18TH LIPOSOME RESEARCH DAYS 2024

DELIVERING INNOVATION AND DRIVING APPLICATIONS

2024

JUNE 26 TO 29, 2024

Technology and Innovation Centre (TIC), University of Strathclyde Glasgow, Scotland

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Harris Makatsoris

Harris is Professor Of Manufacturing Systems in the Department of Engineering at King's College London and the founder of Centillion Technology Limited, a UK based biotech specialising in the rapid scaling and manufacture of RNA-based therapeutics and vaccines. He has a process engineering background with 27-years experience in both industry and academia. In all his past and present roles, he is managing interdisciplinary projects that require integration and coordination. Harris is an expert in continuous RNA manufacturing. His work is focusing on addressing the challenges in the rapid design, development and scalable manufacture of RNA and other nucleic acids and has pioneered the application of flow technologies in RNA manufacture, of various types. His research has attracted over £26m and he is currently leading a unique multi-disciplinary, multi-million pound programme comprising both industry and academia, building the Biofoundry-in-a-Box (BiaB). The BiaB is a unique portable, multi purpose RNA microfactory designed for the rapid design and deployment of a range of therapeutics and vaccines, with Low and Middle Income Countries in mind. He has several patents in his name in the space of RNA manufacture and continuous bioprocessing. He is highly experienced in technology transfer to industry through a variety of commercial routes.

BIOFOUNDRY-IN-A-BOX: BY DESIGN RNA DRUG PRODUCT DEVELOPMENT AND MANUFACTURE FOR RAPID RESPONSE

Our work is focusing on ensuring the equitable access to RNA based vaccines by everyone, everywhere. This vision is underpinned by the creation of flexible manufacturing networks comprising autonomous and multipurpose RNA manufacturing and discovery nodes in any geography. The nodes work together at times of emergency and peak demand, as an integrated virtual enterprise to respond to emergency scenarios with the manufacture of advanced RNA-based vaccines, whilst can utilise spare capacity for the manufacture of any RNA drug products at times of low demand. In this talk, a brief overview of the BiaB technology will be given, focusing then on our Quality-By-Design framework with examples.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Alberto Gabizon

Gabizon pioneered the development of a new generation of long-circulating liposomes known as Stealth liposomes which greatly improved liposome stability and selective accumulation in tumors. His inventorship and research contribution played a key role in the development of DOXIL® (pegylated liposomal doxorubicin), a unique anticancer formulation extensively used in the clinic with important pharmacologic and safety advantages over conventional chemotherapy. Gabizon was first to identify the cardioprotection of liposome delivery in doxorubicin-based chemotherapy. His recent inventions include two liposome products for cancer therapy: Promitil® (pegylated liposomal mitomycin-C prodrug), a formulation currently in clinical studies with improved safety over the parent drug mitomycin C; and, pegylated liposomal alendronate of doxorubicin (PLAD), a hybrid therapeutic product with chemotherapeutic and immunotherapeutic properties currently in research and development phase.
He has received the National Prize of Medicine of Spain Ministry of Education, the Hebrew University Kaye Innovation Award for the invention "*Liposomal Doxorubicin for Cancer Treatment*", and the Alec Bangham Life Time Achievement Award of the International Liposome Research Society.
Gabizon is active in medical oncology practice and early phase clinical trials. His research focuses on liposomes in drug delivery, targeting of drugs, and experimental cancer therapy. He has published over 180 articles and book chapters, and is an inventor of 15 USPTO and EPO-approved patents.
Gabizon is full Professor at the Hebrew University-Faculty of Medicine and director of the Nano-oncology Research Center at Shaare Zedek Medical Center in Jerusalem, Israel.

MULTI-MODALITY THERAPY TO IMPROVE EFFICACY OF NANOMEDICINES

Nanoparticles can provide effective control of the release rate and tissue distribution of their drug payload, leading to major pharmacokinetic and pharmacodynamic changes vis-à-vis the free drug. Liposomes are among the most frequently used nanoparticle systems for parenteral delivery of drugs. Pegylated liposomes are of particular interest because of their prolonged circulation time and enhanced accumulation in tumors via the enhanced permeability and retention (EPR) effect.
Nanomedicines are an attractive tool for multimodality therapy in conjunction with radiotherapy, immunotherapy and mechanotherapeutics. Combination with radiotherapy may enhance the EPR effect and thereby the radiosensitizing effect. Combination of nano-chemotherapeutics with immune checkpoint inhibitors, particularly when using immunogenic cell death-inducing drugs, has a strong biological and pharmacological rationale that is yet to be explored in the clinic. Mechanotherapeutics can allow for changes in the tumor micro-environment and improved intratumor diffusion of nanomedicines.
Furthermore, co-encapsulation of drugs with different mechanisms of action, such as chemotherapy and immunomodulation, can also be considered a multimodality platform. For example, co-encapsulation of alendronate and doxorubicin in pegylated liposomes leads to a unique formulation assembling two drugs with non-overlapping toxicities, and blending together chemotherapeutic and immunomodulatory effects.
Rational use of multimodality therapy may help tap the unfulfilled added value of nanomedicines in cancer therapy and allow for a quick translation to the clinic.

References

- Gabizon AA, de Rosales RTM, La-Beck NM. Translational considerations in nanomedicine: The oncology perspective. *Adv Drug Deliv Rev.* 2020;158:140-157.
- Gabizon A, Ohana P, Amitay Y, Gorin J, Tzemach D, Mak L, Shmeeda H: Liposome co-encapsulation of anti-cancer agents for pharmacological optimization of nanomedicine-based combination chemotherapy. *Cancer Drug Resist* 2021, 4(2):463-484.
- Sapir E, Pfeffer R, Wygoda M, Purim O, Levy A, Corn B, Amitay Y, Ohana P, and Gabizon A: Pegylated liposomal mitomycin C lipidic prodrug in combination with external beam radiotherapy in patients with advanced cancer: a Phase 1B study. *Int'l Journal of Radiation Oncology, Biology, and Physics (Red Journal)*, 2023, 117(1):64-73.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Dr Anna Blakney

Dr. Anna Blakney is an Assistant Professor and Tier 2 Canada Research Chair in the Michael Smith Laboratories and School of Biomedical Engineering at UBC. She received her Bachelor of Science in Chemical & Biological Engineering from the University of Colorado at Boulder, and her PhD in Bioengineering from the University of Washington. She completed a postdoctoral fellowship at Imperial College London on the development of molecular and biomaterial engineering strategies for delivery of self-amplifying RNA. Her lab uses bioengineering, molecular biology and immunology approaches to develop the next generation of RNA vaccines and therapies. Her research has been published in a variety of top tier journals including ACS Nano, Nature Communications, Molecular Therapy, Biomaterials, Journal of Controlled Release, and Advanced Materials. She is also a passionate science communicator and runs a TikTok channel dedicated to educating the public about RNA biotechnology, which now has >250,000 followers and >18M views.
Dr. Blakney has received numerous awards and recognitions in addition to the Tier 2 Canada Research Chair in Nucleic Acid Bioengineering, including the 2023 MIT Tech Review's 35 Innovators Under 35, 2022 Gairdner Early Career Investigator Award, the 2021 UBC President's Award for Public Education Through Media and the 2022 Controlled Release Society Gene Delivery and Editing Focus Group Young Investigator Award.

OPTIMIZATION OF LIPID NANOPARTICLE IMMUNOGENICITY FOR VACCINE OR THERAPEUTIC INDICATIONS

Lipid nanoparticles (LNPs) are the leading technology for RNA delivery, given the success of the Pfizer/BioNTech and Moderna COVID-19 messenger RNA (mRNA) vaccines, and small interfering RNA (siRNA) therapies (patisiran). However, the immunogenicity of lipid nanoparticles is not well understood, although there is a growing appreciation in the field that the lipids themselves have adjuvant properties. We anticipate that LNP formulations for different applications will require tailored immunogenic properties. For example, the LNP-induced inflammation may be beneficial for a vaccine indication, but detrimental for a therapeutic. Here, we explore the cellular activation that is caused by all components of the LNPs, including the cargo (messenger RNA or self-amplifying RNA) and each of the lipids (ionizable lipid, phospholipid, cholesterol, PEGylated lipid). We transfected primary human peripheral blood mononuclear cells (PBMCs) and analyzed the inflammation in each cell using single-cell RNA sequencing (scRNAseq). We generated a 'fingerprint' of activation that is caused by the payload (RNA) or the lipids themselves in different cell types. Then we used two iterations of Design of Experiments (DoE) (Definitive Screening Design and Box Behnken Design) to optimize RNA formulations using the leading, FDA-approved ionizable lipids (MC3, ALC-0315 and SM-102). We identified three formulations to minimize cellular activation, maximize cellular activation or meet a CQA profile while maximizing protein expression. These compositions and parameters may be useful for designing formulations for a range of applications, such as vaccines or protein replacement therapies.

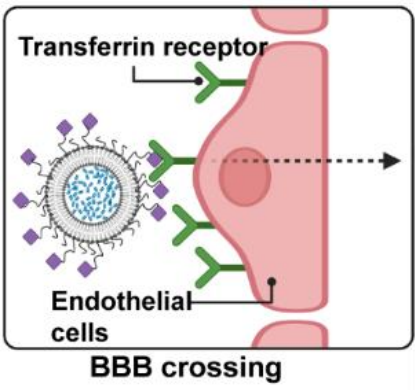
Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Avi Schroeder

Avi Schroeder is a Professor of Chemical Engineering at the Technion – Israel Institute of Technology, where he heads the Laboratory for Targeted Drug Delivery and Personalized Medicine Technologies https://www.schroederlab.com/.
Dr. Schroeder conducted his Postdoctoral studies at the Massachusetts Institute of Technology (MIT), and his PhD jointly at the Hebrew and Ben Gurion Universities.
Avi is the recipient of more than 30 national and international awards, including being named a KAVLI Fellow, the Intel Nanotechnology-, TEVA Pharmaceuticals-, and the Wolf Foundation Krill Awards. Avi is the author of more than 60 papers, the inventor of 19 patents, and co-founder of multiple startup companies based on these discoveries.
Schroeder is a former member of the Israel Young National Academy of Sciences, is a current member of Israel's National Council for Civilian Research and Development, and the President-elect of the Controlled Release Society (CRS).

BRAIN-TARGETED NANOPARTICLES FOR TREATING PARKINSON'S DISEASE: FROM BIOLOGICS TO SYNTHETIC CELLS



Nanotechnology holds numerous potential benefits for treating disease, including the ability to transport complex molecular cargoes, including RNA and proteins, as well as targeting specific tissues, including the brain. Brain-targeted nanoparticles enhance the delivery of monoclonal antibodies (mAbs) across the blood-brain-barrier (BBB) and into neurons, thereby allowing the intracellular and extracellular treatment of Parkinson's disease. 100-nm BTL cross human BBB models intact and are taken up by primary neurons. Within neurons, SynO4 is released from the nanoparticles and bound to its target - alpha-synuclein (AS), thereby reducing AS aggregation, and enhancing neuronal viability. In vivo, intravenous administration results in a seven-fold increase in mAbs in brain cells, decreasing AS aggregation and neuroinflammation, and improved behavioral motor function and learning ability in mice. Targeted nanotechnologies offer a valuable platform for drug delivery to treat brain neurodegeneration.
The evolution of drug delivery systems into *synthetic cells*, programmed nanoparticles that have an autonomous syn-bio capacity to synthesize diagnostic and therapeutic proteins inside the body, and their promise for treating disease, will be discussed.

References:

1. Theranostic barcoded nanoparticles for personalized cancer medicine, Yaari et al. Nature Communications, 2016, 7, 13325
2. Synthetic cells with self-activating optogenetic proteins communicate with natural cells, Adir et al. Nature Communications, 2022, 13, 2328
3. Brain-Targeted Liposomes Loaded with Monoclonal Antibodies Reduce Alpha-Synuclein Aggregation and Improve Behavioral Symptoms in Parkinson's Disease, Advanced Materials, 2304654, 2023

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Dr Mangala Rao

Dr. Mangala Rao is currently the Chief of the Laboratory of Adjuvant and Antigen Research in the Military HIV Research Program (MHRP) at the Walter Reed Army Institute of Research (WRAIR). She received her Ph.D. in Biochemistry from The Indian Institute of Science, Bangalore, India. She completed her postdoctoral fellowship on IgE receptors on B lymphocytes in the laboratories of Dr. Arnold Froese, University of Manitoba, Canada, and Dr. Daniel H. Conrad, Johns Hopkins University School of Medicine, Baltimore, MD. She joined WRAIR in 1990 as an NRC Senior Research Associate in the Department of Membrane Biochemistry, Division of Biochemistry, and then became a research chemist in 1994. The department later merged with MHRP. The focus of the Rao laboratory has been to develop Army Liposome Formulations (ALF) as carriers of antigens and vaccines and elucidate the mechanism(s) of ALF adjuvants, develop novel technologies for delivery of antigens and vaccines and conduct preclinical testing of vaccines. These projects have utilized malaria, Ebola, dengue, anthrax, HIV, and SARS-COV-2 antigens, with a particular focus on HIV-1 antigens. In addition, the Rao lab is also evaluating the effect of ALF adjuvants on HIV-1 infection in human macrophages and T cells *in vitro* and its effects on cell surface receptors, understanding the role of neutralizing and non-neutralizing antibodies in preventing the early entry of HIV into cells, and evaluating the suitability of humanized DRAGA mice as a model for HIV-1 pathogenesis and cure. A complete list of publications can be accessed at
https://www.ncbi.nlm.nih.gov/myncbi/mangala.rao.1/bibliography/public/

SAFETY AND IMMUNOGENICITY OF MALARIA, SARS-CoV-2, AND HIV-1 VACCINES ADJUVANTED WITH ALFQ

We have developed an anionic liposome formulation known as Army Liposome Formulation comprising saturated phospholipids, 55 mole% cholesterol, and two immunostimulants, monophosphoryl lipid A and a saponin QS21 (ALFQ). Full-length circumsporozoite malaria protein FMP013 (Falciparum Malaria Protein 013), a self-assembling SARS-CoV-2 recombinant spike ferritin nanoparticle (SpFN), and the envelope protein for HIV-1 were formulated with ALFQ and evaluated for safety and immunogenicity in phase 1 clinical trials in healthy adults. FMP013/ALFQ was tested at 20 µg (low dose group, n=5; 0.5 mL ALFQ), or at 40 µg (high dose group, n=5; 1 mL ALFQ). Both doses elicited equivalent immune responses; a Th1-biased cytokine response, strong binding antibody responses, inhibition of invasion of *P. falciparum* sporozoites, and positive opsonophagocytosis activity. SARS-CoV-2 seronegative and unvaccinated adults were randomly assigned (5:5:2) to receive SpFN/ALFQ vaccine (25 or 50µg) or saline. SpFN/ALFQ elicited strong and durable binding and Nabs against a broad panel of SARS-CoV-2 variants and other sarbecoviruses, providing support for SpFN/ALFQ as a promising broadly protective coronavirus vaccine platform. Participants (n=65) without HIV were randomized to receive 1 of 3 doses of ALFQ (200-, 100-, or 50µg MPLA) with 300µg each of the A244 and B.63521 HIV envelope proteins. Binding antibody titers measured by Luminex using a custom multiplex array of 30 HIV antigens and by ELISA, and CD4 T cell responses showed ALFQ dose-dependent responses. These first-in-human studies with the antigens and ALFQ demonstrated an acceptable safety and tolerability profile with no vaccine associated SAEs or deaths. These trials highlight that ALFQ is a safe and potent adjuvant that induces robust immune responses.

This research was conducted under a cooperative agreement between the Walter Reed Army Institute of Research and the Henry M. Jackson Foundation for the Advancement of Military Medicine.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Anne Grobler

Prof Anne Grobler, the current project manager of the SaVaC project, has a PhD in Pharmaceutics (North-West University) and an MSc in Medical Biochemistry (Stellenbosch University). Her interest is the design and construction of nucleotide-based vaccines and therapeutics and bio-agricultural delivery systems. She has worked at the University of Stellenbosch and North-West University, the SAMRC, and in the private sector (head of R&D at MeyerZall Laboratories, at Austell Pharmaceuticals and now heads the Pheroid Cluster Incubator (www.pheroidcluster.com). She is a co-author of the SA Synthetic Biology Strategy, the SA Bio-Design Initiative and the Ministerial Review of STI Institutions (2017). She has founded spin-off companies: The Pheroid Cluster Incubator NPC, BioPher Pty Ltd, Antech Pharmaceuticals (Pty) Ltd and Inopher (Pty) Ltd. She has delivered many PhD and MSc students, both locally and internationally, authored/co-authored more than 140 ISI publications and is an inventor/author of 9 patients granted or under examination. Her awards include: NIPMO Innovators Award for most disclosures with commercial potential at the NWU (2019), BioFundi Award for Research by the Gauteng Province and Innovation Hub (2018), the NWU Innovation Evangelist Award (2017), the NSTF-BHP Billiton Award for her contribution to SETI (2014); the Swiss Bio-technology Innovation Award, Switzerland (2011); two Vice Chancellor's Honorary Award countries (2010).

APPLICATION OF THE LIPID-BASED PHEROID DELIVERY SYSTEM IN ANIMAL HEALTH IN SOUTHERN AFRICA

The economic impact of infectious diseases caused by insects and parasite in animals is significant, with estimates ranging in the hundreds of billions of dollars each year. In sheep, L. cuprina (flystrike) causes reduction in weight- and lambing percentage, wool quality, death of animals or cost associated with preventative control. In the case of Haemonchus contortus infestation in sheep production alone, the global loss is more than $2 billion each year due to decreased productivity, including reduced growth rates, lower fertility, and increased mortality.

Insecticides used for flystrike prevention include synthetic pyrethroids, organophosphates, and macrocyclic lactones, whereas anthelmintic drugs, specifically the benzimidazole, macrocyclic lactone, and imidazothiazole are commonly used to treat anthelmintic conditions. However, due to the increasing prevalence of both insect and anthelmintic resistance, more effective strategies are needed.

A lipid-based self-assembly delivery system (Pheroid) was used to improve ineffective veterinary formulations against or blowfly strike, and H. contortus. The results of in vitro and in vivo studies will be presented. Our research is aimed at providing more effective and safer veterinary therapies for common veterinary diseases, particular when drug resistance is a complicating factor in therapy.

This research was supported by the DSI Africa Health RDI Programme.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Dr Carl R. Alving

Dr. Alving has been a research investigator at the Walter Reed Army Institute of Research (WRAIR) in Silver Spring, Maryland, since 1970. He received a B.S. from Haverford College; an M.D. from University of Miami Miller School of Medicine; and an internship and residency in medicine and a fellowship in pharmacology at Barnes Hospital and Washington University in St. Louis. He served 30 years on active duty in the U.S. Army Medical Corps and retired as a colonel. After that he was a civilian medical officer, lab chief, and supervisory scientist at WRAIR, and now emeritus senior scientist.

He developed an early application of liposomes as drug carriers for treatment of leishmaniasis. He is the co-inventor of the technique of needle-free transcutaneous immunization. He has been an author or coauthor on >330 scientific publications in the fields of adjuvants, antigens, antibodies, complement, lipid biochemistry and immunology, and liposomes as drug carriers and carriers of vaccines, and he sits on several editorial boards. He has created adjuvants for many types of experimental vaccines, including vaccines to malaria, HIV, meningococcal infection, heroin addiction, biological threat agents, prostate and intestinal cancer, traveler's diarrhea, and SARS-CoV-2. He holds 34 U.S. patents, the latest of which is Army Liposome Formulation with QS21 (ALFQ). He was the third recipient of the Alec Bangham Award for contributions to liposome research. He is a Fellow of the American Association for the Advancement of Science, and a Fellow of the US National Academy of Inventors.

ALFQ: A UNIQUE GIANT (>1 MICRON) UNILAMELLAR LIPOSOMAL CARRIER OF MONOPHOSPHORYL LIPID A AND QS21 SAPONIN AS ADJUVANTS FOR VACCINES

ALFQ is a vaccine adjuvant formulation which consists of anionic liposomes containing saturated phospholipids, cholesterol with >50 mol% cholesterol (when compared to the phospholipids), monophosphoryl lipid A (MPLA), and QS21 saponin. In the creation of ALFQ, nanosized SUV liposomes (known as ALF55) are created which contain saturated phospholipids, 55% cholesterol, and monophosphoryl lipid A (MPLA). Upon exposure of the ALF55 vesicles to aqueous QS21, an extraordinary spontaneous fusion reaction occurs leading to the creation of ALFQ which has a polydisperse size distribution of vesicles with diameters ranging from ~50 nm to ~30,000 nm. ALFQ has completed several phase 1 or phase 1/2a clinical vaccine trials with several different antigens, and the ALFQ adjuvant exhibited high immune potency and safety with little reactogenicity.

We have now discovered that upon purification of the giant (>1 μm) unilamellar vesicles (GUV) from ALFQ by centrifugation, the total bulk phospholipids are divided in large fractions between the SUVs and GUVs, but the cholesterol, MPLA, and QS21 are almost exclusively present in the GUVs rather than the SUVs. This unique ALFQ GUV formulation is now being examined further both for its biophysical and adjuvanticity characteristics.

This research was conducted under a cooperative agreement between the Walter Reed Army Institute of Research and the Henry M. Jackson Foundation for the Advancement of Military Medicine.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Dan Peer

Dan Peer is a Professor and the Director of the Laboratory of Precision NanoMedicine at Tel Aviv University (TAU). He is also the Vice President for Research and Development at Tel Aviv University. From 2017 - Present, he is the Founding and Managing Director of the SPARK program of Translational Medicine at TAU.

Prof. Peer's work was among the first to demonstrate systemic delivery of RNA molecules using targeted nanocarriers to the immune system and he pioneered the use of RNA interference (RNAi) in immune cells. His lab was the first to show systemic, cell specific delivery of mRNA in an animal to induce therapeutic gene expression of desired proteins. This has enormous implications in cancer, inflammation and infection diseases. In addition, his lab was the first to show systemic high efficiency, cell specific therapeutic genome editing in cancer.

Recently, his lab showed the first bacterial mRNA vaccines approach against highly lethal, antibiotic resistance strain.

Prof. Peer has more than 145 pending and granted patents. Some of them have been licensed to several pharmaceutical companies and one is currently under registration (as a new biological drug in Inflammatory Bowel Disease). In addition, based on his work, four spin-off companies were generated aiming to bring innovative personalized medicine into clinical practice.

Prof. Peer received more than 35 awards and honors and he serves on the scientific advisory board and as Board Member of more than 15 companies, and on the editorial board of more than 20 journals. In 2014, he was elected to the Israel Young Academy and in 2023 he was elected to the US National Academy of Engineers (NAE).

TARGETED LIPID NANOPARTICLES WITH RNAS ARE GOING BEYOND THE LIVER: FROM VACCINES TO THERAPEUTIC GENOME EDITING IN CANCER

Objectives: Modulating gene function that can lead to cell death in the case of tumors or to change of expression of desired proteins for vaccines or editing of cells for knockout or knockin of genes is a major challenge and an unmet need.

Methods: We have developed several strategies to target unique cell surface receptors and developed a very large library of ionizible lipids with two special features: highly immunogenic or less immunogenic (that can be used for repeated doses). In addition, we developed novel mRNA sequences with more potent immunogenicity that can be utilized against bacterial infection.

Results: In this talk, I will share several examples ranging from new therapeutic targets identified for cancer (e.g. CKAP5) to the first bacterial mRNA vaccines and will also share some data on gene editing for cancer therapeutics.

Conclusions: Cell specific delivery of RNA payloads is feasible and represent the next generation milestone in personalized medicine.

References:

1. Kon E. Kon E., Levy Y., Elia U., Cohen H., Hazan-Halevy I., Aftalion M., Ezra A., Bar-Haim E., Naidu GS, Diesendruck Y, Rotem Y., Ad-El N., Goldsmith M., Mamroud E., Peer D.*, Cohen O. A Single Dose F1-Based mRNA-LNP Vaccine Provides Protection Against the Lethal Plague Bacterium. Science Advances 2023. Mar 10;9(10):eadg1036.
2. Chatterjee S., Naidu GS., Hazan-Halevy I., Grobe H., Ezra A. Sharma P., Goldsmith M., Ramishetti S., Sprinzak D., Zaidel-Bar R., Peer D. Therapeutic Gene Silencing of *CKAP5* leads to lethality in genetically unstable cancer cells. Science Advances 2023 Apr 5;9(14):eade4800.
3. Naidu G.S., Yong S-B, Ramishetti, S. Rampado R., Sharma, P., Ezra A., Goldsmith M., Hazan-Halevy I. , Chatterjee S., Aitha A. Peer D. A Combinatorial Library of Lipid Nanoparticles for Cell Type-Specific mRNA Delivery. Advanced Science 2023. Apr 24:e2301929. doi: 10.1002/advs.202301929.
4. Tarab-Ravski D., Hazan-Halevy I.,, Goldsmith M., Stotsky-Oterin L. , Breier D., Naidu G.S., Aitha A., Diesendruck Y., Ng B.D., Barsheshet,, H. Berger T., Vaxman J., Raanani P., Peer D. Delivery of Therapeutic RNA to the Bone Marrow in Multiple Myeloma using CD38-Targeted Lipid Nanoparticles. Advanced Science 2023. May 12:e2301377. doi: 10.1002/advs.202301377.
5. Granot-Matok Y. Ezra A., Ramishetti S. Sharma P., Naidu Gonna S., Benhar I. and Peer D. Lipid Nanoparticles-loaded with Toxin mRNA Represents a New Strategy for the Treatment of Solid Tumors. Theranostics 2023.13(11):3497-3508.
6. Kon E., Ad-El N., Hazan-Halevy I., Stotsky-Oterin L. and Peer D. Targeting cancer with mRNA-lipid nanoparticles: key considerations and future prospects. Nature Reviews Clinical Oncology, 2023 Aug 16 doi: 10.1038/s41571-023-00811-9.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Daniel J. Siegwart

Daniel J. Siegwart is a Professor in the Department of Biomedical Engineering, Department of Biochemistry, and the Simmons Comprehensive Cancer Center (SCCC) at the University of Texas Southwestern Medical Center. He holds the W. Ray Wallace Distinguished Chair in Molecular Oncology Research and serves as the Director of the Program in Genetic Drug Engineering, Director of the Drug Delivery Program in Biomedical Engineering, and Co-leader of the Chemistry and Cancer Program in the NCI-designated SCCC. He received a B.S. in Biochemistry from Lehigh University (2003), and a Ph.D. in Chemistry from Carnegie Mellon University (2008), studying with Professor Krzysztof Matyjaszewski. He also studied as an NSF EAPSI Research Fellow at the University of Tokyo with Professor Kazunori Kataoka (2006). He then completed an NIH NSRA Postdoctoral Fellowship at MIT with Professor Robert Langer (2008-2012). He has received awards including a CPRIT Scholar Award, an American Cancer Society Research Scholar Award, the Young Innovator Award in Nanobiotechnology, Biomaterials Science Emerging Investigator Award, and election to the Controlled Release Society (CRS) College of Fellows and the American Institute for Medical and Biological Engineering (AIMBE) College of Fellows. His research laboratory utilizes materials chemistry to enable targeted nanoparticle delivery of genomic medicines. Their efforts led to an understanding of the essential physical and chemical properties of synthetic carriers required for therapeutic delivery of siRNA, miRNA, tRNA, pDNA, mRNA, and gene editors. His lab has been at the forefront in the design of synthetic carriers for gene editing and has applied these technologies for correction of genetic diseases and treatment of cancer. They reported the first non-viral system for in vivo CRISPR/Cas gene editing. Recently, they developed Selective ORgan Targeting (SORT) lipid nanoparticles (LNPs), which was the first strategy for predictable tissue specific mRNA delivery and gene editing. They ultimately aspire to utilize chemistry and engineering to make a beneficial impact on human health.

Bone Marrow Homing Lipid Nanoparticles for Genome Editing in Diseased and Malignant Hematopoietic Stem Cells

Therapeutic genome editing of hematopoietic stem cells (HSCs) would provide long-lasting treatments for multiple diseases. However, in vivo delivery of genetic medicines to HSCs remains challenging, especially in diseased and malignant settings. In this presentation, I will report on a series of bone marrow homing lipid nanoparticles (LNPs) that deliver mRNA to a broad group of at least 14 unique cell types in the bone marrow, including healthy and diseased HSCs, leukemic stem cells, B cells, T cells, macrophages, and leukemia cells. Details on lipid chemistry and LNP engineering will be covered. CRISPR/Cas and base editing is achieved in a mouse model expressing human sickle cell disease phenotypes for potential fetal hemoglobin reactivation and sickle to non-sickle allele conversion. Bone marrow homing lipid nanoparticles were also able to achieve Cre recombinase-mediated genetic deletion in bone marrow-engrafted leukemic stem cells and leukemia cells. We show evidence that diverse cell types in the bone marrow niche can be edited using bone marrow homing lipid nanoparticles.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Dr Gary Matyas

Dr. Gary Matyas received his Ph.D. in biology from Purdue University and completed his postdoctoral studies at the National Institute Neurological, Communicative Disorders and Stroke at the National Institutes of Health. These studies were centered on the biochemistry and function of glycolipids. In 1988, Dr. Matyas joined the Walter Reed Army Institute of Research as a research chemist in the Department of Membrane Biochemistry, Division of Biochemistry, which later merged with US Military HIV Research Program. The focus of his research is on vaccines for HIV and other infectious diseases, using liposome adjuvants and transcutaneous immunization. He has studied liposomes as adjuvants for vaccines, including HIV, malaria, Campylobacter, anthrax, and COVID-19. He oversees the cGMP manufacture of Army Liposome Formulations (ALF) including ALF43 and ALFQ. He is the principal investigator for a comparative adjuvant phase 1 clinical trial that studies the effect of adjuvants on DNA immunization and HIV-1 envelope protein boosts. The trial was conducted in Kenya. Dr. Matyas has participated in multiple clinical trials with ALF and ALFQ for HIV, malaria, Campylobacter, cancer, and COVID-19. In 2012, Dr. Matyas was awarded the Avant-Garde Award for Medications Development from the NIH National Institute on Drug Abuse to develop a combination heroin/HIV vaccine. As part of this award and extended research, Dr. Matyas has developed ALF-based vaccines that block the biological effects of opioids such as heroin and fentanyl. His heroin vaccine was effective in preventing overdose in animal studies and is funded for a phase 1 clinical trial.

HEROIN AND FENTANYL VACCINES ADJUVANTED WITH ARMY LIPOSOME FORMULATION

Opioid use disorder (OUD) and fatal overdose due to consumption of fentanyl-laced drugs are global concerns. Fatal overdose cases were 106,363 over the last year with 73,845 due to synthetic opioids, predominantly fentanyl and fentanyl derivatives. There are only 3 pharmacotherapies approved to treat OUD including methadone, buprenorphine, and naltrexone or their combinations. Their efficacies are diminished by the availability of more potent fentanyl derivatives. Active immunization with opioid conjugate vaccines as complementary treatment strategies to current therapies for OUD is a promising approach. We developed 6-AmHap as a hapten for a heroin vaccine and *para*-AmFenHap as a hapten for a fentanyl vaccine. The haptens were conjugated to tetanus toxoid (TT) and adjuvanted with Army Liposome Formulation (ALF) containing monophosphoryl lipid A and aluminum hydroxide. The heroin vaccine protected mice and rats from both subcutaneous and intravenous heroin challenge and induced antibodies that cross-reacted with heroin, morphine, and other opioids, but not the therapeutics for OUD. The fentanyl vaccine protected mice from fentanyl challenge and induced antibodies that cross-reacted with other fentanyl analogs, but not the therapeutics. When combined to form a bivalent vaccine, both heroin's and fentanyl's effects were attenuated in mice models. The binding affinities (K_d) of induced antibodies to heroin and fentanyl from the bivalent vaccine were less than 0.5 nM, demonstrating high affinity antibody production. This work was supported by the National Institutes of Health through the NIH HEAL Initiative under award number UG3DA048351, Avant Garde Award 1DP1DA034787-01, and under a cooperative agreement between US Department of Defense and the Henry M. Jackson Foundation for the Advancement of Military Medicine.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Gert Storm

Gert Storm is a (bio)pharmaceutical scientist specialized in Targeted Drug Delivery/Nanomedicine. He keeps professor positions at the at the Department of Surgery at the National University of Singapore, Department of Pharmaceutics of the Utrecht University (Utrecht, The Netherlands), and at the Department Advanced Organ Bioengineering and Therapeutics of the University of Twente (Enschede, The Netherlands. He is the (co-)author of more than 650 publications (H-index 125, Google Scholar, December 2023), and since 2014 every year in the Highly Cited Researcher lists of Clarivate Analytics (Researcher ID: O-8696-2016).

NOVEL NANOTARGETING STRATEGIES TO MAKE CANCER IMMUNOTHERAPY MORE EFFECTIVE

The last decades were marked by impressive developments in the field of tumor immunology. Therapies aimed to harness the immune system in the fight against cancer have become clinically relevant next to surgery, radio- and chemotherapy. Our understanding of the functions and the components of the immune system in the context of cancer treatment has increased substantially. The potency of the immune system to attack cancer has become very clear by the success of checkpoint inhibitor therapy. However, only a minority of the patients respond to this treatment which is correlated with a too low (pre-existing) immune response against tumor antigens. This lecture will report on novel lipid nanoparticle-based targeting strategies to make cancer immunotherapy more effective.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Dr Juliana Haggerty

Juliana (Jules) Haggerty is Head of the UK's Intracellular Drug Delivery Centre, a CPI led collaborative programme which brings together UK expertise in the design, formulation, manufacture and characterisation of nano-delivery systems such as LNPs. She has worked at CPI since 2014, supporting their RNA vaccine programmes for the UK Vaccine Taskforce in 2020 and providing expert advice and due diligence on legacy activities and onshoring throughout 2021. Jules sits on the Technology and Innovation committee of the UK Medicines Manufacturing Industry Partnership and has significant expertise in the use of public/ private funding and collaborative R&D models to advance technology and innovation. Jules has a BSc (Hons) degree in Physiological Sciences and an EngDoc in Biopharmaceutical Process Development from Newcastle University. In her early career, she spent 8 years at global Life Sciences company, Millipore, working on advanced technology development and best practice for biopharmaceutical manufacture and further developed expertise in image analysis, machine learning and algorithm development during her doctoral studies.

NEW APPROACHES TO ACCELERATE LNP FORMULATION DEVELOPMENT AND MANUFACTURE – USING COLLABORATIVE PATNERSHIPS TO DE-RISK AND ENHANCE LNP ENABLED MEDICINES

This talk will give an overview of recent collaborative programmes at CPI, which are helping develop and test new approaches to LNP formulation, manufacture, and characterisation. The talk will provide the most recent research updates from the UK's Intracellular Drug Delivery Centre. The case studies covered will include advanced high throughout screening and characterisation, the use of adaptive DoE to enhance our understanding of structure-function relationships, and intensified and continuous LNP manufacturing approaches.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Hideyoshi Harashima

Hideyoshi Harashima is a Distinguished Professor of Laboratory of Innovative Nanomedicine, Faculty of Pharmaceutical Sciences, Hokkaido University. He received B.S., M. S. and Ph. D. from The University of Tokyo. After a post-doctoral training in School of Medicine at Stanford University, he became an Associate Professor at Faculty of Pharmaceutical Sciences, The University of Tokushima in 1989. He was appointed a Full Professor of Laboratory for Molecular Design of Pharmaceutics at Hokkaido University in 1999 until 2023. He was also appointed Professor of a newly build Laboratory of Innovative Nanomedicine in 2009 until now. He is a Distinguished Professor of Hokkaido University from 2022 until now.
He served as an Associate Editor of the Journal of Controlled Release (2009 – 2020) and Cancer Science (2009 – now) and as an Executive Editor of Advanced Drug Delivery Reviews (2012 – 2020). He was a president of Academy of Pharmaceutical Science and Technology of Japan (APSTJ: 2012 - 2014). He received The Nagai Award from Japanese Society of Drug Delivery System in 2007, Distinguished Science Award from FIP in 2010, Fellow from Controlled Release Society in 2013, APSTJ award and 19th SONG EUM Med-Pharm Award from Song Eum Academy Foundation in 2016. He also received Høst Madsen Medal from FIP in 2021 and PSJ Award in 2023. He published 454 original research articles, 69 invited reviews, 16 Book Chapters and 92 patents included submissions.
His interest is a "controlled intracellular trafficking" of nanoparticles and its application to Nanomedicines.

AN IMPACT OF HELPTER LIPIDS ON EXTRA-HEPATOCYTE DELIVERY OF NUCLEIC ACIDS BASED ON IONIZABLE CATIONIC LIPIDS

We have been developing a new library of ionizable cationic lipids (iCL). From in vivo screening, we have identified a few ionizable cationic lipids such as CL4H6 which can exert silencing activity of siRNA more efficient than MC3 in hepatocytes after intravenous administration. CL4H6-LNP can also be applied for genome editing successfully. We established to formulate CRISPR/Cas9 ribonucleoprotein (RNP) into LNP. Intravenous administration of RNP-LNP can induce more than 70 % of genome editing in liver to achieve 80% reduction of serum TTR protein level. We challenged to find a new system which can target activated hepatic stellate cells (aHSC) which play an important role in the progression of liver fibrosis based on our library of iCL. After screening in both in vivo as well as in vitro liver fibroblast model, we have identified CL15A6 (pKa=7.3, one double bond in lipid tail), which has different hydrophilic head group and hydrophobic lipid tail from CL4H6 (pKa=6.25, two double bonds in lipid tail). It was found that CL15A6-LNP can be taken up by aHSC via ApoE independent manner, possibly PDGFRb-mediated endocytosis, and could not be taken up by liver efficiently in healthy condition. Transfection efficiency of mRNA in aHSC is deeply dependent on helper lipids. Another example is an optimized formulation to target splenic B-cells for pDNA, which can induce efficient antitumor effects via enhanced CTL activity. It was found that enhanced transfection activity in splenic B-cells could result from being taking-up via a complement receptor-mediated endocytosis, which increased translational efficiency by 3-orders of magnitude. This research was supported by Kakenhi Kiban (A) 19H01170.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Jai Prakash

Jai Prakash is a Professor and Chair of Engineered Therapeutics at the Department of Advanced Organ Bioengineering and Therapeutics at the University of Twente, The Netherlands. He is a pharmaceutical and entrepreneurial scientist with a background in targeted (nano)therapeutics against fibrosis and the tumor microenvironment. His research combines multidisciplinary fields of peptide chemistry, nanomedicine, bioengineering. He obtained PhD (cum laude) in 2006 from University of Groningen, The Netherlands in the field of drug targeting to treat renal fibrosis. Thereafter, he worked as a Vice President – Preclinical Research at BiOrion Technologies with a joint position at University of Groningen. Then, he joined Karolinska Institutet in Stockholm (Sweden) as Assistant Professor in the Department of Oncology-Pathology, followed by a Tenure-Track Professor at University of Twente to set up his new research line on novel therapeutics against fibrosis and cancer. He spent his sabbaticals at the School of Engineering and Applied Sciences at Harvard University as a visiting scientist. He has published >100 peer-reviewed publications and is also a (co)-inventor on several international patents. He is also the Founder and CSO of ScarTec Therapeutics, focusing on the development of novel peptide therapeutics against fibrotic diseases and pancreatic cancer. He is a co-founder of the CRS BeNeLux and France Local chapter and served as the President from 2021-23. He is also the Founder and Chair of the International Conference on *Nanomedicine meets the Tumor Microenvironment* (NanoTME). He serves as an expert referee and/or panel member on more than 30 national and international grant agencies.

NOVEL LIPOSOMAL STRATEGY TO TARGET TUMOUR-INDUCING MACROPHAGES IN PRIMARY TUMOR AND METASTASIS

Tumor innate immune cells such as tumor-associated macrophages (TAMs) play a pivotal role in the tumor progression, metastasis and immunosuppression. Strategies to target and re-program TAMs are therefore highly interesting to reverse their pro-tumoral function and kill the tumor effectively. Liposomes have contributed tremendously to the field of cell-specific targeting. In this study, we developed "tail-flipping" liposomes to target tumor-inducing M2-type TAMs both in the primary tumor and metastatic nodules and modulate these cells by delivering specific compounds. By using the biomimicry of M2-type macrophages to detect dying cells by recognizing specific phospholipids, we recently developed 'tail-flipping' liposomes incorporating a specific phospholipid (i.e. 1-palmitoyl-2-azelaoyl-sn-glycero-3-phosphocholine; PAPC). PAPC possesses a terminal carboxylate group at its sn2-fatty acid chain. These liposomes were efficiently taken up by M2 macrophages than M1 type in vitro and in vivo in 4T1 breast tumor model. Delivery of muramyl tripeptide (MTP) using these liposomes resulted into 70% reduction in the tumor growth in 4T1 tumor model. Furthermore, the combination of MTP-targeted liposomes with anti-PD1 immunotherapy enhanced their therapeutic effects in CT26 mouse tumor model. Recently, we also found that our PAPC liposomes efficiently accumulated into M2 macrophages in the metastatic site of 4T1 tail-vein injection model. Altogether, these liposomes serve as a novel platform to target and re-program M2 macrophages in both primary tumor and metastasis. This research was supported by Phospholipid Research Centre, Heidelberg, Germany.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Dr János Szebeni

Dr. János Szebeni, MD, PhD, DSc, Med. Habil., immunologist, co-founder and CEO of SeroScience Ltd. is also director of the Nanomedicine Research and Education Center at Semmelweis University in Budapest and full professor of immune biology at Miskolc University in Miskolc, Hungary. He has held various guest professor and scientific positions in Hungary and the United States where he lived for 22 years and worked at the University of Arizona, NCI/NIH, Walter Reed Army Institute of Research, and Harvard University. His research on various themes in hematology, membrane biology and immunology resulted in over 200 publications (H-index: 60, citations > 14,000) and 2 books "The Complement System: Novel Roles in Health and Disease" (Kluwer, 2004) and "Immune Aspects of Biopharmaceuticals and Nanomedicines" (Pan Stanford Series on Nanomedicine Vol. 3, 2018). He was primary investigator in more than a dozen European and Hungarian research grants and > 30 CRO projects over the past 20 years. Dr. Szebeni is a regular speaker at international conferences and seminars with over 60 presentations in the past five years. He is an ad hoc consultant for the FDA. Three fields stand out where he has been most active: artificial blood, liposomes and the complement system. His original work led to the CARPA concept, i.e., that complement activation underlies numerous drug-induced (pseudo)allergic infusion reactions. CARPA has been included in a recent EMA guideline as a recommended preclinical safety test.

INNATE IMMUNE STIMULATION BY MRNA-LNP: MECHANISMS AND RELEVANCE TO ADVERSE REACTIONS

A small fraction of people vaccinated with mRNA-lipid nanoparticle (mRNA-LNP)-based COVID-19 vaccines display, among other adverse events (AEs), acute or subacute inflammatory symptoms whose molecular mechanisms are poorly understood. To fill this gap in knowledge we carried out in vitro analysis of vaccine-induced induction of two major inflammatory processes: complement (C) activation and release of proinflammatory cytokines. Incubation of Pfizer-BioNTech's Comirnaty and Moderna's Spikevax with 75% human serum led to highly correlating increases in C activation markers, C5a, sC5b-9 and Bb, but not C4d. This pattern indicates alternative pathway C activation whose causes may include exposure of serum to mRNA complexes with the vaccines' ionizable lipids. In other experiments, incubation of Comirnaty with peripheral blood mononuclear cell (PBMC) suspension supplemented with 20% human autologous serum resulted C activation with paralleling secretion of proinflammatory cytokines in the following order: IL-1α < IFN-γ < IL-1β < TNF-α < IL-6 < IL-8. Heat-inactivation of serum, a method of C depletion, prevented the rises of IL-1a, IL-1b, and TNF-a, suggesting that the production of these cytokines is C-dependent. These findings suggest that the inflammatory AEs of mRNA-LNP vaccines may be due, at least in part, to stimulation of both arms of the innate immune system, whereupon C activation may be causally involved in the induction of some, but not all inflammatory cytokines. This information helps in developing new predictive and preventive measures against the inflammatory AEs of mRNA-LNP vaccines and other therapeutics. Supported by: EU Horizon 2020 825828 (Expert) and NKFIH 2020-1.1.6-JÖVŐ-2021-00013, 00010.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Kostas Kostarelos

Kostas is ICREA Research Professor in Life & Medical Sciences and Severo Ochoa Distinguished Professor at the Catalan Institute of Nanoscience and Nanotechnology (ICN2) in Barcelona (Spain) leading the Nanomedicine Lab. He is also Professor of Nanomedicine at the Centre for Nanotechnology in Medicine, Faculty of Biology, Medicine & Health and the Manchester Cancer Research Centre at the University of Manchester (UK).

He read Chemistry for his BSc at the University of Leeds (UK) and obtained his Diploma in Chemical Engineering and PhD in Chemical and Particle Engineering from the Department of Chemical Engineering at Imperial College London (UK), studying the steric stabilization of liposomes using block copolymer molecules (with Th.F.Tadros and P.F.Luckham).

Kostas carried out his postdoctoral training in various medical institutions in the United States with D.Papahadjopoulos (UCSF, CA, USA), G.Sgouros (Memorial Sloan-Kettering, NY, USA) and R.G.Crystal (Weill Medical College of Cornell University, NY, USA) using liposomes to transport pDNA, radionuclides, viruses and small molecules for various therapeutic purposes.

Kostas was Assistant Professor of Genetic Medicine & Chemical Engineering in Medicine at Cornell University Weill Medical College in 2002 when he relocated to the UK as the Deputy Director of Imperial College Genetic Therapies Centre in London (UK). In 2003 he joined the Centre for Drug Delivery Research (CDDR) at the London School of Pharmacy (later UCL) as the Deputy Head of the Centre. He was promoted to the first personal Chair of Nanomedicine in the United Kingdom and Head of the CDDR in 2007. The entire Nanomedicine Lab was embedded within the Faculty of Medical and Human Sciences and the National Graphene Institute at the University of Manchester in 2013, working closely with Kostya Novoselov (Physics Nobel Laureate, 2010).

He has been invited Fellow of the Royal Society of Chemistry (FRSC), Fellow of the Royal Society of Medicine (FRSM), and Fellow of the Royal Society of Arts (FRSA) all in the United Kingdom. In 2010 he was awarded the Japanese Society for the Promotion of Science (JSPS) Professorial Fellowship with the National Institute of Advanced Industrial Science and Technology (AIST) in Tsukuba, Japan (hosted by Sumio Iijima and Masako Yudasaka).

BACK TO THE FUTURE: CREATIVE REVISITING OF THE PEGYLATED LIPOSOME FROM BIOMARKER SCAVENGERS TO BRAIN TRANSPORTERS

Liposomology has featured at the center-stage of nanotechnology and nanoparticle engineering translated to medical and clinical use since the inception of nanoscience as a field. Liposome engineering has been systematically developed, particularly in the context of *lipid vesicle structure–pharmacological function* relationships, since the late 70s and throughout the 80s with the culmination of multiple pharmaceutical products. One such liposome engineering principle with enduring significance and impact has been the vesicular steric stabilization by surface decoration with polyethylene glycol chains. These forms of PEGylated liposome surfaces have resulted in a wide range of clinically used pharmacological agents, from liposomal cancer therapeutics to lipid- or liposome-based vaccines. PEGylated liposome forms have been some of the most well studied nanoparticle structures today, considered by contemporary nanoscientists lacking in novelty and to a large extent considered scientifically exhausted. During the last few years we have sought to creatively revisit PEGylated liposomes as one of the most robust and well-understood nanoparticle platforms hypothesizing that they can reveal novel compelling use cases. Two such examples will be presented in this talk. The first one is in the context of blood scavengers for the discovery of novel blood-based, low-abundance biomarkers, to enable high-precision liquid biopsies. The second one is in the context of identifying temporal windows of opportunity in cases of neurovascular compromise through injury (e.g. in stoke) to achieve effective brain tissue translocation. Our efforts have illustrated how an established and clinically accepted nanoparticle platform, such as the PEGylated liposome, can be creatively revisited to offer compelling solutions in very topical clinical challenges, in what we call *'Back to the Future'* liposomology.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Dr Marcel Bally

Dr. Bally has focused his career on development of much needed novel drugs, drug combinations and drug delivery systems designed for use in patients with cancer. Dr. Bally received his BSc (1977) and MSc (1979) degrees in biology from Texas A&M University. He obtained his PhD from the Department of Biochemistry at the University of British Columbia (1984). He has recognized expertise in pharmacology/toxicology, drug formulations and preclinical cancer models. He is qualified to conduct preclinical safety studies under Good Laboratory Practices and has completed training in Good Manufacturing Practices. His scientific works (scientific articles, abstracts, book chapters and patents) have been cited > 30,000 times and has a Google Scholar h-index of 90. He has trained >75 highly qualified personnel; many of which now hold significant positions in industry, academia and medicine. He has co-founded multiple companies including Lipex (acquired by Northern Lipids), Inex (now Arbutus), Northern Lipids (renamed Transferra and purchased by Evonik in 2016), Celator (purchased by Jazz in 2016) and Cuprous Pharmaceuticals. Dr. Bally was one of the co-founders of Canada's NCE Centre for Drug Research and Development (joined with NEOMED to form adMare BioInnovations in 2019) as well as the Canada's NCE Nanomedicine Innovation Network. The research completed contributed to the success of three marketed drugs (Myocet- for metastatic breast cancer; Marqibo- for relapsed ALL and Vyxeos - for high risk AML).

CAN LIPOSOMAL SMALL MOLECULES BE USED TO OVERCOME THE LIMITATIONS OF LNP RNA THERAPEUTICS?

While remaining focused on liposomal formulations of small molecules my team has had to address the question- "LNP RNA therapeutics - Why work on anything else?" Driven by the wishes of students wanting to understand LNP formulation approaches and the potential therapeutic value of RNA therapeutics, studies were initiated to combine liposomal small molecules with LNP RNA therapeutics with the goal of enhancing potential therapeutic effects. These studies are assessing approaches to modulate RNA expression and the potential to define combinations for cancer immunotherapy. Once again, it is clear that the goals and visions of students can drive innovation and can help a supervisor remove their blinders.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor María José Alonso

María José Alonso is Professor of Pharmaceutical Technology at the University of Santiago de Compostela, Spain. Her lab has pioneered numerous discoveries in the field of nanomedicine, notably in the area a vaccination, transmucosal drug delivery and precision medicine in oncology.
She has coordinated consortia financed by the WHO, the Gates Foundation and the European Commission and has authored more than 315 scientific contributions with H factor >100. She is the inventor of 23 patent families, most of them licensed to industry and she has been directly part of 3 start-up ventures and, indirectly of 2 more. She has been among the TOP TEN in Pharmacology (THE, 2010). She has been in the "Power List" of the most influential researchers in the field of Biopharmaceuticals (*The Medicine Maker*)
She has hold high responsibilities as Vicerrector of Research and Innovation, Trusty of the Spanish Research Council and Adviser to the Ministries of Sciences and Innovation and Health. She si now a member of the Council of the Spanish Agency of Research.
She was President of the CRS in 2018-19 and she is Editor-in-Chief of the *Drug Delivery and Translational Research,* an official journal of the CRS*. S*he is part of the editorial board of 12 journals.
She has received 55 awards, among them the "National Research Award", considered as the highest distinction from the Spanish Government, the Jaume I Award and the Founders, WIS and Outstanding Service Awards of the CRS, Inc.
She is a member of 5 Academies in Spain and of the Royal Academy of Medicine of Belgium and of the US National Academy of Medicine (NAM). She was awarded with an "Honoris Causa" doctorate by the University of Nottingham.

ENGINEERING OF POLYMER/OIL-BASED NANOCAPSULES FOR SIZE SPECIFIC RNA DELIVERY

Our laboratory initiated the development of polymer-based nanocarriers in the late 90s, aiming to facilitate the delivery of polynucleotides. We successfully generated polymeric nanoparticles (such as PLGA-PEG, chitosan, polyarginine, and protamine) loaded with DNA and RNA. These nanocarriers were specifically designed for the treatment of ophthalmic diseases and immunotherapy.

In recent years, we have made significant advancements by creating hybrid polymer/lipid-based nanocapsules for RNA delivery to precise target sites. Noteworthy our efforts have been focused on delivering RNA to the brain, targeting lung and pancreatic tumors, and developing nanocarriers to deliver RNA to dendritic cells for vaccination purposes.

Our findings indicate that both the choice of components and their structural arrangement play crucial roles in determining the performance of these nanocarriers.

This work was supported by European Union's Horizon 2020 research and innovation program (grant agreement No. 721058), FEDER Funds, Ref. COV20/00214. ISCIII thorough AES 2020, Award N. AC20/00028 and within the framework of EuroNanoMed III". FEDER/Ministerio de Ciencia, Innovación y Universidades – AEI/ PID2020-119368RB-I00

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Neill Liptrott

Prof. Liptrott, Chair in Pharmacology and Immunocompatibility at the University of Liverpool has pharmacology, immunology, and molecular cell biology expertise. As the principal investigator of the Liverpool Immunocompatibility Group, Coordinator of the Liverpool Nanotherapeutics Hub, and Platform manager (Nanotherapeutics) for the Infection Innovation Consortium (iiCON), he oversees critical research initiatives. His roles extend to serving as a member of the Liverpool City Region Health & Life Sciences Board; biocompatibility leads for the Centre of Excellence for Long-acting Therapeutics (CELT) and steering board member for the Intracellular Drug Delivery Centre (IDDC).
Prof. Liptrott's research investigates the biological interactions of complex medicines, advanced therapeutics, and biomaterials, assessing their biocompatibility, immunomodulatory potential, and risk. Notably, his work has supported the successful translation of solid drug nanoparticle formulations through GMP manufacture for HIV treatment. Moreover, he supports developers in navigating the complexities of advanced therapeutics for clinical studies.
Furthermore, Prof. Liptrott contributes significantly to various organisations, serving as a member of the Executive Board and Core Expert Team for the European Nanomedicine Characterisation Laboratory (EUNCL) and as Academic in Residence at the National Measurement Laboratory, among other roles. He is actively involved in initiatives such as creating the British Society for Nanomedicine and serves as an elected Trustee, emphasising immunological safety. At the University of Liverpool, he spearheaded the establishment of the MSc in Pharmacology and Toxicology, where he serves as programme director.

INVESTIGATING THE IMMUNOCAPATIBILITY OF COMPLEX MEDICINES – CHALLENGES AND APPROACHES FOR A NOVEL THERAPEUTIC STRATEGY FOR OSTEOARTHRITIS, DEVELOPED BY THE siNPAIN CONSORTIUM

The evolution of complex medicines has an enormous advantage for treating many diseases by exploiting alternative delivery routes, long-acting therapeutics, and the inclusion of genetic technologies. However, the translation of these complex medicines can be hampered by the complexity of the materials involved, often with many components of the final product being at differing technology readiness levels (TRL). This talk aims to give an overview of our work in assessing the compatibility of complex medicines, including lipidic nanoparticles, using our work in the siNPAIN project as an example. siNPAIN is an ambitious project to develop a game-changing therapeutic for the treatment of osteoarthritis, combining siRNAs, nanoparticle delivery systems, and biomimetic biomaterials for intraarticular injection in patients. We will discuss our approaches and highlight our recent achievements.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Olivia Merkel

Olivia Merkel has been a Professor of Drug Delivery at LMU Munich since 2015 and Chair since 2022. She is a Registered Pharmacist, received a MS (2006) and a PhD (2009) in Pharmaceutical Technology as well as numerous awards, including an ERC Starting Grant, ERC Proof-of-Concept Grant and ERC Consolidator Grant, the APV Research Award and the Carl-Wilhelm-Scheele-Award. Merkel is the author of over 100 articles and book chapters. She served as NIH reviewer from 2014-2015, SNF reviewer from 2018-2022, is an Editorial Board member for JCR, EJPB, Molecular Pharmaceutics and other journals, Associate Editor for DDTR and WIREs Nanomedicine and Nanobiotechnology, was the President of the German Controlled Release Society in 2020 and the Chair of the CRS Focus Group on Transdermal and Mucosal Delivery from 2020-2022, and currently is a scientific advisory board member of Coriolis Pharma, Carver Biosciences, AMW, and Corden Pharma as well as a co-founder of RNhale. Her research focuses mainly on RNA formulation and pulmonary delivery for the treatment of a variety of lung diseases.

INHALABLE DRY POWDER LNPs FOR GATA3 SILENCING IN SEVERE ASTHMA

RNA therapies for pulmonary diseases in clinical trials are currently administered either through nebulization of fluid suspensions or intravenous (IV) injection, both of which face limitations. Nano-Embedded Microparticle (NEM) technology, designed to overcome these hurdles, encapsulates RNA-loaded lipid nanoparticles (LNPs) within an excipient matrix, and results in dry powder formulations for inhalation. We demonstrate its potential in treating severe type-2 asthma by targeting the transcription factor GATA3, a crucial factor in the disease's pathophysiology. Our results confirm that RNA-loaded lipid nanoparticles can be spray-dried to obtain an inhalable dry powder, and that our optimized process does not affect the integrity of the GATA3 siRNA. The obtained dry powders can be stored for 18 months at RT with maintained bioactivity. Neither lung tissue nor cytokines showed any signs of toxicity in vivo in mice with symptoms of allergic asthma, however, Th2-related cytokines as well as eosinophile counts are efficiently downregulated through sequence-specific treatment. This research was supported by ERC-2022-PoC1-101069308, ERC-2014-StG – 637830, And the German Excellence Strategy.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Dr Philipp Uhl

Philipp Uhl studied pharmacy at the Ruprecht-Karls-University of Heidelberg from 2008-2013. After obtaining his PhD in 2017 (title of thesis: "Oral availability of peptide drugs by liposomal formulations"), he worked as project leader of translational nanocarrier projects at Heidelberg University Hospital till 2022.
In 2022, Dr. Uhl was appointed Junior Professor of Pharmaceutical Technology and Biopharmacy at Heidelberg University with special focus on phospholipids ("Lipoid-Stiftungsprofessur").
In his research, he primarily focuses on the reactivation of established antibiotics, the development of optimized antibiotics formulations as well as on delivery systems for oral delivery of macromolecular drugs in general. The work on oral bioavailability of peptide therapeutics was honored with the "Thudichum Young Scientist Award" in 2019 and the "Galenus Technology Award" in 2021.
More than 40 publications and 7 patent applications related to this research could be published.

CELL PENETRATING PEPTIDE MODIFIED LIPOSOMES: A TECHNOLOGY FOR ORAL PEPTIDE DELIVERY

Despite the high medical need for oral administration of peptide therapeutics, instability in the gastrointestinal tract and low mucosal permeation impede this preferred route of administration [1]. To overcome this hurdle, we developed a liposomal nanocarrier decorated with cell-penetrating peptides [2]. This approach enables the design of a nanocarrier with synergistic properties. Tetraether lipids derived from archaea are incorporated into liposomes to provide the particles with the stability required to traverse the stomach [3]. When the surface of the resulting inert particles is modified with cell-penetrating peptides, mucosal permeation can be achieved. The designed nanocarrier was proven effective for two model compounds: vancomycin and FU002, a vancomycin-conjugate in preclinical development. Efficacy in vivo was demonstrated in naïve rats and beagle dogs, where a highly increased oral bioavailability is obtained for vancomycin, a drug known to be minimally absorbed.

References: [1] Mühlberg, E.; Burtscher, M.; Umstätter, F.: Fricker, G.; Mier, W. and Uhl, P. Trends in liposomal nanocarrier strategies for the oral delivery of biologics. Nanomedicine, 2021, 16, 1813-1832. [2] Uhl, P.; Sauter, M.; Hertlein, T.; Witzigmann, D.; Laffleur, F.; Hofhaus, G. and Mier, W. Overcoming the Mucosal Barrier: Tetraether Lipid-Stabilized Liposomal Nanocarriers Decorated with Cell-Penetrating Peptides Enable Oral Delivery of Vancomycin. Advanced Therapeutics, 2021, 4, 2000247. [3] Uhl, P.; Pantze, S.; Storck, P.; Parmentier, J.; Witzigmann, D.; Hofhaus, G. and Fricker, G. Oral delivery of vancomycin by tetraether lipid liposomes. European Journal of Pharmaceutical Sciences, 2017, 108, 111-118.

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Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Raymond Schiffelers

Raymond Schiffelers studied Bio-Pharmaceutical Sciences at Leiden University (1990-1995). After an industrial traineeship at SmithKline Beecham Pharmaceuticals (UK) he did his PhD at Erasmus University Rotterdam on liposomal targeting of antimicrobial agents (1996-2001). Subsequently he became post-doc at Utrecht University working on liposomes targeting tumor vasculature. In 2002-2003, at Intradigm Co (USA) he moved to delivery of RNA. After his return to Utrecht University he became assistant and then associate professor. He received an ERC Consolidator Grant in 2010 to investigate extracellular vesicles as biological drug delivery systems for RNA. After he moved to University Medical Center Utrecht in 2011 he became professor of nanomedicine working on bio-inspired and synthetic drug delivery systems. He coordinates two H2020 projects, B-SMART (6 M€) and EXPERT (15 M€), a Horizon Europe project, NANO-ENGINE (3 M€), and an NWA-ORC project NANOSPRESSO-NL (9 M€), all devoted to RNA delivery. He is editor for the International Journal of Pharmaceutics, Journal of Controlled Release and Journal of Extracellular Vesicles, and is founder of EXCYTEX-an extracellular vesicle-based company. Since 2021 he also works part-time for Nanocell Therapeutics as VP Preclinical R&D and has been elected president of the European Technology Platform Nanomedicine since 2021.

EXTRACELLULAR VESSICLES VERSUS LIPID NANOPARTICLES

Lipid nanoparticles have taken center-stage in the current revolution in nucleic acid therapeutics. They couple a good delivery efficiency with manufacturability in a GMP process. The success of the COVID-vaccines has been followed up by an avalanche of clinical activity on mRNA therapeutics and inspired the first clinical gene editing approaches based on these systems.
Still, for many applications expression is insufficient or the tropism of the lipid nanoparticles is not suited for the application. In our lab we have investigated extracellular vesicles as a biological alternative to synthetic lipid nanoparticles. Although these vesicles face challenges in loading efficiency, characterization and scalable and GMP manufacture, they possess intriguing capabilities. Stoichiometric comparisons between vesicles and nanoparticles revealed that vesicles are more potent in delivery than clinically used lipid nanoparticle formulations. This could be related to different internalization pathways and specific interactions with endosomal components.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Sarah Brockbank

Sarah Brockbank leads the strategy for Complex Medicines at Medicines Discovery Catapult.
In this role she draws on internal expertise and the external environment, through membership of national programmes and a portfolio of client projects, to develop and implement a core strategy for complex medicines that is responsive to the needs of this emerging area.
Sarah has 35 years' experience in the pharmaceutical industry. She is a molecular biologist with a focus mainly in target identification & validation and has worked across a broad range of disease areas. Sarah was a Drug Discovery Project Leader at AstraZeneca, and she also has extensive experience in the leadership and management of large public-private consortia and collaborations.

ANALYTICAL PLATFORM TO SUPPORT RATIONAL DESIGN OF LNPS

The successful application of LNPs as delivery agents for vaccines is well known. To realise the potential of LNPs in the development of new therapeutics we need to overcome the significant challenges associated with a biodistribution limited to the liver, a restricted cell tropism and inadequate cell delivery due to poor endosomal escape.
Medicines Discovery Catapult (MDC) has established expertise and capabilities to support the discovery and analysis of nanomedicines including biodistribution, tissue penetration, cellular uptake, and biological activity. Using a range of cell and molecular techniques, in vitro and in vivo imaging modalities, mass spectrometry and advanced microscopy, we can characterize a potential medicine's cell and tissue targeting properties, the mechanisms and kinetics of cellular uptake and intracellular release and the analyses of tissue response.
MDC along with CPI and leading Universities across the UK have come together to establish a brand new Intracellular Drug Delivery Centre, which will provide a Centre of Excellence to support innovators in their discovery and development of nanomedicines. In this programme, innovation development will include a focus on increased throughput of MDC's analyses to support rational design of LNPs for the development of therapeutics.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Assaf Zinger

At the Technion-Israel Institute of Technology, my research group is developing biomimetic nanoparticles (NP) to treat neurodegenerative pediatric diseases, traumatic brain injuries, and breast and ovaria cancers. Our lab's main goal is to be one of the world's leading research groups in developing targeted biomimetic NP that can encapsulate a wide range of therapeutic molecules, including mRNA, proteins, and small molecules, thus revolutionizing how we treat numerous dieases. For exmaple: (1) We improved the therapeutic outc ome of pancreatic cancer treatment using a controlled-release enzyme delivery system. (2) We mimic white blood cells binding to inflammatory sites and develop a macrophage biomimetic drug delivery system. (3) We developed the first ever neuron biomimetic nanoparticles that mimics how neurons bind to other neurons through homotypic cell-cell adhesion protein. All these breakthroughs were published in top-tier journals (1737 citations and h-index 17).
Personally, I was awarded more than 15 international and national excellence awards, among them: the Alon Scholarship for Outstanding Young Scientists, the most prestigous scholarship from the Israeli Council for Higher Education; the interational Umbrella Award, focusing on Life Science and Engineering; the Norman Seiden Fellowship in Nanotechnology and Optoelectronics, Career Advancement Chair, and the Young Investigator Award, from the Interational Controlled Release Society focus group. I was also chosen as a member of the Global Young Academy and the Lindau Noble Laureates Meeting and organized three international and three national conferences. I am hoping two Adjunct Assistant Professor positions in the Cardiovasuclar Science and Neurosurgery Departments at Houston Methodist Academic Institute, TX, USA, and will be appointed as a Visiting Professor at the University of Turin, Italy, this April. Finally, last year, I was awarded the prestigous ERC-starting grant for exploring how human breast milk biomimetic nanoparticles might pave the way for a new oral drug delivery system.

UNLOCKING THE CELLULAR BLUEPRINT: PRECISION TARGETING OF DISEASED TISSUES WIH BIOMIMETIC NANOPARTICLES

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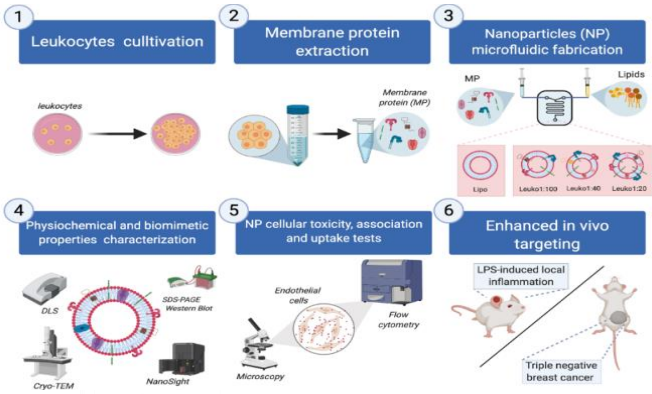


Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Tatsuhiro Ishida

Professor Tatsuhiro Ishida graduated from Tokushima University, Japan, in 1993 and then received his Master degree in 1995 and his PhD in 1998 from the Faculty of Pharmaceutical Sciences, Tokushima University. From 1998 to 2000, he was a postdoctoral fellow at the University of Alberta, Canada (Prof. T.M. Allen's laboratory). In 2000, he became an Assistant Professor in Faculty of Pharmaceutical Sciences at Tokushima University, and was promoted to an Associate Professor in 2003. He has been a full Professor there since 2014. He has published 196 peer-reviewed papers, 22 review articles, and 16 book chapters. He has given 34 presentations as an invited speaker at international conferences. He is interested in delivery of nucleic acids and anti-cancer therapeutics. He is also interested in immunological responses to PEGylated therapeutics, namely PEG, and the mechanisms behind the such anti-PEG responses.

IMMUNOLOGICAL RESPONSES AGAINST PEGYLATED MATERIALS: THE INDUCTION OF ANTI-PEG ANTIBODIES

Polyethylene glycol (PEG) is considered as non-toxic and non-immunogenic materials. However, we have shown that PEG on the liposomes and proteins become immunogenic and can induce anti-PEG antibodies. Also, we have elucidated that anti-PEG IgM, secreted in response to the first dose of PEGylated materials, is responsible for the rapid clearance of the second dose via initiation of complement activation. The existence of naturally occurring anti-PEG antibodies in normal individuals who have never received PEGylated therapeutics is reported. We very recently attempted to find an explanation for the source of pre-existing anti-PEG antibodies in healthy individuals. In a murine study, we observed that topically applied PEG derivatives, present in two commercially available cosmetic products, primed the immune system, inducing anti-PEG IgM production. This indicates that PEG derivatives in cosmetic products may be an important contributor to the source of the pre-existing anti-PEG antibodies that have been detected in healthy individuals. When PEGylated formulations were given to such individual, the formulations might display unexpected pharmacokinetic behavior, resulting in less therapeutic efficacy or even cause undesirable side-effects. Therefore, we believe that a deep understanding of the prevalence and clinical implications of anti-PEG immunity is a prerequisite for the continual clinical application of PEGylated therapeutics. This research was supported by KAKENHI 19KK0279, 21H05526, 23H03739 (JSPS).

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Tomohiro Asai

Apr. 1999 to Mar. 2002	University of Shizuoka Graduate School of Pharmaceutical Sciences, Shizuoka, Japan. (Ph. D.)
Research Fellowships of the Japan Society for the Promotion of Science	
Apr. 2002 to Jan. 2004	Researcher, Mitsubishi Pharma Corporation, Japan.
Feb. 2004 to Mar. 2013	Assistant Professor, Department of Medical Biochemistry, University of Shizuoka School of Pharmaceutical Sciences, Japan.
Oct. 2005 to Dec. 2005	Visiting Scholar, Division of Drug Delivery and Disposition, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, the U.S.
Jul. 2011 to Jun. 2012	Visiting Scholar, Division of Molecular Pharmaceutics, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, the U.S.
Apr. 2013 to Mar. 2018	Associate Professor, Department of Medical Biochemistry, University of Shizuoka School of Pharmaceutical Sciences, Japan
Apr. 2018 to present	Professor, Department of Medical Biochemistry, University of Shizuoka School of Pharmaceutical Sciences, Japan
Nov. 2021 to present	Chief Technology Officer, Luna RD co., ltd., Japan

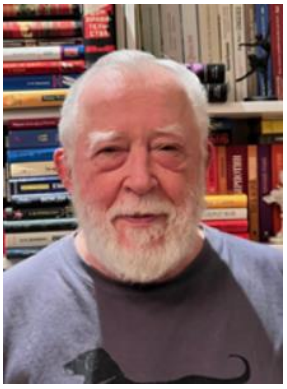
DESIGN OF CHARGE-REVERSIBLE LIPID NANOPARTICLES FOR RNA DELIVERY

Lipid nanoparticle (LNP) technology has enabled the clinical use of RNAs. Ionizable lipids, a main lipid component of commercialized LNP formulations, are essential for encapsulation, cellular uptake, and endosomal escape of RNAs. In this study, we have designed pH-responsive charge-reversible (CR) lipids that have different properties from ionizable lipids and have developed CR LNPs for RNA delivery. The net charge of the head group of the CR lipids changes from negative to positive depending on pH. Since the head group of the CR lipids is almost electrically neutral at neutral pH and positively charged at acidic pH, their pH responsiveness is similar to that of ionizable lipids. The difference of CR lipids from ionizable ones is the polarity of the head group at neutral pH. The head group of ionizable lipids is not ionized and less polar at neutral pH, while that of CR lipids is ionized and thus more polar. We obtained highly dispersible and stable LNPs using CR lipids. Targetability of CR LNPs can be customized depending on the applications. We encapsulated siRNA or mRNA in CR LNPs by the microfluidic technology and investigated their pharmacological effects in mice. Combination treatment with anticancer siRNA encapsulated in CR LNPs and anti-PD-1 antibody suppressed tumor growth in vivo. Intramuscular injection of antigen-coded mRNA encapsulated in CR LNPs induced antigen-specific antibody with relatively low inflammation reactions. In this meeting, we would like to introduce our recent findings on the physicochemical properties and in vivo applications of CR LNPs encapsulating siRNA or mRNA. A part of this research was supported by AMED under Grant Number 21ak0101171h0001.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Vladimir Torchilin



Vladimir Torchilin got his M.S, Ph.D., and D.Sc. degrees from the Moscow State University and currently serves as a University Distinguished Professor and Director, Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston. He has published more than 450 original papers, more than 200 reviews and book chapters, wrote and edited 15 books, and holds more than 40 patents. Google Scholar shows more than 90,000 citations of his papers with H-index of 132. He is Editor-in-Chief of *Current Drug Discovery Technologies*, Co-Editor of Current Pharmaceutical Biotechnology and on the Editorial Boards of many other journals. He received more than $20 M from the governmental and industrial sources in research funding. He has multiple national and international honors and awards and in 2011, Times Higher Education ranked him number 2 among top world scientists in pharmacology for the period of 2000-2010. In 2021 Elsevier/Stanford analysis ranked him as a single highest-cited researcher among more than 130,000 ranked researches in the area of Pharmacology/Pharmacy. He is also selected by Clarivat as the 2023 Citation Laureate.

NETs AS THE UNIVERSAL TARGET FOR THE CARRIER-MEDIATED DRUG DELIVERY IN DIFFERENT PATHOLOGIES

An important aim in targeted drug delivery research is to identify novel and specific biological targets in sites of pathology. Neutrophil extracellular traps (NETs) are composed of processed chromatin bound to granular and selected cytoplasmic proteins and released by neutrophils. NETs consist of smooth filaments composed of stacked nucleosomes. Fully hydrated NETs have a cloud-like appearance and occupy a space 10–15-fold larger than the volume of the cells they originate from. DNases are the enzymes that cleave extracellular DNA including NETs. Together with their protective role in microbial infections, NETs are involved in multiple pathological processes and represent key events in cancer, autoimmunity, and cardiovascular disease. Sites of NETs concentration are dangerous for the host if the process of NETs formation becomes chronic or the mechanism of NETs removal does not work. NETosis has been linked to the development of thrombosis, periodontitis, cystic fibrosis, type 2 diabetes, COVID-19 or rheumatoid arthritis as well as cancer progression and metastatic process. In numerous studies causative association of NETs with disease site inflammation and disease severity was demonstrated and multiple NET-suppressive therapies are in preclinical and clinical studies in connection with all three aforementioned disease group.

Thus, the destruction of NETs in is of primary significance in many pathologies. On the other hand, NETs may serve as an ideal universal target to specifically deliver drugs into disease zone in multiple pathologies. Currently, the major targets of vehicles used in targeted delivery are certain cell surface antigens specific to a disease site, or some extracellular matrix antigens, specific to the disease site. However, these targets differ for different pathologies and require different vehicles for targeting, while NETs could serve as a universal target. It is specifically related to NETs chromatin, which is an obligatory constituent of every NETs, contrary to other NETs components. Thus, NETs may be considered as a universal target in many diseases and specific Ab-modified delivery systems can serve as a universal platform for targeting multiple pathologies.

Monoclonal antibody 2C5 was discovered by us as a nuclear-reactive autoantibody from the B–cell repertoire of normal aged mice. This Ab was shown to have a nucleosome-restricted specificity and used intially to target cancer cells via the cancer cell surface-bound nucleosomes. Recently, mAb 2C5 has been proven to effectively recognize NETs of different etiologies, including compacted NETs. We confirmed the specificity of 2C5 toward NETs by ELISA, which showed that it binds to NETs with the specificity like that for purified nucleohistone substrate. We further utilized that feature to create two delivery systems (liposomes and micelles) in particular for DNase I enzyme to destroy NETs, and assume that these drug delivery vehicles can also (or simultaneously with DNase) be loaded with drugs for the treatment of the primary disease accompanied by NETs formation, such as thrombolytic enzyme for the treatment of thrombosis or chemotherapeutics for treating cancer.

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Wafa Al-Jamal

Wafa Al-Jamal is a Professor of Advanced Nanotherapeutics at Queen's University Belfast (QUB), School of Pharmacy. She completed her PhD in Drug Delivery and Nanomedicine from the School of Pharmacy, University of London (now known as UCL-School of Pharmacy). Wafa joined the University of East Anglia, Norwich, as a Lecturer in Drug Delivery (2013-2017) after working as a Senior Research Fellow at the University College London and King's College London. She joined QUB in 2017 as a Reader in Nanomedicine. Wafa was awarded a 5-year Career Development Fellowship (2014-2019) from Prostate Cancer UK for developing targeted nanomedicines for prostate cancer.

Her research focuses on engineering novel nanomaterials for biomedical applications. Her current research aims to design smart vectors for combinatory therapy and theranostic applications. Wafa's long-term research career is to facilitate the translation of nanoparticle-based therapeutics from the lab to the clinic.

Wafa received the GSK Emerging Scientist Award 2015 and Gro Brundtland Award 2017 for her contribution to the nanomedicine field. Her multidisciplinary research (~3M) has been funded by the Royal Society, Prostate Cancer UK, The Engineering and Physical Sciences Research Council (EPSRC), Rosetrees Trust, MRC, and the Phospholipid Research Centre. She has published over 60 research articles in high-impact journals and 5 book chapters. She has been an invited speaker to many national and international meetings and conferences. Wafa is also the EDI/SWAN Co-champion at the School of Pharmacy, promoting EDI and gender equality.

FORMULATION OPTIMIZATION, BIOCOMPATIBILITY, AND IN VIVO CLEARANCE OF BIODEGRADABLE LIPOSOME-INDOCYANINE GREEN J-AGGREGATES FOR PHOTOTHERMAL THERAPY

Photothermal therapy is an attractive and safe approach to treating cancer. It consists of the in-situ generation of heat caused by the irradiation of a photoabsorbent compound with a laser at a determined wavelength. Substances with different natures possess this heating capacity, but organic compounds present greater biocompatibility and biodegradability than inorganic molecules. Cyanine dyes are among the organic compounds with potential for photothermal therapy, from which indocyanine green (ICG) is the only dye currently approved by the FDA and the EMA. However, the clinical applications of ICG are hampered by its low photo-, thermal-, and light stability, combined with a very short circulating time.

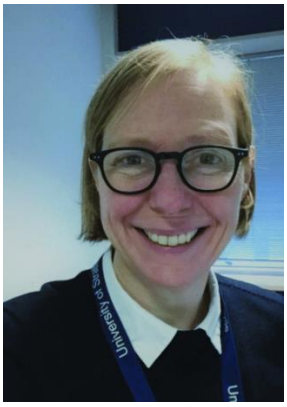
The generation of ICG J-aggregates (IJA) has improved the overall ICG stability and heating capacity. Our group has developed a novel and quick approach for producing IJA-loaded liposomes as biodegradable photothermal agents. In the present work, we investigated the effect of lipid bilayer composition on the physicochemical properties, heating capacity and stability of the engineered IJA-loaded liposomes, followed by their in vitro biocompatibility and toxicity in combination with 808 nm laser. Finally, their tumour targeting, body clearance and in vivo safety following intravenous administration were assessed in mice.

This research was supported by the Phospholipid Research Centre, Germany (WAJ-2021-097/1-1).

Meet the Speakers

18TH LIPOSOME RESEARCH DAYS 2024

Professor Yvonne Perrie



Professor Yvonne Perrie is the Chair in Drug Delivery within Strathclyde Institute for Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, Scotland. Prior to this appointment, she was Professor in Drug Delivery, within Aston University, Birmingham, England (2007-2016). Yvonne has a BSc (First-Class Hons) in Pharmacy from Strathclyde University and she attained her PhD from the University of London under the supervision of Prof Gregoriadis. Yvonne's research is multi-disciplinary and is focused on the development of drug carrier systems to facilitate the delivery of drugs and vaccines, providing practical solutions for current healthcare problems. Yvonne has published approximately 150 peer-reviewed papers, 5 patents and 4 text books. She is a Fellow of the Society of Biology, a Fellow of the Royal Society of Chemistry, the Royal Pharmaceutical Society, a member of the College of Fellows for the Controlled Release Society, and an Eminent Fellow of the Academy of Pharmaceutical Sciences. Yvonne was appointed a Member of the Order of the British Empire (MBE) in His Majesty the King's New Year Honours List 2024 for services to pharmaceutical innovation and regulation.

FROM LIPIDS TO PRODUCTION: NAVIGATING LNPs MANUFACTURING LANDSCAPE (WHILST WORKING AT PRECLINICAL VOLUMES)

Within our laboratories, we have been working on the intricate journey from lipid design to production strategies in the realm of Lipid Nanoparticles (LNPs) at preclinical volumes. We explore the foundational principles of lipid selection and formulation optimization crucial for successful LNP development and consider the challenges in bridging the gap from bench to clinic in a cost-effective and sustainable way. By navigating through the interplay of formulation design (from the choice of lipid to the buffer selection) and production strategies, through to effective pre-clinical potency screening, our work aims to provide valuable insights into overcoming barriers and unlocking the full potential of LNPs for preclinical applications. Our findings reveal that despite consistent preparation of LNPs with diverse lipid compositions, characterized by typical critical quality attributes (CQAs) such as size, polydispersity index (PDI), zeta potential, and mRNA encapsulation, there existed discrepancies in the potency observed between in vitro and in vivo studies. Specifically, the choice of pegylated lipid in conjunction with the ionizable lipid significantly impacted the potency outcomes. These findings contributes significant insights to the ongoing landscape of mRNA research, highlighting that while CQAs serve as indicators of production process quality, they do not necessarily reflect treatment potency. Furthermore, conventional in vitro assessments alone do not adequately predict in vivo potency.