

Background

Dr. Dobrovolskaia is Laboratory co-Director, Director of Operations and the Head of Immunology Section at the Nanotechnology Characterization Laboratory (NCL). In her role as the Director of Operations, Dr. Dobrovolskaia leads the NCL operations to provide preclinical nanoparticle characterization services to the nanotechnology research community, advance the translation of promising nanotechnology concepts from bench to the clinic, and contribute to the education of the next generation of scientists in the field of preclinical development of nanotechnology-based products, the activities emphasized in the NCL mission. She also directs the performance of Immunology, Client Relations and Administrative sections of the NCL. Closely integrated functioning of these sections plays a critical role in advancing the NCL's key strategic goals, and in supporting the missions of the Frederick National Laboratory for Cancer Research. In her role as the Head of the Immunology Section, Dr. Dobrovolskaia leads a team conducting preclinical studies to monitor nanoparticles' toxicity to the immune system both in vitro and in vivo using variety of immune function animal models. Prior to joining the NCL, Dr. Dobrovolskaia worked as a Research Scientist in a GLP laboratory at PPD Development, Inc. in Richmond, VA, where she was responsible for the design, development and validation of bioanalytical ligand-binding assays to support pharmacokinetic and toxicity studies in a variety of drug development projects. She received her M.S. degree from the Kazan State University in Russia; Ph.D. from the N.N. Blokhin Cancer Research Center of the Russian Academy of Medical Sciences in Moscow, Russia; and MBA from the Hood College in Frederick, MD. Since 2016, she is also a member of the Project Management Institute and a certified Project Management Professional.

Presenter:

Dr. Jeffrey D. Clogston
Principal Scientist

Affiliation

Nanotechnology Characterization Laboratory, Frederick National Laboratory for Cancer Research sponsored by the National Cancer Institute

Presentation Title and Abstract

Physicochemical Characterization of Lipid-based Delivery Systems: What we know and what we still need to know

The National Cancer Institute's (NCI) Nanotechnology Characterization Laboratory (NCL) conducts preclinical characterization including physicochemical (analytical), in vitro, and in vivo of nanoparticles intended as cancer therapeutics and diagnostics. This presentation will highlight the characterization parameters, methods, and considerations related to the physicochemical characterization of lipid-based delivery systems from the testing of more than 450 nanotechnology-based candidate cancer treatments and diagnostics, and are based on the characterization aspects found in the chemistry, manufacturing, and controls (CMC) section in the FDA's industry guidance document for liposome drug products. Furthermore, the current gaps and needs in the physicochemical characterization of lipid-based delivery systems will be discussed.

Funded by NCI Contract No. 75N91019D00024.

Background

Dr. Jeffrey D. Clogston is a Principal Scientist and the Head of the Physicochemical Characterization Section at the Nanotechnology Characterization Laboratory (NCL). In his position, Dr. Clogston conducts physicochemical characterization and standardization of nanoparticles, develops new analytical methodology for critical quality attributes, and assesses current instrumentation for nanoparticle characterization. Prior to joining the NCL in March 2006, Dr. Clogston received his Ph.D. in Chemical Engineering from The Ohio State University. His research dissertation was on the application of the lipidic cubic phase for drug delivery, wastewater remediation, and membrane protein crystallization. His areas of expertise include physicochemical characterization of and in vitro release from lipid-based drug delivery systems, analytical methodology, and protein and lipid biochemistry.

Presenter:

Dr. Fanny Caputo
Research Scientist

Affiliation

SINTEF

Presentation Title and Abstract

Measuring physical properties of liposomes and of lipid-based nanoparticles for RNA delivery with multidetector asymmetric flow field flow fractionation (MD-AF4): from method development to standardization

Asymmetric-flow field-flow fractionation (AF4) has been recognized as an invaluable tool for the characterisation of nano-enabled therapeutics and vaccines. To apply MD-AF4 in the pharmaceutical setting, robust and high quality standard operating procedures (SOPs) needs to be developed, tailored on specific sample properties, and according to identifies parameters necessary to validate methods. We will describe how a unique international collaboration led to the development of robust SOPs for the characterisation of liposomal products and lipid-based nanoparticles for RNA delivery (LNP-RNA). Examples of how MD-AF4 methodologies have been validated and used for the analysis of key quality attributes, such as particle size, shape, stability, particle concentration, aggregation and drug loading will be described. MD-AF4 is used as a successful example to describe the pathway from SOPs to standardisation and how the work done on liposomal products can open a fast track for the development of methods for LNP-RNA.

Background

Researcher at SINTEF (Norway) since 2019, Dr Funny Caputo was previously working at CEA (France). Her main interest lies in the physical-chemical assessment of nanomaterials and nanopharmaceuticals for safety and quality assessment and in the standardization of characterization methods for regulatory purposes. She is the chair of the safety and characterization WG of the Nanomedicine European Technology platform and active member of the ASTM E 56 where she is contributing to the first standard test methods on MD-AF4 for testing of liposomal products.

Presenter:

Dr. Dora Mehn
Project Officer

Affiliation

European Commission's Joint Research Centre

Presentation Title and Abstract

Analytical Ultracentrifugation in nanomedicine characterization

Analytical Ultracentrifugation is a classical technique developed for protein molecular mass measurements. In our studies, Analytical Ultracentrifugation (AUC) was applied not only as a confirmatory method for light scattering based ensemble sizing techniques, but as a true orthogonal solution in nanomedicine characterization that uses fundamentally different principles from light scattering for measuring particle size distributions. Moreover, AUC might provide information on homogeneity of very small nanoparticles such as monoclonal antibodies, on antibody-antigen interactions, on particle density (including density of floating particles), and in some cases on drug loading and release in complex medium. The presentation will illustrate the potential of AUC in these applications and highlight the possible benefits of developing validated AUC protocols for medical nanoparticle characterization.

Background

Dr. Dora Mehn is a project officer at the Consumer Products Safety Unit of the European Commission's Joint Research Centre (Ispra, Italy). She earned her degree as a teacher of Biology and Chemisty (1997) and her PhD in Environmental Chemistry (2002) from the University of Szeged (Hungary). After post-doctoral fellowships at the University of Namur (Belgium) and at the University of Szeged (nanoparticle synthesis and characterization) she joined Solvo Biotechnology (Szeged, Hungary, 2005-2008, head of the fee for service screening laboratory). After 3 years at the Joint Research Centre (Ispra, Italy, 2008-2011, grantholder) and 2.5 years at the Fondazione Don Gnocchi (Milan, Italy, researcher) she became an official of the European Commission in 2014. Since then, she has been working on nanoparticle characterization using various separation and size measurement methods and on the extraction and spectroscopic identification of micro- and nanoplastics.

Presenter:

Dr. Shan Zou — **Senior Research Officer**

Affiliations

Team Leader for the Nanoscale Measurement Disciplines at the Metrology Research Centre of the National Research Council Canada. Adjunct Professor in the Department of Chemistry at the Carleton University.

Presentation Title and Abstract

Certified reference materials for lipid-based nano-delivery systems – development and unique challenges

Through the Innovative Solutions Canada program, the National Research Council of Canada (NRC) and Integrated Nanotherapeutics Inc. (INT) are working together to develop stable drug carrier formulations, in order to support the development of drug product submissions, streamline the regulatory approval process and improve the manufacturability of drug delivery formulations. Six formulations of liposomes and lipid nanoparticles (LNP) using INT's proprietary scaffold lipid technology have been produced with three different sizes and three different surface charges (neutral, positive or negative). The size, polydispersity and zeta potential of each formulation were characterized by dynamic light scattering. Formulations were prepared at a specific concentration in the presence of sucrose for long term storage at -70 °C. Strategies and challenges to improve the stability and reduce the variability of formulations will also be discussed.

Background

Dr. Zou obtained her PhD in studying the supramolecular interactions and stimuli-responsive polymers from the University of Twente, The Netherlands in 2005. After her postdoc work at the University of Toronto, she joined NRC in 2007. Her research focuses on the development of nanoscale measurement methods including the integrated multimodal techniques for characterization of nanomaterials and quantitative detection of cancer cells and cellular mechanical responses to drug treatments. Dr. Zou has expertise in nanomechanics, cytotoxicity measurements of nanomaterials, surface and interface characterizations. She seeks to contribute to a greater understanding of the effects of nanomaterials on the environment and living systems, and to promote the safe and responsible use of nanotechnology tools and nanomaterials. She currently serves as the the Secretary for the ASTM International E56 Nanotechnology Committee (2018-2022) and was the Secretary of the Canadian National Committee for IUPAC (2014-2020). In representing Canada she is also the member of BIPM-CCQM Cell Analysis Working Group.