Friedrich Merz Guest Professorship 2023

GOETHE UNIVERSITÄT FRANKFURT AM MAIN

MERZ

International Symposium

EMERGING APPROACHES FOR DRUG DELIVERY

Abstract Booklet

November 9th 2023
9.00 am – 7.30 pm

Goethe University Frankfurt
Campus Riedberg

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FROM BACKPACKING TO HITCH HIKING – NOVEL APPROACHES FOR SITE-SPECIFIC DRUG DELIVERY

Prof. Dr. Samir Mitragotri

School of Engineering and Applied Sciences, Harvard University, Boston, USA and Wyss Institute for Biologically Inspired Engineering, Boston, USA

Abstract

Nanoparticle-based drug delivery systems are widely explored to improve the biological outcome of chemo and immunotherapy. However, poor vascular circulation, limited targeting and the inability to negotiate many biological barriers are key hurdles in their clinical translation. Biology has provided many examples of successful "carriers" in the form of circulatory cells, which routinely overcome the hurdles faced by synthetic nanoparticle systems. We have explored "cellular hitchhiking and backpacking" approaches which involve combining synthetic particles with circulatory cells to drastically alter the in vivo fate of the particles as well as the cells. I will provide an overview of the principles and examples of hitchhiking and backpacking approaches for drug and cell therapy.

PERSPECTIVES ON INNOVATIONS IN DRUG DELIVERY

Prof. Dr. Stefan De Smedt

Department of Pharmaceutics, Ghent University, Ghent, Belgium

Abstract

Delivery of – especially biological – drugs into the various tissues remains an enormous challenge. In the first part of my talk I will highlight some recent findings from our group, including the potential of 'galsomes' and the attractiveness of the co-encapsulation of various types of nucleic acids in nanoparticles. In the second part I will speak about the potential of pulsed laser light to cross biological barriers. I will introduce photoporation of cell membranes for the delivery of macromolecular drugs; a special emphasis will be on recent findings which show the capacity of photoporation for drug delivery into the epithelium and endothelium of the cornea. In the third part of my lecture I will explain how pulsed laser light and photosensitizers allow to safely destroy pathological collagen aggregates which appear upon aging in the vitreous of the eye and which heavily disturb vision. Finally, I will introduce photoporation of the inner limiting membrane and how this might be of interest to improve transport of nucleic acids into the retina.

TAILORING PROTEIN-SURFACE INTERACTIONS ON A NANOSCALE FOR TARGETED DRUG DELIVERY

Prof. Dr. Volker Mailänder

Max Planck Institute for Polymer Research, Mainz, Germany and Dermatology Clinic, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

Abstract

Nanocarriers have been envisioned to be synthetically equipped with surface and targeting functions. Dawson et al. have shown that surfaces of nanocarriers are covered with adsorbed proteins. While this has been first seen as a hinderance to targeting we demonstrated that adsorbed proteins can give an explanation to why some materials like polyethylene glycol (PEG) have “stealth” properties, i.e. these materials are not recognized by the immune system. Actually, not the avoidance of protein adsorption is key here, but rather adsorbing the right proteins provides the stealth effect. Furthermore, we employed the adsorption of proteins on nanocarrier surfaces – termed protein corona – for targeting with antibodies. This adsorption needs to be tuned as it is occurring under conditions – here pH – which need optimization. Then this can have quite promising and durable effects. These can even outperform chemically coupled antibodies. I will show how one can determine if the protein corona influences uptake, and how to investigate the protein corona proteome. We may even dwell into research on how PEG is immunogenic by itself in some cases.

INFECTION AT THE INTERFACE: NANOTECHNOLOGY ADVANCEMENTS FOR LUNG-SPECIFIC THERAPEUTICS

Prof. Dr. Claus-Michael Lehr

Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Helmholtz Center for Infection Research (HZI), Department of Drug Delivery (DDEL) and Saarland University, Department of Pharmacy, Saarbrücken, Germany

Abstract

Urgently needed anti-infective drugs and vaccines must reach their targets safely and efficiently. Not only the body's outer epithelia, like e.g., gut, skin and lung, but also the bacterial cell envelope as well as the polymer matrix of bacterial biofilms represent important biological barriers which may delimit the transport of anti-infectives to their site of action ("bacterial bioavailability").

To model the air-blood barrier of the peripheral human lung, our group was the first who published a protocol for growing monolayers of human alveolar epithelial cells in primary culture (hAEpC) to develop functional tight junctions and high transepithelial electrical resistance (TEER). Later we introduced a first polyclonal human alveolar epithelial (hAELVi) and just recently a monoclonal cell line (Arlo) with similar properties. These epithelial cells may be implemented in various micro-physiological systems, also to study the effect of breathing and co-cultivated with other cells types, like e.g., macrophages or endothelial cells. A particular challenge is the mixed culture with bacterial biofilms to model chronic lung infections, which can meanwhile be realized most elegantly by 3D bioprinting.

Such complex in-vitro models aim to reflect the (patho)physiology of specific organs or tissues either in healthy or reduce diseased state and to generate clinically meaningful readouts. They have been used for developing novel anti-infectives, like e.g., quorum sensing inhibitors, aiming to eradicate pathogens without inducing antimicrobial resistance. Aerosolizable nano-antibiotics are also being investigated to combat intracellular infections, such as e.g., tuberculosis or viral infections by Crispr/CAS-like approaches.

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ENGINEERED AMPHIPHILIC CYCLODEXTRIN NANOPARTICLES AS DRUG DELIVERY PLATFORM

Dr. Sarah Vogel-Kindgen, Felix E.B. Brettner, Jonas, Schreiner, Maike Windbergs

Institute of Pharmaceutical Technology, Goethe University Frankfurt, Frankfurt am Main, Germany

Abstract

Cyclodextrins (CDs), a group of naturally occurring oligosaccharides, are well known pharmaceutical excipients. They form inclusion complexes with drugs, resulting in increased drug solubility, stability, absorption, and permeability across biological barriers. Grafting of aliphatic chains onto native CDs renders them amphiphilic and enables self-assembly into supramolecular drug nanocarriers (NCs), having the potential to protect drugs from biodegradation, to improve their solubility, and to control their release. Since the choice of aliphatic chain will determine the extent of hydrophobic interactions during self-assembly, drug encapsulation, and drug release, tailor-made engineering of physicochemical NC properties, release kinetics, and biological interactions is possible. We synthesized a library of amphiphilic CD derivatives and systematically investigated their self-assembly into NCs encapsulating model drugs. Upon nanoprecipitation, all CD derivatives spontaneously self-assembled into nano-sized carriers with a uniform size distribution (PDI>0.2) and a negative surface charge. Further, CD nanocarriers were able to accommodate different model drugs with a broad range of physicochemical profiles as well as molecular weights. Size, surface charge, and encapsulation efficiency were not only dependent on the physicochemical properties of the drug molecule but also on the molecular composition of the CD derivative. Similarly, a synergistic effect of molecular composition of CD derivative and physicochemical properties of the drug molecule on release profiles, was observed. Further, the nanoparticles exhibited a significant inherent anti-inflammatory effect, downregulating the expression and secretion of crucial pro-inflammatory markers and cytokines. In conclusion, amphiphilic CD derivatives are multifunctional biomaterials providing a dual-functionality platform for designing self-assembling anti-inflammatory nanocarriers with tailor-made control over physicochemical properties, drug encapsulation and release profiles.

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MICRONEEDLES IN DRUG DELIVERY: OPPORTUNITIES AND DIFFICULTIES

Sophie-Luise Meiser and Peter Langguth

Department for Biopharmaceutics and Pharmaceutical Technology, Johannes Gutenberg University Mainz, Mainz, Germany

Abstract

The development of effective therapeutic drugs requires consideration beyond just the chemical structure or pharmacological profile; ultimately it is about reaching the target destination within the body. Especially in dermal drug application, the therapeutic effect significantly depends on the administration platform whether it is a cream, patch or other formulations. Due to this, the reasonability for developing existing as well as new technologies for dermal drug delivery emerges. Lately, microneedle arrays (MNAs) as innovative transdermal delivery technology have been a rising topic of research. MNAs for dermal drug application were first described in the late 1990s. Ever since the number of publications on the topic has been growing every year. Due to their ability to deliver therapeutics for numerous applications as transcutaneous immunization, and delivering biomolecules or nanoparticles, they address scientific problems of current interest.

As the skin takes the function of a barrier and a guard for all underlying organs, it challenges and limits the formulation of bioavailable therapeutics. Through a MNA delivery system, the stratum corneum as the upper, hydrophobic and lipid-rich layer of the skin can be bypassed, allowing the drug substance(s) to penetrate the viable epidermis. Different target sites as the skin by itself, the skin hosted immune cells or blood vessels for systemic effects can be addressed. By using different manufacturing processes, tip geometries and the smart selection of excipients, drug delivery can be precisely controlled and modelled. However, new technologies not only exhibit advantages but also limitations and difficulties. Keeping these in mind, the delivery system MNA will be discussed highlighting the areas of great opportunities, their performance and impact on drug delivery as well as the challenges we need to face and deal with.

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MULTICOMPONENT SUPRAMOLECULAR POLYMERS FOR THE DESIGN OF FULLY SYNTHETIC ANTITUMOR VACCINES

Jessica Erlenbusch[1], Moritz Urschbach[1], David Straßburger[1], Riem Attariya[1,2], Natascha Stergiou[2], Tobias Bopp[2], Edgar Schmitt[2], Pol Besenius[1]

[1]Department of Chemistry, Johannes Gutenberg University Mainz, Mainz, Germany

[2]Institute of Immunology, University Medical Center Mainz, Mainz, Germany

Abstract

Classical synthetic vaccine approaches commonly utilize immunogenic carrier proteins of biological origin to immobilize antigens. These bioconjugation approaches suffer from problems regarding batch-to-batch variations and poor characterizability of the products. Deviations in the antigen loading are inevitable and may cause issues in vaccination outcome and efficacy. Supramolecular polymers have emerged as a versatile platform for the development of advanced materials that combine high internal order and dynamics through reversible intermolecular bonds. This approach holds tremendous promise in creating structures similar to those found in living systems, offering unique properties like responsiveness to stimuli and adaptation to the environment. In particular, peptide-based supramolecular materials presents an exciting avenue for the generation of novel dynamic materials, especially in the biomedical field, owing to their inherent biocompatibility and the diverse range of well-defined physical properties of various amino acids. By developing a universal supramolecular polymer platform, we construct depot-forming antitumor vaccines, that combine the activity of protein conjugates with the facile handling, precise composition and increased stability of traditional small molecule pharmaceutical compounds. Each monomer can be individually functionalized and comprise a targeting structure, immunostimulant or antigen. Simple mixing in aqueous solution results in the formation of co-polymers which harbor all desired features on their surface and are able to trigger an antigen-specific humoral immune response. The supramolecular platform is employed for versatile multivalent presentation of different epitopes and capable of inducing a strong immune response directed against tumor-associated MUC1, comprising an ST_N antigen, in C57BL/6 mice.

ENZYME-CATALYZED POSTERIOR EYE SEGMENT DEPOTS FOR BIOLOGICAL THERAPEUTICS

Prof. Dr. Dr. Lorenz Meinel

Institute for Pharmacy and Food Chemistry, University of Wuerzburg, Wuerzburg, Germany and

Helmholtz Institute for RNA-based Infection Biology (HIRI), Wuerzburg, Germany

Abstract

The delivery of drugs to the posterior segment of the eye has been extensively studied through intravitreal or periocular administration. A significant challenge is the rapid drug diffusion from the vitreous space, which requires frequent follow-up administrations. However, this is limited due to risks such as endophthalmitis, retinal tear, retinal detachment, or vitreous bleeding. To address the challenges of posterior segment drug delivery, we present a bioinspired approach compatible with microneedle application, reduces revisits to the eye, is biocompatible, offers ultimate flexibility in drug choice, and allows for intravitreal administration. Nature uses transglutaminases to bind molecules covalently to tissue. We have taken this inspiration from nature to create our covalent drug depots for ophthalmic purposes within the intravitreal space. This method does not alter the retinal biomechanics and securely attaches drugs to the superior retinal capillaries within a wide range of the drugs' molecular weight. These depots can potentially transform the long-term administration of drugs to the back of the eye.

IMPROVING ORAL DRUG ABSORPTION WITH LIPID BASED CARRIER SYSTEMS

Prof. Dr. Anette Müllertz

Department of Pharmaceutics and Analytical Chemistry Bioneer: FARMA, The Faculty of Pharmaceutical Sciences, University of Copenhagen, Copenhagen, Denmark

Abstract

Oral administration of therapeutic peptides has been desired by patients and the pharmaceutical industry since the discovery of insulin in the early 1920s. Several companies are developing oral peptide products, and presently a few oral products are on the marked, however, achieving bioavailability around 1%. Due to the low bioavailability, a very long half-life is needed to achieve a satisfactory therapeutic profile. The large and hydrophilic nature of peptides are the major factors for the low absorption from the gastrointestinal tract. First, peptides are prone to degradation by the low pH in the stomach and proteases in both the stomach and the small intestine. Secondly, peptides have a poor permeability across both the intestinal mucus layer and membrane due to their relatively large size and hydrophilicity. Successful oral delivery of peptides thus include protection from degradation in the lumen during transit of the stomach and the upper part of the small intestine. To facilitate absorption across the epithelium, permeation enhancers, e.g. decanoic acid or lyso-phospholipids, have to be included in the formulations. In addition, it is important that the peptide and the permeation enhancer are co-released and are co-localized at the site of absorption. Self-nanoemulsifying drug delivery systems (SNEDDS) have shown potential the fulfill these criteria. SNEDDS are isotropic systems based on lipids and surfactants that form nanoemulsion droplets upon dispersion in aqueous media. Recently, we have shown that it is possible to incorporate the hydrophilic GLP-1 analogue, exenatide, into SNEDDS, after complexing it with phospholipids or anionic lipids. This way the peptide is protected against proteases in the gastrointestinal tract, and more importantly, peptide permeation is increased. We have been able to increase the bioavailability, after oral dosing to rats, to around 5%, which is higher than what is obtained with the commercial products.

ENGINEERING NANOCARRIERS FOR TARGETING RNA TO THE INNATE IMMUNE SYSTEM

Prof. Dr. Roy van der Meel

Laboratory of Chemical Biology, Department of Biomedical Engineering and Institute for Complex Molecular Systems, Eindhoven University of Technology, Eindhoven, The Netherlands

Abstract

Nucleic acid therapeutics harbor great potential for silencing, expressing, or editing genes. In this talk, I will introduce a nanodelivery platform based on natural lipoproteins, which prevents premature degradation of small interfering RNA (siRNA), ensuring its targeted and intracellular delivery to hematopoietic stem and progenitor cells (HSPCs) in the bone marrow. After establishing a prototype apolipoprotein lipid nanoparticle (aNP) that stably incorporates siRNA in its core, we built a comprehensive library of which we thoroughly characterized the individual aNPs' physicochemical properties. Following the in vitro screening of all formulations, we selected eight siRNA-aNPs that are representative of the library's diversity, and determined their capacity to silence lysosomal-associated membrane protein 1 (LAMP1) in immune cell subsets in mice, using an intravenous administration regimen. Our data show that using different aNPs, we can achieve functional gene silencing in immune cell subsets and their bone marrow progenitors. Beyond gene silencing, the aNP platform's inherent capacity to engage immune cells provides it with considerable potential to deliver other types of nucleic acid therapeutics to HSPCs.

EXPLORING ULTRA-HIGH DRUG-LOADED MICELLES FOR ENHANCING DRUG DELIVERY EFFICIENCY

Prof. Dr. Robert Luxenhofer

Soft Matter Chemistry, Department of Chemistry and Helsinki Institute of Sustainability Science, Faculty of Science, University of Helsinki, Helsinki, Finland

Abstract

Polymeric micelles have been investigated for decades for solubilization/formulation/delivery of poorly soluble active pharmaceutical ingredients (API). However, scanning the literature space, it is apparent that the amount of API that can be stably dispersed is often rather limited, typically below 20 wt.% and below 10 g/L. But is this physico-chemical limitation relevant for their application? Arguments have been put forward for and against benefit of high-drug loading.

This open question notwithstanding, it is an interesting and important question as to how highly drug loaded micelles can be realized. There are only very few micellar systems with drug loading significantly higher than 30 wt.%. In particular, poly(2-oxazoline)s and poly(2-oxazine)s based micelles are able to formulate unusually large amounts of the extremely water insoluble paclitaxel and other APIs and API combinations with up to 50 wt.% incorporated in the polymer micelles. In some cases, higher drug loading was found to be beneficial for therapeutic efficacy. We have identified pronounced effects of small structural variations in the polymers on the formulation capacity for a variety of different drugs. In addition, we have found that the hydrophilic shell of the polymer micelles is strongly involved in the drug interactions, which, depending on the polymer structure, can severely compromise drug loading, stability and dissolution rates. Using large scale all-atom simulation, we have recently investigated molecular interactions between drug molecules, polymers and water in these drug loaded micelles at different drug loadings. The results suggest that difference in the number and life-time of hydrogen bonds between all the different components correlate will with the observed maximum drug loading, and therefore might explain the observed, highly unusually high drug loading. Current studies are testing this hypothesis further and hopefully lead to a much improved molecular understanding of drug loaded polymer micelles.

LIPID NANOPARTICLES FOR OVERCOMING BIOLOGICAL BARRIERS TO mRNA DELIVERY

Dr. Rohan Palanki

Department of Bioengineering, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Abstract

Recent years have witnessed tremendous developments and breakthroughs in the field of RNA-based therapeutics and vaccines. The distinct mechanisms of exogenous RNAs and analogs, including messenger RNAs, small interfering RNAs, microRNAs, and antisense oligonucleotides, have brought them unprecedented potential to treat a variety of pathological conditions. However, the widespread application of RNA therapeutics and vaccines is hampered by their intrinsic features and formidable host barriers. Development of safe and efficient vectors is key for successful delivery and translation of RNA therapeutics and vaccines.

The talk will present engineered lipid nanoparticle (LNP) platforms that enable the delivery of RNA therapeutics and vaccines to a range of target cells and tissues in the body. New therapeutic strategies utilizing these LNPs including in vivo reprogramming of immune cells for cancer immunotherapy and vaccination and the mRNA prenatal therapeutics for treating pregnancy disorders such as pre-eclampsia, and in utero gene editing for treating disease before birth.

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