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PDDS 2019

3rd Edition of Global Conference on

PHARMACEUTICS AND DRUG DELIVERY SYSTEMS

June 24-26, 2019 - Paris, France

Theme: *Addressing current challenges in the development and delivery of medicinal agents*

Holiday Inn Paris - Marne La Vallee
2 boulevard du Levant, 93160 Noisy-le-grand, Paris, France

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PDDS 2019

BOOK OF ABSTRACTS

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Theme:

Addresing current challanges in the development and delivery of medicinal agents

JUNE 24-26, 2019

PARIS, FRANCE

PDDS 2019

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Thank You All...

Welcome Message

Dear participants of PDDS 2019,

The 1st and 2nd editions of the Global Conference on Pharmaceutics and Drug Delivery Systems (PDDS 2017 and PDDS 2018) held in Valencia and Rome respectively proved to be extremely fitting platforms for fruitful scientific exchange and collegial professional engagement. By courtesy of the Magnus Group, you are now cordially invited to participate at the 3rd edition of the conference, to be held in Paris in June 2019, with its theme "Addressing current challenges in the development and delivery of medicinal agents." This conference offers a wide spectrum of presentations on current topics ranging from pre-formulation studies to the development of highly sophisticated drug delivery systems, and likewise promises to be of significant intellectual value and utility to all participants.

Worldwide demand for safe and effective drugs relies on the initiative and skills of experts in many fields. This will be evident from the scientific program to be presented at PDDS 2019, which features oral and poster presentations to be contributed by experts working in numerous niches of pharmaceutical development including drug formulation, preclinical studies, drug delivery strategies, nanomedicine and drug regulatory issues. Participation at this conference presents a unique opportunity to share your expertise and gain new insights into recent advancements in these fields. The potential for networking and creating new collaborations is another major attraction of the PDDS conferences.

We look forward to your participation and trust that PDDS 2019 will be a memorable event in your scientific career!

Mino R Caira
Univesity of Cape Town, South Africa

Welcome Message

Dear participants of PDDS 2019,

On behalf of the Magnus Group and the Organizing Committee, it is a pleasure to invite you to participate in the **"3rd Edition of the Global Conference on Pharmaceutics and Drug Delivery Systems"**, that will take place in Paris from June 24 to 26, 2019.

This conference is an opportunity for academics, start-ups and big pharma to interact and to exchange with experts on drug discovery, pharmacology, clinicians, biotechnology, biotherapy etc.

This conference will be the opportunity to establish new collaborations between scientists working in complementary research areas. In addition, this conference will be the link between basic and applied research, in which new ideas will emerge at the interface between disciplines.

We look forward to seeing you in Paris, France!

Dr Angelita Rebollo
DR Inserm, CSIC Sorbonne University
Paris, France

Welcome Message

Dear participants of PDDS 2019,

On behalf of the Organizing Committee I welcome participants to the 3rd Global conference on Pharmaceutics and Drug delivery systems which is the continuation of previous highly successful meetings featuring novel drug delivery strategies.

The conference covers the entire spectrum from drug, peptide and vaccine formulation through to manufacturing and regulatory affairs. The delivery of both new or established drugs in new dosage forms to their disease target in the body at a therapeutic concentration with no adverse effects for the patient is essential part of drug delivery.

PDDS 2019 has attracted a range of scientists and global speakers from academia and industry, who will introduce and discuss cutting edge research in diverse areas such as pre-formulation, delivery routes and drug delivery technologies. Major drug delivery challenges, relevant physiological considerations, drug targeting across diverse applications from nanotechnology to polymer drug delivery systems will be discussed and I am confident that all participants will greatly benefit from attending PDDS 2019 and I'm looking forward to an interesting and informative meeting with stimulating discussion.

Robert Houlden
Formulation Director, Formulytica Pty. Ltd
Australia

Welcome Message

Dear participants of PDDS 2019,

On behalf of Magnus Group and the conference organizing committee, it is our pleasure to invite you to attend the third Global Conference on Pharmaceutics and Drug Delivery Systems, June 24-26, 2019 in Paris, France.

This conference is not only an opportunity to learn about new developments in the pharmaceutical community, but an incredible networking opportunity. It is an assemblage of scientists and research professionals in the field of Pharmaceutics and Drug Delivery systems, where you will have a great opportunity to share ideas and knowledge as well as collaborate with scientists and leaders in pharmaceutical arena. The topics of discussion will appeal to a wide variety of international professionals from research laboratories, medical practices, academia and industry. There is something of value for everybody attending the conference.

Thank you for your continued support. We look forward to seeing you in Paris, France!

Robert P. Bianchi
President Prescription Drug Research Center, USA

keynote speakers

Vladimir P. Torchilin
Northeastern University
USA

Robert Houlden
Formulytica Pty. Ltd
Australia

Robert P. Bianchi
Prescription Drug Research
Center, USA

Georgina K Such
The University of Melbourne
Australia

Gillian Hutcheon
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About MAGNUS GROUP

Magnus Group (MG) is initiated to meet a need and to pursue collective goals of the scientific community specifically focusing in the field of Sciences, Engineering and technology to endorse exchanging of the ideas & knowledge which facilitate the collaboration between the scientists, academicians and researchers of same field or interdisciplinary research. Magnus group is proficient in organizing conferences, meetings, seminars and workshops with the ingenious and peerless speakers throughout the world providing you and your organization with broad range of networking opportunities to globalize your research and create your own identity. Our conference and workshops can be well titled as 'ocean of knowledge' where you can sail your boat and pick the pearls, leading the way for innovative research and strategies empowering the strength by overwhelming the complications associated with in the respective fields.

Participation from 90 different countries and 1090 different Universities have contributed to the success of our conferences. Our first International Conference was organized on Oncology and Radiology (ICOR) in Dubai, UAE. Our conferences usually run for 2-3 days completely covering Keynote & Oral sessions along with workshops and poster presentations. Our organization runs promptly with dedicated and proficient employees' managing different conferences throughout the world, without compromising service and quality.

About PDDS 2019

PDDS 2019 serve as a podium for the interaction between experts in the areas of pharmaceutics, drug delivery, nanomedicine, biotechnology, and nanotechnology around the world and aims in sharing some unique research and translational studies on various advances in the related fields. The conference opens the doors for many researchers in academia, clinicians, and industry representatives working in these exciting areas. It is expected to bring together both reputable scientists in advanced stages of their career and young researches from many related disciplines. The conference expects many new ideas to emerge at the interfaces between disciplines aiming to solve the most important problems relating to the health and wellbeing of the humanity.

With its strong emphasis on innovative approaches, the conference offers a chance for scientists and physicians working in different areas of drug development to learn new ideas that could help them advance their own research and forge new professional relationships and collaborations.

Our expert honorary speakers will provide you with the most clinically up-to-date relevant information, you'll leave better educated and more invigorated than you thought possible.

PUBLISHING PARTNER

pharmaceutics

an open access journal by MDPI

Pharmaceutics (ISSN 1999-4923) is an open access journal which provides an advanced forum for the science and technology of pharmaceutics and biopharmaceutics. It publishes reviews, regular research papers, communications, opinions, commentaries, and short notes. Covered topics include pharmaceutical formulation, process development, drug delivery, pharmacokinetics, biopharmaceutics, pharmacogenetics, and interdisciplinary research involving, but not limited to, engineering, biomedical sciences, and cell biology. Our aim is to encourage scientists to publish their experimental results and theoretical assumptions in as much detail as possible. There is no restriction on the length of the papers. The full experimental details must be provided so that the results can be reproduced. In addition, this journal presents the following unique features:

- Manuscripts regarding research proposals and research ideas will be particularly welcomed
- Computed data or files regarding the full details of the experimental procedures can be deposited as supplementary material if it is not possible to published them in the Material and Methods section, as usual
- We also accept manuscripts addressed to a broader audience, regarding research projects financed by public funds

Note: PDDS 2019 participants will receive a benefit of 20% waiver on article processing charges

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DAY 1

KEYNOTE FORUM

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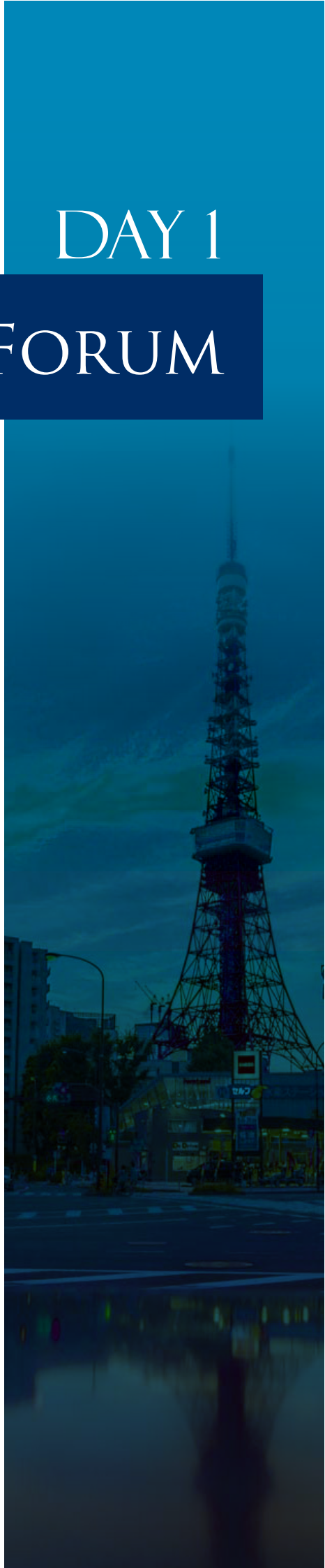

Biography

Vladimir P. Torchilin, Ph.D., D.Sc. is a University Distinguished Professor of Pharmaceutical Sciences and Director, Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston. His interests include drug delivery and targeting, nanomedicine, multifunctional and stimuli-sensitive pharmaceutical nanocarriers, biomedical polymers, experimental cancer therapy. He has published more than 400 original papers, more than 150 reviews and book chapters, wrote and edited 12 books, and holds more than 40 patents. Google Scholar shows more than 60,000 citations of his papers with H-index of 108. He is Editor-in-Chief of Current Drug Discovery Technologies, Drug Delivery, and OpenNano, Co-Editor of Current Pharmaceutical Biotechnology and on the Editorial Boards of many other journals. He received more than $30 M from the governmental and industrial sources in research funding. He has multiple 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.

Novel developments in lipid-based multifunctional combination nanopreparations for multidrug resistant cancer

Vladimir P. Torchilin, Ph.D., DSc
Northeastern University, USA

Therapy of multidrug resistant cancers could be significantly enhanced by using siRNA down-regulating the production of proteins involved in cancer cell resistance, such as Pgp or survivin. Even better response could be achieved is such siRNA could be delivered to tumors together with chemotherapeutic agent. This task is complicated by low stability of siRNA in biological surrounding. Thus, the delivery system should simultaneously protect siRNA from degradation. We have developed several types of lipid-based delivery system, such as liposomes and polymeric micelles made of PEG-phospholipid or PEI-phospholipid conjugates, which are biologically inert, demonstrate prolonged circulation in the blood and can firmly bind non-modified or reversibly-modified siRNA. Additionally, these nanopreparations can be loaded into their aqueous core (liposomes) with soluble drugs, such as doxorubicin, or into the lipidic core (micelles) with poorly water soluble chemotherapeutic agents, such as paclitaxel or camptothecin. In experiments with cancer cell monolayers, cancer cell 3D spheroids, and in animals with implanted tumors, it was shown that such co-loaded preparations can significantly down-regulate target proteins in cancer cells, enhance drug activity, and reverse multidrug resistance.

In order to specifically unload such nanopreparations inside tumors, we made them sensitive to local tumor-specific stimuli, such as lowered pH, redox conditions, hypoxia, or overexpressed certain enzymes, such as matrix metalloproteases. Using pH-, hypoxia-, redox- or MMP2-sensitive bonds between different components of nanopreparations co-loaded with siRNA and drugs, we were able to make the systems specifically delivering biologically active agents in tumors, which resulted in significantly improved therapeutic response.

Presentation Learning Outcome

- The advantages of using combination preparation of RNA/drug in treating multidrug resistant tumors
- How to engineer liposome- and micelle-based drug delivery system for combination tumor therapy
- How to make drug delivery systems responsive to local tumoral conditions

Biography

Robert is Formulation Director at Formulytica, a leading contract R&D company in Melbourne serving Australia, USA and South East Asia. Previously with GlaxoSmithKline and Stiefel Laboratories he has been in the formulation area for over 30 years and is experienced in development of pharmaceutical emulsions, gels and aerosols for drug delivery. One of Robert's main passions is rheology and he has spent 10 years using this technique to characterize emulsions to predict their attributes when applied to the skin and develop more cosmetic elegant emulsions for his customers.

Robert has 8 patents principally in the area of dermatology and is the author of multiple papers.

Taking your active from the lab to scale-up formulation development of a topical delivery systems

Robert Houlden

Formulytica Pty. Ltd, Australia

The presentation will discuss (with practical examples) the steps required to take a pharmaceutical active from the research lab to developing a topical oil-in-water vehicle or gel for drug delivery. Preformulation steps such as methods to increase solubility and skin penetration will be examined. Stability and in-vitro performance testing methods are discussed including suitable animal models which can predict efficacy prior to incurring the high clinical costs in late stage development. The issue of identifying critical process parameters prior to scale-up to batch sizes for toxicity testing will be introduced.

Presentation Learning Outcome

- The presentation gives practical examples of Topical delivery of an NCE obtained from over 20 years of formulating experience with pharmaceutical actives. While the examples will be for a new drug entity, the techniques are applicable to new topical formulations of existing actives.
- Insights on how to solubilize a new molecule or salt will be presented offering insights into how to overcome common low solublility issues.
- Common pitfalls and methods for performance testing against a reference listed drug will be discussed.
- Critical Process Parameters that should be explored during development prior to scale-up will be detailed.

Biography

Mr. Bianchi is currently the President and Chief of Scientific and Technical Affairs at the Prescription Drug Research Center, Bradenton, FL. He retired as a laboratory director for the Drug Enforcement Administration after 34 years of federal service, where he held increasingly responsible positions as an analytical chemist for the FDA and DEA to the chief of DEA's Laboratory Operations Section. Mr. Bianchi was also director of the DEA Special Testing and Research Laboratory where extractability experiments were conducted more than twenty years ago.

Since 2005 he has been working with the pharmaceutical industry and FDA on developing in vitro protocols to evaluate abuse deterrent formulations and has been actively involved is sharing his experience with the regulatory, treatment, pharmaceutical abuse and law enforcement community. For the last decade, he has participated dozens of category 1 studies on abuse-deterrent opioid formulations, appeared as a panelist and presenter at abuse deterrent formulation & prescription drug abuse professional meetings. Mr. Bianchi has provided drug related consultations to more than thirty organizations/companies concerned about OTC & prescription drug abuse and has made numerous presentations to the regulatory, treatment, pharmaceutical, abuse and law enforcement communities. He has also presented in vitro laboratory data to the FDA Advisory Committee for a new immediate release oxycontin formulation.

Mr. Bianchi is also a Special Government Employee for participation in the FDA Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee meetings.

Government and industry response to the US opioid epidemic

Robert P. Bianchi

Prescription Drug Research Center, USA

Prescription drug abuse has been declared an epidemic in America by the Centers for Disease Control and Prevention and the president of the United States which makes up 4.6 percent of the world's populations but consumes 81 percent of the world supply of oxycodone. The FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs while assuring patient access. This is a responsibility shared with the pharmaceutical industry, treatment facilities, educational institutions, and Federal, state and local law enforcement agencies.

FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.

Toward that end, the FDA issued Guidance for Industry in April 2015 under the title, "Abuse-Deterrent Opioids-Evaluation and Labeling", which contains the following statement:"The goal of the laboratory-based studies, Category 1, should be to evaluate the ease with which the potentially abuse-deterrent properties of a formulation can be defeated or compromised".

The FDA also issued draft guidance for industry in March 2016 (finalized November 2017) the "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products".

This presentation will discuss abuse deterrent technology currently approved or in development and the required in vitro studies designed to evaluate extractability or tamperability. The FDA position on abuse deterrent delivery systems and the history of abuse deterrent opioid development will also be discussed. Studies on the efficacy of a new formulation to deter abuse will also be discussed.

Biography

Dr Georgina Such completed her PhD in 2006 from the University of New South Wales. After her PhD, Dr Such commenced postdoctoral work in the Nanostructured Interfaces and Materials Science (NIMS) group headed by Professor Frank Caruso. In 2013, she commenced a Future Fellowship in the School of Chemistry, The University of Melbourne, enabling her to start her own research group in the area of stimuli-responsive materials. Dr Such is now a senior lecturer at the University of Melbourne. Dr Such has authored 71 peer-reviewed publications including 3 book chapters. Her work has been recognized with the David Sangster Polymer Science and Technology Achievement Award and the 2011 L'Oreal Women in Science Fellowship. Her research interests include polymer synthesis, self-assembly and stimuli-responsive materials.

The use of self-immolative polymers to control cellular delivery

Georgina K Such
The University of Melbourne, Australia

Nanoparticles are of interest for the delivery of therapeutics as they are capable of targeting drug release specifically to diseased cells and tissue. Self-assembled polymeric carriers have generated particular attention for drug delivery applications due to their simple and versatile synthesis. However, such carriers are still limited by inefficient delivery to target regions within the cell. Therefore, there is a need to better understand their cellular response. One of the key limitations for the delivery of biological therapeutics such as DNA or proteins is delivery to the cytosol. It is well known that nanoparticles are internalised into acidic, cellular compartments (lysosomes/endosomes) and need to efficiently escape from this region to be effective. To design such materials one interesting pH responsive polymer is poly(2-(diethylamino)ethyl methacrylate) (PDEAEMA), as it undergoes a transition from hydrophobic to hydrophilic in a pH range consistent with endosomal compartments. Nanoparticles using this polymer have shown the potential to facilitate endosomal escape based on pH induced change in the nanoparticle structure. However, the extent of endosomal escape and the mechanism is still unclear. Another type of polymer with potential application in targeted delivery is self-immolative polymers, which undergo depolymerisation after cleavage of a responsive end-cap.

In this presentation, we discuss the synthesis of nanoparticles combining pH responsive and self-immolative building blocks. It was shown these nanoparticles disassembled in response to variations in pH. Fluorescence imaging and leakage assays were combined to study the interactions of the nanoparticles with the endosomal membrane. This interaction could be tuned by the combining the polymer components in different ratios. These modular and responsive nanoparticles have tunable interaction with endosomal compartments and thus offer potential for the delivery of biological therapeutics.

Presentation Learning Outcome

- Explain how self-immolative polymers can be used to engineer responsive delivery systems
- Demonstrate how particle structure can be used to tune cellular delivery
- Explain how fluorescence imaging techniques can be used to study mechanisms of nanoparticle interactions with cells

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DAY 1

SPEAKERS

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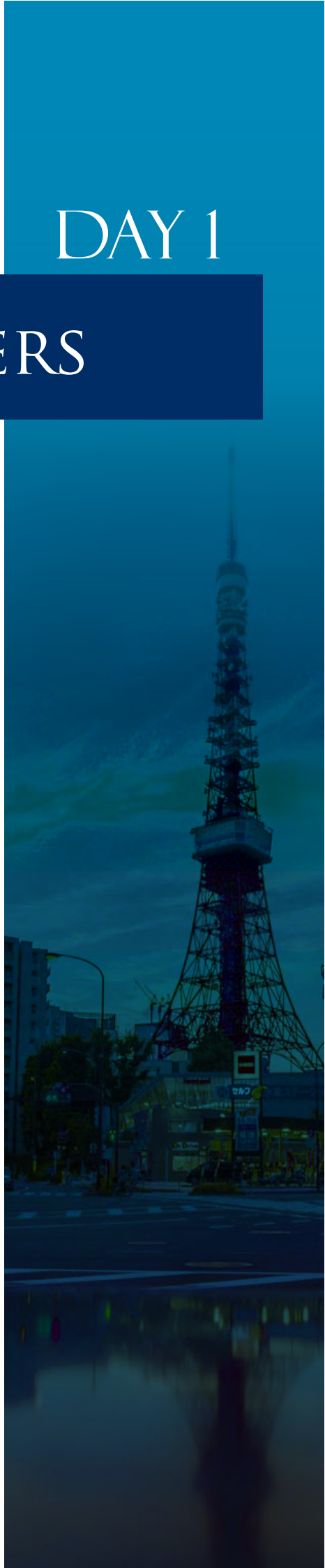

Docetaxel-liposomes prepared by the dual centrifugation method: Effect of propylene glycol and lipid charge on liposomal characteristics

Dr Ann Mari Holsæter[1*], MPharm Kristina Wizgird[1,2], Prof. Dr Natasa Skalko-Basnet[1]
[1]Department of Pharmacy, University of Tromsø The Arctic University of Norway, Norway
[2]Department of Pharmaceutical Technology and Biopharmacy, University of Freiburg, Germany

Docetaxel (Doc) is a highly lipophilic anticancer drug. The current Doc treatment gives several side effects that might be prevented when Doc is incorporated in liposomes. The first aim of this study was to adapt the Dual Centrifugation (DC) method as a preparation technique for Doc-liposomes, and secondly, to investigate how propylene glycol (PG) and liposomal charge affect the vesicle characteristics, namely Doc-entrapment, liposomal size, polydispersity index (PI) and zeta potential (ZP).

First, the DC-settings were standardized with regards to time (30 min), speed (3500 rpm) and batch size (0.5 g vesicular phospholipid gel (VPG) containing 40 % phospholipids (PL)). Doc was added in a 1:10 w/w ratio to the PL content, and homogenization aid (1.4 mm zirconium beads) in a 1:1 w/w ratio to the VPG content. The DC-machine applied was a SpeedMixer™ (DAC 150.1 FVZ-K, Synergy Devices Limited, UK). After DC-homogenization, the VPGs were diluted into liposomal dispersions adding distilled water to a total volume of 2 mL. The Doc-entrapment was determined by HPLC after removing free drug crystals by centrifugation. The liposomal size, PI and ZP were determined using the Malvern Zetasizer, Nanoseries ZS. PG decreased the vesicle size when included in neutral Soy phosphatidylcholine (SPC)-liposomes; the SPC-PG-liposomes with and without Doc had a size of 97.9 ± 2.0 and 107.1 ± 6.1 nm, respectively. Moreover, inclusion of PG assured a higher Doc-entrapment as compared to the non-PG containing SPC-liposomes; 86.2 ± 8.3 % relative to 41.5 ± 3.7 %, respectively. However, PG was not beneficial in liposomes incorporating charged lipids into the membranes. When positively charged DOTAP replaced 20 % (w/w) of the SPC, the liposomal size increased to 518.0 ± 34.6 nm in the presence of PG, whereas the Doc-DOTAP-liposomes without PG had a size of 170.1 ± 0.5 nm. The Doc-entrapment was also reduced in the presence of PG both for positively charged DOTAP and negatively charged DMPG SPC-liposomes, resulting in only 40-50 % Doc-entrapment. Doc-liposomes with 20 % DOTAP and no PG was found to be the best formulation (97.3 ± 5.1 % Doc entrapment). Considering inclusion of DMPG in liposomes, all SPC:DMPG ratios gave acceptable liposomal sizes (< 200 nm). Although the 20 % DMPG formulation without PG showed an increased drug entrapment (88.0 ± 1.1 %) upon production, the Doc-entrapment was at the same level as for the neutral liposomes contain only SPC after 4 weeks of storage in the fridge.

In conclusion, DC-homogenization proved to be a suitable and reproducible method for preparing Doc-liposomes. The effect of PG on both liposomal size and Doc-entrapment varied with the charge of lipids. The most promising formulations containing either 10 % or 20 % DOTAP and no PG, and achieved a Doc-entrapment of approximately 100 % and suitable liposomal size (< 200 nm).

Presentation Learning Outcome

- The applied DC-method – dual centrifugation, is a novel and efficient small-scale preparation method with several advantages, especially in early formulation screening and when working with toxic compounds, as it does not require any sample transfer and all preparation steps take place in a closed container.
- Docetaxel is a highly lipophilic drug that has some challenging features regarding a stable entrapment within the liposomal bilayers.
- The observed positive effect of the positively charged lipid 1,2-Dioleoyl-3-trimethyl-ammoniumpropane chloride (DOTAP) with regards to docetaxel entrapment is interesting considering a clinical formulation, whereas the drastic change in liposomal size upon addition of propylene glycol is worth a closer investigation.

Biography

Dr. Ann Mari Holsæter was borne in Trondheim, Norway, 30th of January 1974. She works as Associate Professor at The University of Tromsø The Arctic University of Norway, Norway, in the Drug Transport and Delivery Research Group at the Department of Pharmacy. She is a pharmacist by background and gained her PhD within pharmaceutical technology in 2004. Her research focus today is on advanced drug delivery systems and drug targeting, and liposomes, nanofibers and hydrogels as drug delivery systems in particularly. Her publication portfolio includes per Nov 2018, 53 items, including 18 original per-review journal research articles, one review article and one book chapter.

Delivering type I interferon to dendritic cells empowers tumor eradication and immune combination treatments

J. Tavernier[1*], A. Cauwels[1], S. Van Lint[1], F. Paul[2], G. Garcin[2], A. Van Parys[1], S. Gerlo[1], N. Kley[1], & G. Uzé[2]
[1]Cytokine Receptor Laboratory, VIB Medical Biotechnology Center, Ghent University, Belgium
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An ideal generic cancer immunotherapy should mobilize the immune system to destroy tumor cells without harming healthy cells and remain active in case of recurrence. Furthermore, it should preferably not rely on tumor-specific surface markers, as these are only available in a limited set of malignancies. Despite approval for treatment of various cancers, clinical application of cytokines is still impeded by their multiple toxic side effects. Type I interferon (IFN), for instance, has a long history in the treatment of cancer, but its multifaceted activity pattern and complex side effects prevent its optimal clinical use. Here we develop AcTakines (Activity-on-Target cytokines), optimized (mutated) immunocytokines that are up to 1000-fold more potent on target cells, allowing specific signaling in selected cell types only.

As conventional Dendritic Cells (cDC) are essential for IFN antitumor efficacy, we targeted type I IFN-derived "AcTaferon (AFN)" to Clec9A$^+$ cDC. Clec9A-AFN therapy displayed strong antitumor activity in murine melanoma (B16), breast carcinoma (4T1) and lymphoma models (A20), as well as against human RL lymphoma in immunodeficient NSG mice reconstituted with a human immune system. In sharp contrast to wild-type IFN therapy, the antitumor efficacy of Clec9A-AFN was not accompanied by any detectable toxicity, assessed by body weight and several hematological parameters. Clec9A-AFN effects were lost in CD8-depleted or Batf3-/- mice, and depended on IFN signaling in cDCs but not in T lymphocytes. Combined with anti-PDL1 immune checkpoint blockade, Treg-depleting anti-CTLA4 + anti-OX40 therapy, immunogenic chemotherapy, or low-dose TNF, complete tumor regressions and long-lasting tumor immunity (memory) were obtained, still without any adverse effects. Our findings thus indicate that DC-targeted AFN provides a highly efficient, off-the-shelf and safe cancer immunotherapy, with possible application in a broad range of malignancies.

Biography

Jan Tavernier obtained his Ph.D. degree in 1984 on the cloning of interferon and interleukin genes. After an extended stay at Biogen and later at Roche, he returned in 1996 to Ghent University at the VIB Centre for Medical Biotechnology where he founded the Cytokine Receptor Laboratory. His main areas of expertise are cytokine receptor activation and signal transduction, and the analysis of protein-protein interactions. He is currently developing AcTakines: a novel class of safe, generic and off-the-shelf immunocytokines. Jan Tavernier published over 300 refereed manuscripts and holds over 50 patent applications. He is a member of Royal Belgian Academy of Sciences and The Arts.

Lipid and carbohydrate based delivery vesicles for gene therapeutics: Approaching difficult diseases

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RNA therapeutics is a broad group of RNA oligo- and polymers that knock down, insert or replace a disease associated RNA. RNA therapeutics act *via* diverse biological mechanisms including e.g. antisense oligonucleotides (ASOs), RNA interference oligonucleotides, mRNAs and sgRNA/CRISPR systems. Some RNA therapeutics have already reached clinical trials and have been approved by FDA. For instance, Eteplirsen, a 30nt long phosphorodiamidate morpholino oligomer (PMO), characterized as a splice switching oligo (SSO) and has been used for the excision of exon 51 in dystrophin RNA which results in production of functional dystrophin gene in Duchene muscular dystrophy (DMD) patients. Improved symptoms, however, were observed in only 16% of patients, pointing on unmet need for further improvements.

In my talk I will describe recent advances in RNA bioconjugation and nanoparticle technology for the delivery of appealing RNA therapeutics. In particular, I will describe the utility of novel lipid and carbohydrate conjugation technologies as promising approach for targeted delivery of RNA to human cells.

There is currently an unmet need for reliable, specific delivery options for gene therapeutics. Specifically, RNA targeted therapy has been dramatically developed over the last decade. Multiple cell types and tissues are especially hard to target by RNA therapeutics. This includes neuronal cells in brain, well protected by blood brain barrier, and metastatic, rapidly migrating malignant cells. Using conjugations is a modern paradigm that integrates an interdisciplinary chemistry and biology, to provide new delivery options for biological drugs including DNA and RNA therapeutics. Herein, I will give a review of our most recent acquired knowledge within the field of the RNA conjugates as gene therapeutics for treating HIV-1 in brain and metastatic non small cell lung cancer.

Presentation Learning Outcome

- The audience will get an update on novel bioconjugation strategies for labelling of sensitive molecules.
- New methods for drug design in context of RNA gene therapeutics will be discussed.
- My presentation will also help the audience to make an efficient design of gene therapeutics targeting difficult cell types, including neuronal cells in brain and metastatic malignancies.

Biography

Kira Astakhova is an Associate Professor at the Department of Chemistry, Technical University of Denmark. Dr. Astakhova received multiple awards and honor fellowships including Jorck research award, Lundbeck research fellow, Marie Curie Early Stage Training and Carlsberg Foundation Elite Award. She is a coauthor of 50 scientific articles and 5 approved patents and patent applications.

In vitro modeling of the blood-brain barrier to assess CNS drug delivery

Pr. Fabien Gosselet
Blood-brain barrier laboratory, Artois University, Lens, France

The development of novel therapeutical molecules to treat central nervous diseases (CNS) requires the evaluation of blood-brain barrier (BBB) permeability and toxicity. The BBB is located at the endothelial cells (ECs) of the brain microvessels level and is very complex to study in alive animals. Therefore, the development and the use of in vitro models of the BBB is compulsory for initial drug screening before in vivo studies. For this reason, several in vitro BBB models have been developed since the early 90's consisting to extract and purify ECs from animals. Recently, significant differences in the BBB have been reported among species suggesting that human BBB models must be privileged. During this oral presentation, the last studies related to the development and optimization of human in vitro BBB models will be discussed. In particular, the development and the use of the brain-like endothelial cells (BLECs) developed in my laboratory will be explained. This model consists to isolate $CD34^+$-hematopoietic stem cells from human umbilical cord blood and to differentiate these cells into ECs. Then, these cells are seeded on matrigel-coated inserts before being co-cultured with brain pericytes to acquire the BBB phenotype in few days. The BLECs express tight junctions and transporters typically observed in brain endothelium and maintain expression of most in vivo BBB properties for at least 20 days. The model is very reproducible since it can be generated from stem cells isolated from different donors and in different laboratories. Using the BLECs model, it is thus possible to investigate the role of the BBB in CNS physiology and to predict CNS distribution of proteins, nanoparticles, drugs. Studies relative to cells, viruses or bacteria transmigration can also be performed. Importance of the insert choice, calculation methods, coating will be discussed.

Presentation Learning Outcome

- The blood-brain barrier physiology and localization will be discussed.
- Differences in BBB among species will be shown.
- Strategies to reproduce in vitro the BBB will be presented. Several models of the BBB will be presented and discussed. A focus on human BBB models will be done.
- Audience will have very useful information regarding the good practices when using in vitro models of the BBB to calculate molecules passage/transport through this barrier.
- The importance to use adequate inserts, coating, protocols will be presented.

Biography

F.Gosselet graduated in Biology and received a PhD in Cancerology (2006). He completed his education at the blood-brain barrier laboratory (BBB-Lab), located in Lens (France), as post-doctoral fellowship. Then, he obtained an assistant Professor position (2008) and is full Professor since 2016. Since 2015, he is director of the BBB-Lab. This lab routinely uses in vitro BBB models for investigating BBB physiology, its role in neurodegenerative diseases (AD/PD, stroke, brain tumor metastasis,…), for improving drug delivery and for providing data in pharmaco-toxicological field and to pharmaceutical companies. The BBB-lab actively contributes to several national/H2020 research programs. To date, FG published more than 45 research articles.

Prototyping and evaluating a novel Humanoid chewing robot for drug delivery using a medicated chewing gum

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The global pharmaceutical market in 2009 was estimated at $837 billion and the US had a largest market share worth $300 billion per annum. It is estimated that the market could be worth nearly $1.6 trillion by 2020. The global drug delivery market in 2016 was estimated to be worth $510 billion which is a third of the estimated global pharmaceutical market. It is expected that the drug delivery market will be increased to around $900 billion by the year 2025. Medicated chewing gum (MCG) is a new advanced drug delivery method, with a promising future. Its potential has not yet been fully exploited because there is no gold standard methodology currently exists for testing chewing gum dissolution and current *in-vitro* apparatus/chewing machines cannot simulate the human chewing action and forces accurately to influence drug release rate because of the complexities involved in mastication. Also, most of these devices do not have the ability to combine mastication, saliva and chewing gum similar to human and subsequently measure the release of compounds from chewing gums.

The aim of this study is to validate the use of the newly developed humanoid chewing simulator to extract xylitol from commercially available chewing gum by quantifying its release over time using human participants and *in-vitro* chewing.

Presentation Learning Outcome

- Why is there no gold standard methodology that currently exists for testing chewing gum dissolution?
- Why the current in-vitro apparatus machine used for medicated chewing gum cannot simulate the human chewing action?
- Why is the mastication of two devices chosen by Ph.Eur.8,0.2.9.25 apparatus (A and B) not similar to real mastication?
- What is bionic engineering design and how could it help to develop advanced drug delivery systems?

Biography

Kazem Alemzadeh has completed his PhD from the University of Bradford, United Kingdom. He is a senior lecturer in the Department of Mechanical Engineering at the University of Bristol, and he is being part of the Clinical Trials Unit at the Bristol School of Oral and Dental Sciences. He has carried a wide research and has numerous scientific publications and has been serving as an editorial board member.

Multifunctionalized and targeted biocatalytic nanoreactor for combinatory treatment of ER+ breast cancer

Rafael Vazquez-Duhalt*, Kanchan Chauhan, Juan M. Hernandez-Meza, Ana G. Rodríguez-Hernández, Karla Juarez-Moreno, and Prakhar Sengar
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Background: Tamoxifen is the standard endocrine therapy for breast cancers, which require metabolic activation by cytochrome P450 enzymes (CYP). However, the lower and variable concentrations of CYP activity at the tumor remain major bottlenecks for the efficient treatment, causing severe side-effects. Combination nanotherapy has gained much recent attention for cancer treatment as it reduces the drug-associated toxicity without affecting the therapeutic response.

Results: Here we show the modular design of P22 bacteriophage virus-like particles for nanoscale integration of virus-driven enzyme prodrug therapy and photodynamic therapy. These virus capsids carrying CYP activity at the core are decorated with photosensitizer and targeting moiety at the surface for effective combinatory treatment. The estradiol-functionalized nanoparticles are recognized and internalized into ER+ breast tumor cells increasing the intracellular CYP activity and showing the ability to produce reactive oxygen species (ROS) upon UV365nm irradiation. The generated ROS in synergy with enzymatic activity drastically enhanced the tamoxifen sensitivity in vitro, strongly inhibiting tumor cells.

Conclusions: This work clearly demonstrated that the targeted combinatory treatment using multifunctional biocatalytic P22 represents the effective nanotherapeutics for ER+ breast cancer.

Biography

Dr. Rafael Vazquez-Duhalt is full professor at the Center for Nanosciences and Nanotechnology of the National University of Mexico and Head of the Department of Bionanotechnology. He is Industrial Chemical Engineer from the National Polytechnic Institute in Mexico City. Dr. Vazquez-Duhalt completed postgraduate studies in Analytical Chemistry of the Environment at the University of Geneva, Switzerland, and in Human Ecology in a program sponsored by seven European Universities. He earned the PhD degree in Biological Sciences from the University of Geneva, Switzerland. In addition, Dr. Vazquez-Duhalt carried out a three-years Postdoctoral work in the University of Alberta, Canada, and he has been visiting Professor at the University of Maryland and at the University of California, San Diego.

Among others, Dr. Rafael Vazquez-Duhalt has earned the following prizes: The Scopus Prize from Elsevier Publisher to Mexican researcher with higher H factor Biotechnology and Agronomy fields in 2011. The "Thomson-Reuters" Prize to the most cited Mexican research article in Microbiology in the decade 1999-2009 in 2009. Dr. Vazquez-Duhalt is author of four patents, and he has published 2 books and more than 160 scientific articles with more than 4500 cites and an H of 39 (Scopus). Prof. Vazquez-Duhalt is Editor-in-chief of the journal "Biocatalysis" (de Gruyter, Germany) and member of the editorial boards of 5 scientific journals. Dr. Vazquez-Duhalt is Associate Director of the CaliBaja Center for Resilient Materials and Systems at the Jacobs School of Engineering, University of California at San Diego, USA.

New approach to study difference in NSAIDs enantiomer activity, including chiral inversion.

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The difference in the medical properties of the enantiomers of many chiral drugs is a well-known fact. This is a big problem, since most drugs are still used in the form of racemates. The latter is connected with the difficulties of separation. One of the most prominent representatives of drugs in which enantiomers differ not only in degree but also in the directions of therapeutic activity are nonsteroidal anti-inflammatory drugs (NSAIDs). Naproxen is one of the NSAIDs that is available in the form of S isomer only. His R analogue does not exhibit anti-inflammatory properties but has a therapeutic activity in other directions. To understand the reasons of the difference in naproxen (NPX) enantiomers medical activity in this work original approach has been developed. The interaction of (S)- and (R)-NPX with chiral donors in linked systems – dyads have been investigated. These model systems are believed to simulate NPX enantiomers binding with chiral amino acid residues located in active sites of COXs enzymes. Idea is that upon binding some kind of diastereomers analogs are formed. In diastereomers, as it is known, enantiomers may exhibit different reactivities. Spin chemistry and photochemistry study of photoinduced charge transfer (CT) between (S)- and (R)-NPX and (S)-tryptophan and (S)-N-methylpyrrolidine linked by different bridges has shown the stereoselectivity of partial and full CT. The exciplex quantum yields and the rates of its formation are larger for the dyads containing (R)-NPX that let us suggest the greater contribution from CT processes with (R)-optical isomer. This is consistent with fact that (R)-NPX is more active in the processes of the chiral metabolism by the action of cytochrome P450 known to involve electron transfer. Really, (R)-NPX is slightly more active in oxidative metabolism .However, in the enzymatic chiral inversion of NPX-CoA esters by AMACR and other transferases (R)-isomer demonstrates appreciably greater activity than the (S)-analog. (S)-isomer - drug naproxen, according to above results, has to exhibit a more reversible binding with the amino acid donors that is an agreement with the results of biochemical research. In order to establish the nature of abovementioned stereoselectivity in processes with participation of S and R NPX another physical method - spin chemistry was used. The comparison of spin chemistry experimental results with calculation has shown that the reason of difference in R and S reactivity in ET is the distinction of spin density distribution in paramagnetic form of (R,S)- and (S,S)-diastereomers. This result is directly related to the reactivity of the enantiomers since the spin density and the electron density distributions correlate with each other. For example, the formation of hydrogen bonds between naproxen and amino acid residues in the active site of COX can be dependent on the electron density distribution of the enantiomers. The use of this approach also let us to discover the radical path of chiral inversion of R naproxen and detect short-lived radicals responsible for the phototoxicity of another drug, ketoprofen.

The work was supported by the Russian Science Foundation (18-13-00047).

Presentation Learning Outcome

- The potential practical significance of these results is the realization of why the enantiomers of naproxen differ from each other. The lack of such knowledge is a big problem for pharmacology.
- Taking into account that the scope of the NSAIDs is constantly expanding, one can hope that the knowledge of the nature of the differences between the enantiomers will serve to search for new areas of their activity.
- In addition, this report will serve as a source of new knowledge, since the foregoing approach to studying the properties of chiral drugs is completely original.

Biography

Tatyana V. Leshina is Professor of Physical Chemistry in the Institute of Chemical Kinetics and Combustion Siberian Branch of the Russian Academy of Sciences. She works in the area of spin chemistry and is the author of the discovery "A new pattern of radical reactions in solution" (1998), devoted to the observation and explanation of the nature of the influence of inner and external magnetic fields on radical reactions in solutions. Today she applies the spin chemistry and photochemistry methods to study the chemical nature of the difference in medical activity of chiral drugs enantiomers on the examples of model processes.

In situ delivery and production system of anti-cancer molecules with gene-engineered *bifidobacterium*

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Regardless of recent rapid progresses in cancer therapy by molecular-targeting and regulating immune check points, the side effects of those treatments are still troublesome for the patients to be overcome. We have developed an *in situ* Drug Delivery and Production System(iDPS) with non-pathogenic anaerobic *Bifidobacterium* to target hypoxia in cancer tissues. Hypoxic microenvironment is well known to be a causative factor of tumor cell resistance to radiation therapy and chemotherapy, and also recognized as a condition for malignant progression of cancer cells. When the recombinant *Bifidobacteria* carrying genes of anticancer products were *iv* administered, they rapidly disappeared from normal tissues within a few days, and proliferated to produce anti-cancer products selectively in tumor tissues. Administration of bacteria into blood vessels, even if non-pathogenic, may be considered dangerous in that it may induce sepsis, however, our system is not the case. Recently, articles on the effects of cancer treatment with bacteria appeared and brought to light the potential utility of bacteria in cancer treatment. One of our recombinant bacterial clones, which expresses cytosine deaminase converting 5FC (low toxic prodrug of 5FU) to 5FU, is now underway of clinical trial (Phase 1/2) sponsored by AnaeroPharma Science, Inc., a venture company originated from Shinshu University. Additionally, several clones to produce anti-cancer molecules for iDPS, such as anti-HER2 scFv, anti-immune check point scFvs, antitumor cytokines, have been being established. We will discuss the safety and rationale of iDPS by referring to our experimental data.

Presentation Learning Outcome

- It is rationale to target anaerobic condition of cancer microenvironment. The audience can direct their attention to the specificity of cancer tissues, such as hypoxia, rather than cell-specific molecules of cancer, to develop a new anticancer drug.
- We believe that our work help the audience to learn a new idea free from conventional senses.
- Yes, in terms of idea but not concrete techniques.
- I think that even if any sophisticated cancer cell specific drug is developed, resistant cells to the drug will appear soon, because cancer population is heterogeneous. Taking the situation into consideration, it seems to be more effective to deliver a large amount of any toxic molecules selectively to tumor tissues by making use of macroscopic specificity, hypoxia, to overcome problems derived from cellular heterogeneity. Our iDPS is able to produce anti-cancer molecules continuously, so that it may contribute to lower the drug price in the future. We think that bacteria can be regarded as proliferative liposomes.

Biography

Dr. Taniguchi studied Physics as an undergraduate student (-1973) and majored Biophysics at the graduate school, then became an assistant at the Research Institute of Cancer of Kyushu University, Japan. He received his PhD degrees (both Science and Medical Science). After 2 year visiting fellowship supervised by Dr. Kakunaga at NCI/NIH, USA, he obtained the position of an Associate Professor at Kyushu University. He moved to Shinshu University School of Medicine as a professor (1995-2015). His present position is a specially appointed professor of the Medical School. He has published more than 200 research articles in SCI journals.

Influence of mucoadhesivity on the bioavailability of nanoparticulate drug delivery systems

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The oral administration route is by far the preferred one and more than 80% of drugs are taken orally. Since the gastrointestinal (GI) tract is the primary site of drug delivery, many researchers have focused their attention on the mucus layer that covers the GI tract. Indeed, the mucus can trap and coat foreign particulates and pathogens to protect the underlying epithelium so as to represent an important barrier to the absorption of nanoparticulate systems. Mucoadhesive polymeric nanoparticulate systems (NP) have raised interest as vehicles for drug delivery by the oral route, for their potential ability to improve the bioavailability of drugs with low mucosal permeability and/or poor chemical stability in the GI environment. To be absorbed across the intestinal epithelium into the systemic circulation, however, the NP will have to cross the layer of stagnant mucus adjacent to the intestinal membrane. Then, the NP tendency to adhere to the mucus gel can play an important role since on the one hand it opposes the physiologic transit of the delivery system down the GI tract away from the absorption site, thus favoring drug absorption, whereas, on the other hand, it hampers the water-driven transport of NP from luminal to epithelial side of the mucus layer, thus slowing down absorption. In fact, still open to debate is the issue of whether mucoadhesive particles prolong drug residence at the absorption site and enhance drug bioavailability or, instead, aggregate in mucus far away from the absorptive epithelium and lower the bioavailability. Recently we have demonstrated that the oral bioavailability of a drug is higher when this is trapped in a more mucoadhesive rather than in a less mucoadhesive NP type. This data was explained assuming that mucoadhesivity tends to keep the formulation at the absorption site, opposing its physiologic movement from stomach down to large intestine, while the concurrent water movement facilitates NP transport across the mucus layer from lumen to epithelium, where NP can be internalized by the cells. These results convinced us of the importance of the advective water flow present in the mucus, which can greatly influence the NP transport through it. Therefore, this presentation will be focused on the development of new methods to study the NP transport through the mucus, in particular on a method which couples the multiple particle tracking technique with the microfluidics.

Presentation Learning Outcome

- Influence of polymeric NP mucoadhesivity on the bioavailability of the encapsulated drugs
- Various techniques to study NP transport through the mucus lining the GI epithelium
- Some considerations on the structure-activity relationship concerning NP having different surface characteristics

Biography

Prof. Zambito studied Pharmaceutical Chemistry at the University of Pisa, Italy and graduated as MS in 1999. She received her PhD degree in 2004 at the same Institution. In 2007 she obtained the position of researcher at the University of Pisa. She is now full professor of Biopharmaceutics and Pharmaceutical Legislation at the Department of Pharmacy of the University of Pisa. She has published about 50 research articles in SCI(E) journals.

Systemic liver-targeting delivery of a novel DNA/RNA heteroduplex oligonucleotide via an enteral route

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Since the advent of antisense technology, oligonucleotide drugs have attracted a greater deal of attention as next-generation therapeutics, which can be selectively delivered to their target tissue to obtain effective gene silencing. The production of conventional pharmaceutical preparations considering factors such as the oral and rectal dosage form is an essential step in the development of a wide range of oligonucleotide drugs. However, oligonucleotides are macromolecules that are easily disintegrated by nucleases and as such, are generally poorly absorbed by the intestine. We have recently developed a hepatocyte-specific delivery technique for oligonucleotides via an enteral route. The chemical conjugation of siRNA with alpha-tocopherol utilized chylomicrons, which acted as a specific *in vivo* carrier to the liver and were formulated as lipid nanoparticles using unsaturated fatty acid as an absorption enhancer. The method demonstrated effective silencing of the targeted mRNA (*ApoB)* expression in mice in a postprandial state (Murakami, *et al*, Sci. Rep. 2015). In this talk, we will provide an overview of the concept of our enteral delivery technique and discuss our recent results on the development of a DNA/RNA heteroduplex oligonucleotide (HDO) which was newly prepared as a more specific and potent oligonucleotide drug (Nishina K., *et al.* Nat. Commun., 2015). We used a tight junction (TJ) modulator as a para-cellular specific permeation enhancer (Takahashi A, *et al.*, Biomaterials, 2012) and demonstrated that the HDO conjugate with alpha-tocopherol specifically delivered to the liver following rectal administration of the enema in mice and suppressed *ApoB* gene expression, consequently achieved the reduction of plasma triglyceride and cholesterol levels in the model mice with hypercholesterolemia. These findings suggest that our enteral delivery technique via the lymphatic route should be useful for developing a non-invasive conventional preparation for oligonucleotide therapeutics. Applicability of this technology to the other organ-specific oligonucleotide delivery systems using conjugates with different targeting molecules or ligands remains to be investigated.

Presentation Learning Outcome

- Recent development of novel oligonucleotide technology and therapeutics.
- Conceptualization and development of an enteral delivery system for oligonucleotide therapeutics.
- Technology and the benefits of systemic delivery via the enteral lymphatic route.

Biography

Dr. Watanabe performed this work at Dr. Murakami's laboratory when she was an assistant professor of Pharmaceutics in Osaka-Ohtani University. She has been an associate professor of Clinical Pathology in Josai University since 2018. Her research interest is to develop drug delivery systems for biological drugs. She received her bachelor's and master's degrees in Pharmaceutical Science from Toyama University in 1996 and 1998, respectively, and received her Ph.D. degree of Medicine from Osaka University in 2002. She worked as a postdoctoral researcher at Dr. Edward Clark's laboratories of Immunology in Washington University, U.S.A. from 2003 to 2008.

Physicochemical and biophysical study of mechanisms the drugs bioavailability enhancement with new multifunctional delivery systems

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[2]Laboratory of mechanochemistry of organic compounds, Institute of Solid State Chemistry and Mechanochemistry, Novosibirsk, Russian Federation

One of the most important problems of modern pharmaceutics is the low solubility and bioavailability of drug compounds. These problems are solved by using various delivery systems that can form water-soluble "guest-host" complexes with drug molecules. One of the advantages of this approach is a significant reduction in therapeutic dose, as well as a reduction in side effects, which is especially important, for example, in the case of highly toxic anticancer drugs. In our work we focus our attention on oligosaccharides and polysaccharides which are able to form water soluble inclusion complexes with various lipophilic drugs. The examples of such carriers are polysaccharide arabinogalactan (AG), saponin glycyrrhizic acid (GA) and oligosaccharide cyclodextrin.

The report will illustrate the use of various physical methods, primarily nuclear magnetic resonance, to study the inclusion complexes of a wide range of drugs, as well as the effect of drug carriers on the physical and functional properties of cell membranes. In particular, the ability of GA to integrate into the lipid bilayer and its effect on the lipid mobility in the membrane was studied by NMR relaxation and molecular dynamics techniques. The use of these methods made it possible to establish that GA molecule is embedded in the outer half-layer of the membrane and has a significant effect on the mobility of phospholipids in the bilayer. The permeability enhancement by GA and AG carriers for model membrane as well as for erythrocyte cells and myeloid leukemia K562 cells has been demonstrated by PAMPA and NMR techniques. This comprehensive study sheds some light on the mechanism of the drugs bioavailability enhancement in the presence of glycyrrhizin and arabinogalactan and offers the new possibilities of their use as drug carriers. Several examples of the influence of complexation on the drugs stability and reactivity will be presented. In conclusion some evident advantages of mechanochemical technique for development of novel drug formulations will be discussed. This work was supported by Russian Scientific Foundation, grant No. 18-13-00047 and the Russian Foundation for Basic Research, grant No. 18-416-540007.

Presentation Learning Outcome

- New data on the molecular mechanisms of drug delivery by novel natural drug carriers will be interesting to wide audience of scientific researcher in the fields of medicinal chemistry, supramolecular chemistry and membrane biophysics, as well as for education purposes.
- From practical point of view, our experience in this field and new technologies developed in our labs can be helpful for design and development of new drug formulations with predictable properties.

Biography

Dr. Nikolay E. Polyakov is a leading researcher at the Institute of Chemical Kinetics and Combustion of the Russian Academy of Sciences. He received his PhD degree in 1987 at the same institution. After one year postdoctoral fellowship in National Industrial Research Institute of Nagoya (Japan), Dr. Polyakov as a Visiting Professor performed joint project with University of Alabama and University of Utah (USA). The areas of his interest are drug delivery systems and the role of free radicals in biology and medicine. He is the authors of more than 80 scientific papers in these areas.

Designing *ADME* formulations with matching exposures to amorphous solid dosage forms

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Amorphous solid dispersion (ASD) based formulations have been frequently used to improve the bioavailability of poorly soluble drugs. However, common processes to produce ASDs are not feasible for absorption, distribution, metabolism and excretion (ADME) studies with radio-labeled active pharmaceutical ingredients (API) due to contamination concerns. Hence, simple liquid or solid formulations are routinely used to support the ADME studies, though bridging the bioperformance gap between simple formulations that are amenable for use with radioactive API, and amorphous solid dispersion clinical formulations generated through processes such as spray drying and hot melt extrusion can be quite challenging. The challenge is to not only design solid or liquid formulations that would effectively solubilize the API but also inhibit rapid in vitro and in vivo precipitation and recrystallization. This abstract captures two different strategies for developing ADME formulations, one where an ampiphilic polymer, hypromellose acetate succinate (HPMCAS-L) impregnated in a liquid vehicle, polyethylene glycol (PEG-400) provided not only inhibition of crystallization but also resulted in nanoparticle formation that was critical to bioperformance. It was found that the bioavailability of the formulation can be compromised by the presence of undissolved crystalline seeds, and the inclusion of HPMCAS-L can mitigate this effect, as well as potentially facilitate nanoparticle formation. In a second case study, where the compound of interest is insoluble in liquid vehicles, a unique pentahydrate sodium salt was utilized in combination with an HPMC capsule and a dose adjustment strategy to provide comparable exposures to the amorphous solid dispersion clinical formulation. The HPMC polymer from the capsule acted as an inhibitor of precipitation and aided in the overal path forward for the ADME study. As such, two distinct methodologies were successfully employed to enable ADME studies of two different compounds with unique physiochemical characteristics.

Presentation Learning Outcome

- Understanding the challenges with desiging ADME formulations
- Methodologies for desiging ADME formulations
- Understanding impact of polymeric crystallization inhibitors and nanoformers on exposure
- The talk will help the audience in adopting these methodologies for ADME studies in their respective jobs

Biography

Dr. Tatavarti is a Principal Scientist in the Oral Formulation Science and Technology group at Merck Research Laboratories. He has more than 14 yrs. of industry experience with expertise in the areas of immediate and modified release, solubility enhancement and differentiated complex dosage form development. He is the author/co-author of more than 25 published manuscripts, patent applications and abstracts. He holds a PhD in pharmaceutical sciences from the University of Maryland and conducted doctoral research in the area of microenvironmental pH modulation in controlled release systems. Since joining Merck, he has worked across various indications, but has dedicated majority of his time towards designing and advancing complex delivery systems, in the NCE and PVE space, for HIV and Oncology indications. He led the formulation development for approved HIV products, PIFELTRO and DELSTRIGO. He is also a subject matter expert on extrustion-spheronization, pediatric formulations and encapsulation.

Wound healing mats made of layer by layer coated nanoparticles and electrospun nanofibers

Gulcin Arslan Azizoglu*, Erkan Azizoglu, Ozgen Ozer
Ege University, Faculty of Pharmacy Department of Pharmaceutical Technology, 35040 Bornova-Izmir Turkey

Introduction: A broad range of diseases could be altered using layer-by-layer (LbL) based nanoparticles which is an emerging and powerful method to develop multifunctional nanomedicines. In this study, a combined formulation was achieved with LbL coating of silver nanospheres using melatonin, a pineal gland hormone with anti-inflammatory and immunomodulatory effects, between the layers. Electrospun nanofiber mats were prepared with melatonin loaded LbL nanoparticles for wound healing applications.

Methods: Lipoic acid functionalized silver nanospheres (AgNS) (796182 Sigma-Aldrich) were used as core material. 5 mg/mL melatonin was prepared with 500 μM polyethylenimine (PEI) in water to form a polycation layer. Previous studies shown that, MEL has a very low solubility in water. 5% Tween 80 was included in polycation solution to enhance the solubility. Silver nanospheres were mixed with polycation solution and then polyanion solution composed of 500 μM dextran sulfate (DXS) in water added and mixed thoroughly. After each step, particle size, polydispersity index and zeta potential were monitored with Zetasizer (Nano ZS, Malvern Instruments, Malvern, UK). 1 g of polyvinyl alcohol (PVA) was mixed with 10 mL nanoparticle dispersion for 16h at room temperature. Electrospinnner (Ne200 NanoSpinner, Inovenso Turkey) was used for fabrication of nanofiber mats. Characterization studies were evaluated with a rheometer (HR-1 Discovery Hybrid Rheometer with Smart Swap™ 40 mm Peltier Plate geometry) and a conductivity meter (SevenCompact™ Mettler Toledo) to characterize the formulation in terms of viscosity and conductivity. Nanoparticle-PVA dispersion was pumped through a custom nozzle with a 0.8 mm die at 0.3 mL/h flow rate under 15 kV voltage. A flat collector with 15 cm distance from the nozzle was used to collect the nanofiber mat. Optical microscope was used for preliminary imaging studies of the fiber morphology.

Results: AgNS/PEI-MEL/DXS layer by layer nanoparticles with a final particle size of 55 nm and polydispersity index of 0.329 was prepared successfully. The zeta potential was found -25 mV conforming the final coating with DXS. Prior imaging studies showed that electrospinning process was successful and resulted with uniform and straight fibers.

Conclusion/Implications: The studies can be considered as a combination of electrospinning and LbL coating processes which may enable combination of different APIs and release profiles. In addition, electrospun nanofibers prepared with melatonin loaded silver nanospheres could be a promising candidate for the wound healing applications.

Acknowledgment: This work was supported by The Scientific and Technological Research Council of Turkey-TÜBİTAK (Project number: 117S213).

Biography

Gulcin Arslan Azizoglu is a PhD candidate in research of functionalized wound dressings prepared with layer by layer nanoparticles. She is a research assistant at Ege University Faculty of Pharmacy, Department of Pharmaceutical Technology.

In vitro model of diclofenac sodium gel delivery through pig skin

Enkelejda Goci[1,2*], Entela Haloci[1,2]
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[2]Department of Pharmacy, University of Medicine, Tirana, Tirana, Albania

At first sight transdermal drug delivery appears to be a simple form of treatment, but closer examination reveals that dermatological form doses represent one of the most difficult aspects of the science of pharmaceutical formulation. Modern formulation methods nowadays, however, have to concentrate on biopharmaceutical principles. The idea is to formulate topical pharmaceutical drugs that improve the delivery of the active principles in the local target site of action by selection of the best and appropriate vehicles. The vehicle composition can affect drug release, and a number of vehicles, including simple creams, gels and emulsion based formulations (Emulgel) have been utilized in topical preparations. Gel based formulations are better percutaneously absorbed than creams and ointment bases. From the literature, the formulation with HEC gel base exhibited better properties for topical delivery of drugs when compared with the other formulations.

Diclofenac sodium (DS) is a nonsteroidal anti-inflammatory drug (NSAIDs) widely used clinically to reduce inflammation and pain. The present research has been undertaken with the aim to develop topical hydrophilic gels of diclofenac sodium 1% and evaluation of in vitro drug release of diclofenac sodium through pig skin using vertical diffusion cell comparing with diclofenac commercial gels.

In the presented work were prepared three batch hydrophilic diclofenac sodium gels (DC) of hydroxyethylcellulose (HEC). Skin permeability of the preparations were evaluated in vitro using abdominal hairless pig skin, into water medium at 370C and determined using spectrofotometer UV at 276 nm. For each formulation were evaluated the cumulative drug release and were calculated the plots of release rate of DS.

The HEC diclofenac sodium gels were clearly transparent. All preparations were easily spreadable, with acceptable bioadhesion and fair mechanical properties. The pH values ranged from 7.33 to 8.35, which are considered acceptable to avoid the risk of irritation after skin application.

From the study was concluded that HEC gels containing diclofenac showed good homogeneity, spreadability, pH value and rheological properties within the limits allowed for dermatological preparations. HEC DS gels exhibited significantly better drug release when compared to commercial gel.

Presentation Learning Outcome

- A new topical hydrophilic vehicle for dermatological formulation
- An easy way to realize a vertical diffusion cell
- A appropriate in vitro method proposed with the used of abdominal pig skin as a useful dialyze membrane

Biography

Dr. Enkelejda Goci has studied Pharmacy at the University of Tirana, Albania and graduated as Msc in 2003. She received her PhD degree in 2014 at the University of Medicine, Tirana, Albania.

The study of the factors that influence in bioavailability of topical drugs and evaluation of the drug delivery of these formulations were the focus of her PhD studies. She has published and presented many scientific researchers at the pharmaceutical sciences field.

Influence of formulation and freeze drying process variations on protein stability

Paritosh Pande, [1,2*] Mohammed M. AbouGhaly, [3] Prof Elizabeth M. Topp, [3] Prof Michael J. Pikal[1]
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[2]Technology and Process Development Division, IMA Life North America, Tonawanda, NY, USA
[3]Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN 47907, USA

Nearly half of the therapeutic proteins undergo freeze drying process to improve their long-term storage stability but the inability to directly control the product temperature during freeze-drying process can lead to non-uniform distribution of critical quality attributes (CQAs) in product vials, even for biosimilars having similar formulation. Therefore, a better understanding of product temperature variations is needed to assess the influence of distribution in CQAs, like protein degradation and aggregation, on the probability of releasing out of specification drug product. To understand the impact of product temperature variation on distribution of CQAs, following investigations are currently in progress:

1. Analysis of variations in key physical properties like phase composition (i.e. phase separation and crystallinity), specific surface area, and glass transition temperature (Tg) in the product vials, as well as levels of product degradation. Attempts are being made to identify the physical properties that are predictive of chemical degradation and aggregation.

2. Quantification of position-dependent differences in product temperature history caused by differences in ice nucleation temperature and assess whether or not these differences are likely to cause differences in stability, particularly aggregation (which can potentially generate adverse immune response).

Preliminary results indicate that significant intra-batch variations in ice nucleation temperature result in modest variations in specific surface area and higher order protein structure with possible stability consequences, which should be thoroughly investigated, on a case by case basis. Although, the current research focuses on proteins, the general scale-up technology will also apply to generics and vaccine products and an understanding of these variations in CQAs will be key to reduce the probability of releasing out-of-specification product.

Presentation Learning Outcome

- The audience will understand the underlying science responsible for degradation of therapeutic protein formulations and therefore, will be able to improve the design of their biologic formulations and optimize their drug delivery systems.
- Currently 35% of biologic drugs are freeze dried to improve their long-term stability. Therefore, stability and degradation of therapeutic protein formulations is a priority area of interest for regulatory agencies like US-FDA. A deep understanding of degradation processes like chemical degradation and adverse immune response associated with such degradation is critical for improving the formulation and drug delivery of this emerging class of therapeutic molecules.
- As an area of priority research for drug regulatory agencies, the data presented in this US-FDA funded research will bring faculty and researchers up to the speed with current trends and benchmark in US regulatory landscape. Additionally, the research data will help pharmaceutics and drug delivery researchers to optimize their formulation and drug delivery systems from an early stage and avoid the common pitfalls observed in the late stage drug development process.

Biography

Dr. Paritosh Pande is a Research Scientist at IMA Life North America and is actively engaged in optimization of freeze drying process for emerging therapeutic molecules. He received Ph.D. in Chemistry from University of Connecticut, USA in 2012 and as a Postdoctoral Fellow at Prof. Michael J. Pikal's lab, he investigated the influence of formulation and lyophilization processes on the stability of therapeutic proteins. Dr Pande serves as an editorial board member of the Journal of Targeted Drug Delivery and is the current Chair of the prestigious Gordon Research Seminars on Nucleosides, Nucleotides and Oligonucleotides.

Valproic acid encapsulated biodegradable microneedles for treatment of androgenetic alopecia

Shayan Fakhraei Lahiji*, Ph.D., Hyungil Jung, Professor
Yonsei University, South Korea

There are numerous genetic and environmental factors responsible for occurrence of male pattern hair loss known as androgenetic alopecia. Despite considerable medical advancements, the current treating agents, are limited by unsatisfactory cure rate and potential side effects. Valproic Acid, a well-kwon FDA approved anticonvulsant drug, was recently shown to induce hair follicle regrowth with a higher efficiency compared with current therapeutics including Minoxidil. Valproic acid activates several pathways including Wnt/β-catenin which is essential for hair growth. Although the exact action mechanism of valproic acid is not fully understood, previous studies suggested that application of valproic acid inhibits expression of glycogen synthase kinase 3β (GSK-3β), which upregulates β-catenin levels, leading to enhanced hair follicle transition from telogen (rest) to anagen (active) phase. Currently, topical application is the only available administration route of valproic acid to induce hair regrowth. Skin, as a protective barrier of body, however, limits the permeation efficiency of topically applied valproic acid. Thus, to improve its delivery efficiency, we encapsulated valproic acid within dissolving microneedles and applied them onto the skin by utilizing a micro-pillar based applicator. Dissolving microneedles are polymeric biodegradable micro dimensioned needles that encapsulate drugs and release them beneath the skin upon application in a minimally invasive manner. Carboxymethyl cellulose was used as backbone material of dissolving microneedles encapsulated with 50 μl of valproic acid. We found that by encapsulation of valproic acid within dissolving microneedles, the expression level of β-catenin, alkaline phosphatase, proliferating cell nuclear antigen, loricrin and hair follicle stem cell markers, including keratin 15, and CD34 that are responsible for hair growth were remarkably increased compared with the topical application.

Presentation Learning Outcome

- An introduction to a novel drug delivery system, known as microneedle
- A new insight into androgenetic alopecia treatment technologies
- Potential of dissolving microneedles in improving delivery efficiency of drugs, proteins, and vaccines

Biography

Dr. Shayan Fakhraei Lahiji is a postdoctoral associate at Yonsei University in the Department of Biotechnology. Dr. Lahiji's research is focused on the design and development of novel patient-friendly drug delivery systems, known as microneedles. He has developed various technologies to pave the road for replacing hypodermic needles with painless and environmentally-friendly dissolving microneedles. So far, Dr. Lahiji has successfully encapsulated hair-loss treatment agents, insulin, and anti-wrinkle compounds within microneedles. Currently, he is involved in various projects to customize the previously-developed technologies and launch a product that is focused on the market needs.

Since 2014, Dr. Lahiji has published 5 papers as first author, 9 papers as co-author, and applied 4 patents in Korea, U.S., Japan, Europe and China. In addition, he has been the recipient of several awards, including "the best researcher award" at the 3rd World Biotechnology Conference, "the young researcher award" at the 8th Pharmaceutics & Novel Drug Delivery Systems conference, "the best research award" from Yonsei University, and "the best academic poster" from BK21 PLUS.

Therapeutic effects of trehalose liposomes against tumors along with apoptosis

Yoko Matsumoto Ph. D.
Sojo University, Japan

Trehalose stabilizes membranes and proteins in cells most likely by hydrogen bonding. Trehalose liposomes (DMTre) composed of L-α-dimyristoylphosphatidylcholine (DMPC) and trehalose micelles (TreC14) have been produced by sonication of a mixture of DMPC and TreC14 in a buffer solution with no organic solvent. The remarkable inhibitory effects of DMTre on the growth of human colon, gastric, hepatocellular, and lymphobrastic carcinoma cells have been reported. In this study, we investigated inhibitory effects of DMTre against breast cancer and lung carcinoma. Hydrodynamic diameter (dhy) of DMTre composed of 30 mol% DMPC and 70 mol% TreC14 was 100 nm with single and narrow range of size distribution, which can avoid reticular endotherial system in vivo. The thickness of the fixed aqueous layer (TFAL) of DMTreCn was evaluated from the zeta potential and increase in TFAL values of DMTreCn was obtained in a dose-dependent manner. The TFAL values for DMTreCn were larger than that of DMPC liposomes. DMTre inhibited the growth of breast tumor (MCF-7 and MDA-MB-453) cells leading to apoptosis with the activation of caspases. The suppression of tumor weight of xenograft mice model of carcinoma treated with DMTre after inoculation with breast tumor cells was obtained along with apoptosis. The remarkable reducton of volume and weight in subcutaneous tumors on subcutaneous lung carcinoma-bearing mice administered with DMTre were obtained. Dimensions of tumor area of lung on the orthotopic graft-bearing mice of lung carcinoma significantly decreased after the administration with DMTre.

Biography

Prof. Yoko Matsumoto is a Professor of Department of Life Sciences at Sojo University, Japan. She received her PhD in Pharmacy from Kyushu University, Japan. She was a visiting researcher in Colorado University at Boulder with Prof. Tom Cech, USA. Yoko Matsumoto has received Outstanding Female Researcher Award from the Society of Chemical Engineering, Japan. She is one of Director for Japan Nanomedicine Society and Councilor for Japanese Association for Molecular Target Therapy of Cancer. Her current research interest focuses on liposomes for therapeutic applications. She has published more than 130 original papers.

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DAY 2

KEYNOTE FORUM

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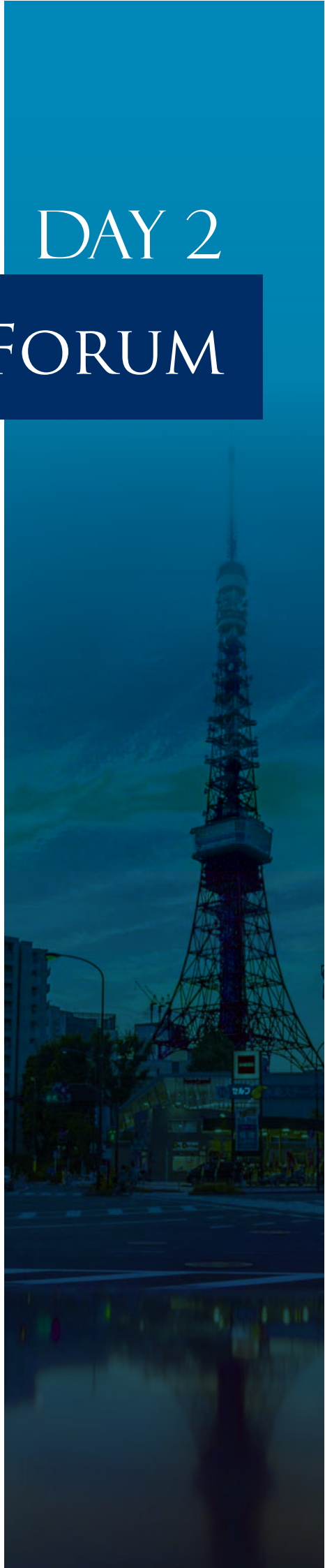

Biography

Professor Gillian Hutcheon graduated from Strathclyde University, Scotland in 1996 with a PhD thesis on Biocatalysts is non-aqueous media. She then undertook postdoctoral research at Queens Medical Centre, Nottingham investigating Protein:Biomaterial interactions. She joined Liverpool John Moores University in 1999 as a lecturer in Organic Chemistry and leads the Formulation and Drug Delivery Research Group. She has evolved her interest in proteins and biomaterials towards drug delivery applications looking at the enzyme catalysed synthesis of novel materials for micro and nanoparticle delivery of small molecule drugs and biomolecules. She is currently Head of the LJMU Institute for Health Research.

Nanoparticle delivery of natural products for the treatment of lung cancer

Gillian Hutcheon

Liverpool John Moores University, UK

Cancer is the leading cause of death worldwide, accounting for 8.8 million deaths, with lung cancer attributing to 1.69million of these deaths in 2015. The application of natural products to treat various diseases, such as cancer, has been an important area of research for many years. Several phytochemicals have demonstrated anitcarcinogenic activity to prevent or reduce the progression of cancer by modulating various cellular mechanisms. For example, phenolic compounds such as Curcumin and resveratrol have been shown to be a potent anti-inflammatory and anti-oxidative activity.

One of the major problems is that cancer cells develop resistance to exisiting chemotherapy drugs either intrinsically (genetic mutation) or over time leading to multiple drug resistance (MDR) which leads to patient relapse and poor prognosis. Plant derived polyphenolics genistein and kaempferol are compounds with proven biochemical and pharmacological properties and have recently been found to modulate the ABC transporters responsible for cancer drug resistance including P-gp and multidrug resistance associated protein (MRCP1).

Although these natural products shows great promise in the prevention and treatment of cancer, they also show low bioavailability which can be overcome by using polymeric nanoparticles to deliver them directly to lung cancer cells. Nanoparticle-mediated lung delivery can also overcome the problem of non-specific targeting/distribution of the anticancer agent and reduce side effects.

The research presented in this talk will demonstrate the applicability of natural products in the fight against cancer and also the design of novel delivery systems to target the lungs.

Presentation Learning Outcome

- An understanding of lung cancer and current therapies
- An introduction to the use of natural products in medicine
- Methods for the formulation of nanoparticles
- Aspects of pulmonary delivery of dry powders

Biography

Following his retirement as Chair of Physical Chemistry at the University of Cape Town (UCT), Professor Mino Caira was appointed as Senior Research Scholar in the same Department in 2015. He has served as Director of the Science Faculty's Centre for Supramolecular Chemistry Research at UCT since 2005, where he supervises the synthesis and physicochemical characterization of multi-component solids containing bioactive molecules (active pharmaceutical ingredients, new drug candidates, bioactive natural products, agrochemicals). He has published over 300 research articles in peer-reviewed journals and several reviews on crystal polymorphism, co-crystallization and cyclodextrin inclusion of drugs.

Synthesis and physicochemical analysis of multi-component phases in drug development

Mino R. Caira
University of Cape Town, South Africa

Supramolecular modification of active pharmaceutical ingredients (APIs) and new chemical entities (NCEs) to enhance their physicochemical properties and improve their delivery can be achieved *via* crystal engineering methods, which involve the generation of alternative, multiple solid forms of a given bioactive compound, including polymorphs, amorphs, solvates, co-crystals and inclusion complexes. Shortcomings such as poor tabletability, hygroscopic tendency, poor aqueous solubility and variable bioavailability have been successfully addressed *via* this approach in recent years, leading to more systematic and rapid optimisation of solid-form selection for eventual formulation. In our laboratory, strong emphasis is placed on X-ray diffraction and complementary methods for analysing newly generated phases. Powder X-ray diffraction allows rapid identification of novel crystalline and non-crystalline bulk phases, while the ability to characterize them at the molecular level using single crystal X-ray diffraction ensures their accurate description, including, for example, the distinction between co-crystals and salts, which is critical for patenting new entities. For solvated solid forms and some inclusion complex phases, thermogravimetric analysis yields stoichiometric information while differential scanning calorimetric techniques enable the identification and quantitative characterization of polymorphic transitions, the resulting data being essential for the construction of an energy-temperature diagram that displays the thermodynamic interrelationships amongst the various phases of a single bioactive compound. In this presentation comprehensive screening for new solid forms of several APIs and NCEs will be described with reference to the use of inexpensive mechanochemical techniques for producing a variety of crystalline and non-crystalline phases, the comprehensive physicochemical characterization of such new phases using X-ray diffraction, thermoanalytical and spectroscopic methods, and assessment of their dissolution properties.

Presentation Learning Outcome

- Utility of mechanochemical methods in crystal engineering to produce small quantities of new solid phases of APIs and NCEs for comprehensive physicochemical characterization will be illustrated
- Advantages of X-ray diffraction and complementary methods for unequivocal characterization of new solid phases will be demonstrated
- The merits of applying crystal engineering at an early stage in the lifetime of an NCE, resulting in improvement of its pharmaceutically relevant properties and thus promoting its rapid development, will be highlighted

Biography

Dr Angelita Rebollo studied Biology at the University of Leon, Spain and got her PhD in 1987. She joined the Institut Pasteur (Paris, France) for a first 6 years postdoctoral position. She was also working as postdoctoral at the MIT (Boston, USA), Ludwig Institute for Cancer Research (Brussels, Belgium) and Institut Cochin (Paris, France). She has a permanent position at Inserm (Paris, France) and CSIC (Madrid, Spain). She has published more than 100 articles and 20 patents.

Preclinical validation of a cell penetrating and interfering peptide

Angelita Rebollo
CIMI Paris, France

The interaction between intracellular caspase 9 and serine/threonine phosphatase PP2A proteins is critical to apoptosis. We have designed a Cell Penetrating and Interfering Peptide (CP and IP), Mut3DPT-C9, which specifically disrupt the interaction caspase 9/PP2A and evaluated its therapeutic potential *in vitro* and *in vivo* using Patient Derived Xenograft models (PDX). The peptide Mut3DPT-C9 induces caspase 9-dependent apoptosis in cancer cell lines and significant tumor growth inhibition in PDX models of triple-negative breast cancer and hormone-positive HER2 negative breast cancer adenocarcinoma. The peptide specifically induces the death of tumor cells without harm to healthy cells. In addition, neither acute and chronic toxicity nor immunogenic responses were observed, even at high doses.

We also analyzed the stability in serum and the pharmacokinetic parameters in mice and performed optimization on its in vivo stability. Point mutations on a protease cleavage site clearly improved peptide stability while keeping the functional activity. Biodistribution studies demonstrated that the modified peptide is able to reach the target tumor and accumulate there at higher concentration than parental peptide. These results strong suggest that Mut3DPT-C9 peptide constitutes a novel therapeutic approach for the treatment of breast cancer patients.

Presentation Learning Outcome

Protein/protein interactions (PPIs) are well recognized as promising therapeutic targets. Consequently, interfering peptides capable of interfering PPIs are receiving increasing attention. In addition, progress on peptide administration, stability, biodelibery and safety are also encouraging the interest in peptide drug development. We consider that our results are of interest for the scientific community working on cancer, cell penetrating peptides, interfering peptides, apoptosis and new therapies against cancer.

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DAY 2

SPECIAL SESSION

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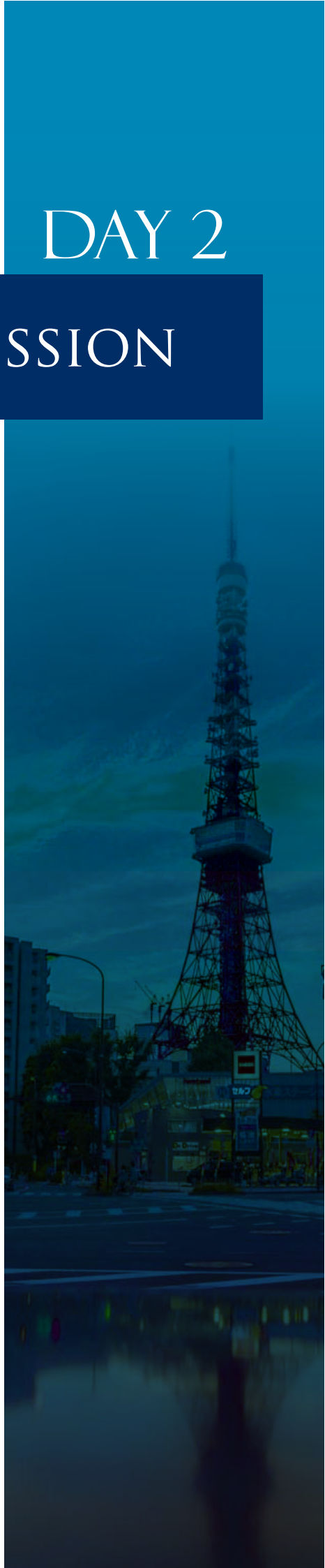


PDDS 2019

Facile preparation and characterization of robust metal-free nitroxide-based magnetic mixed micelles as MRI-visible drug delivery carrier

Rui Tamura
Kyoto University, Japan

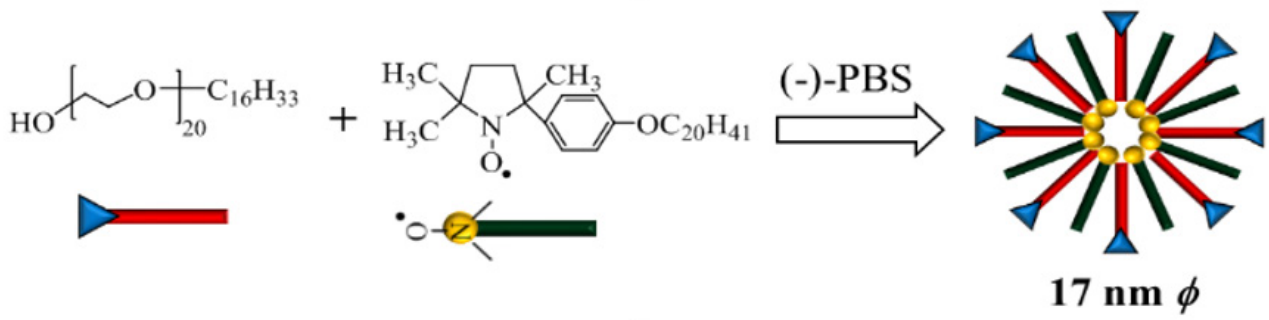
We reported that chiral all-organic rod-like liquid crystalline (LC) compounds with a five-membered cyclic nitroxide unit in the central core position exhibited the spin glass-like inhomogeneous ferromagnetic interactions in the LC phases at high temperatures under low magnetic fields. Such a unique magnetic phenomenon was referred to as 'positive magneto-LC effect'.

With a view to extending the positive magneto-LC effect to other organic radical soft materials, we have prepared robust metal-free magnetic mixed micelles (mean particle sizes: 17 nm) composed of the biocompatible non-ionic PEG-based surfactants and the hydrophobic low-molecular-weight 2,2,5-trimethyl-5-(4-alkoxy)phenylpyrrolidine-N-oxyl radicals in PBS. The spherical structure of the magnetic mixed micelles has been characterized by electron paramagnetic resonance (EPR) spectroscopy, and dynamic light scattering (DLS) and small angle neutron scattering (SANS) measurements. The mixed micelles showed high colloidal stability, low cytotoxicity, enough reduction resistance to excess ascorbic acid, and sufficient contrast enhancement in the proton longitudinal relaxation time (T_1)-weighted MR images in PBS *in vitro* and *in vivo*.

Furthermore, additional hydrophobic anticancer drugs such as paclitaxel could be encapsulated inside the mixed micelles, and the resulting drug-loaded mixed micelles were efficiently incorporated into HeLa cells to suppress the cell growth. We expect that such drug-loaded mixed micelles can be used as a theranostic nanomedicine for MRI-visible targeted drug delivery system.

Biography

Dr. Tamura received his PhD degree in 1980 at the Graduate School of Science, Kyoto University, Japan. After three-years postdoctoral fellowship supervised by Dr. L. S. Hegedus at Colorado State University and Dr. M. F. Semmelhack at Princeton University in USA, he obtained the positions of an Assistant Professor at the National Defense Academy in 1983, an Associate Professor at Ehime University in 1988, at Hokkaido University in 1995 and at Kyoto University in 1997, and a Professor at Kyoto University in 2002. He was retired from Kyoto University in 2018. He has published more than 200 research articles.



Presentation Learning Outcome

- This work presents (1) the facile preparation of the first metal-free magnetic mixed micelles (mean particle size < 20 nm) which can be used as MRI-visible targeted drug delivery carriers in vivo and (2) the characterization of the spherical micelle structure
- The audience can easily prepare the same mixed micelles according to our prescription without failure and use them as robust DDS carriers for their own purpose
- We already have had a joint-research with medical doctors, because they evaluate the mixed micelles as excellent hydrophobic anti-cancer drugs delivery carrier in vivo
- The chemical modification on the hydrophilic surface of mixed micelles is feasible, e.g. attachment of peptides

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DAY 2

SPEAKERS

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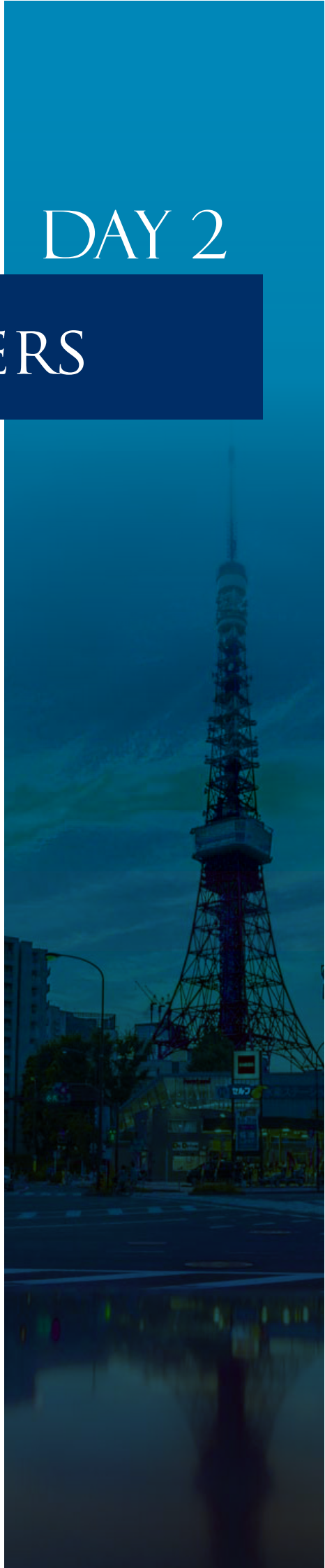

Nano- *versus* micro-particles for S-nitrosoglutathione formulation

Marianne Parent* (PharmD, PhD), Yi Zhou, Mehmet Hobbekaya, Charlène Martin, Isabelle Fries, Caroline Gaucher (PhD)
Université de Lorraine, CITHEFOR, F-54000 Nancy, France

S-nitrosoglutathione (GSNO) is a physiological nitric oxide donor and a promising drug for several acute or chronic diseases (e.g. stroke, atherosclerosis, …). However, this nitrosated tripeptide is highly hydrophilic and easily degraded while exposed to oxygen, light, metallic cations or enzymes. The formulation of GSNO, especially for oral delivery, is therefore very challenging.

In this work, three formulations based on the same raw materials (GSNO and Eudragit RLPO) were prepared with emulsion/solvent evaporation methods: nanoparticles (W/O/W, NP-W), microparticles (W/O/W, MP-W) and microparticles (S/O/W, MP-S). These particles were characterized as regards their size (dynamic light scattering/laser diffraction and scanning electron microscopy), zeta potential, GSNO encapsulation efficiency (EE) (fluorimetry), *in vitro* release (USP IV apparatus), cytocompatibility and intestinal permeability (Caco-2 cells monolayer). Moreover, the three formulations were obtained as dried powders, after optimization of their freeze-drying. Characterization was also performed on these stabilized formulations, including their residual water content (evaluated with a coulometric Karl-Fisher determination).

The three particles were able to encapsulate GSNO with similar EE (NP-W = 28.7 % ±3.3 % (n=11), MP-W = 24.4 % ± 3.7 % (n=7), MP-S = 25.1 % ± 3.6 % (n=5), direct determination). Freeze-drying using sucrose as protectant led to elegant cakes, easy to re-suspend, with similar EE as fresh formulations. On the other hand, particles sizes were not significantly modified by drying (NP-W: 290.7 nm ± 14.5 nm *vs* 299.7 nm ± 12.7 nm, n=6; MP-W: 70.8 µm ± 7.5 µm *vs* 68.5 µm ± 5.5 µm, n=3; MP-S: 147.5 µm ± 38.5 µm *vs* 105.6 µm ± 22.6 µm, n=3). Zeta potential of NP-W remained unchanged and highly positive (around + 55 mV), as expected according to the polymer used. Freeze-dried particles had a residual water content around 5 % and all their characteristics were maintained for at least 6 months after storage at 4°C under inert atmosphere. GSNO release from NP-W was very fast, almost similar to the dissolution profile of the free drug, while MP formulations delayed the release during the 2 first hours of the experiment, with a more progressive profile for MP-S compared to MP-W. All formulations were compatible with Caco-2 cells for up to 8.5 mg/mL of freeze-dried powder (corresponding to 2.8 mg/mL of polymer and 0.017 mg/mL of GSNO, i.e. 50 µM of GSNO). Intestinal permeability of GSNO released from these formulations is currently under evaluation in an *in vitro* intestinal barrier model.

At the end, three different particles loaded with GSNO were obtained as dried and stable formulations, thus facilitating their preclinical use. Among them, microparticles obtained with a S/O/W process could represent the most interesting lead to explore for GSNO oral delivery. Better results in terms of EE and sustained release might be obtained by reducing the size of GSNO powder (currently 40 µm). Due to GSNO fragility, this step is challenging: experiments are ongoing using supercritical fluid technology.

Acknowledgements

The PhD thesis of Mr Yi ZHOU is financially supported by the Chinese Scolarship Council.
The CITHEFOR EA3452 lab is supported by the "Impact Biomolecules" project of the "Lorraine Université d'Excellence" (Investissements d'avenir – ANR). The USP IV apparatus was purchased thanks to a "Contrat Plan Etat region" funding.

Presentation Learning Outcome

- An example of formulation strategy for a very hydrophilic and labile peptidic drug, S-nitrosoglutathione
- A detailed development, characterization and comparison of 3 different polymeric formulations, from the nano- to the micro-meter range, made from the same materials but with different processes
- How this strategy did not work in certain aspects (increasing the encapsulation efficiency) but succeeded in others (more sustained *in vitro* release, getting stable freeze-dried formulations)

Biography

Marianne PARENT is Associate Professor in the pharmaceutical technology department of the Faculty of Pharmacy of Nancy (Université de Lorraine). She was graduated as pharmacist from the Université de Lorraine in 2012 with *summa cum laude*. She obtained her PhD in "Life and Health Science" in 2013 from the same University. She was recruited in 2016 as assistant professor at the Faculty of Pharmacy of Nancy and simultaneously joined the EA 3452 CITHEFOR for her research in formulation.

Her main research is focused on optimization of encapsulation and release of nitric oxide donors.

Pseudomonas aeruginosa type 3 secretion system mediated antigen delivery for cancer immunotherapy

B. Toussaint[1*]., Le Gouellec A[1]., Hannani D[1]., and Chauchet X[2]
[1]Univ.Grenoble Alpes, CNRS, CHU Grenoble Alpes, Grenoble INP, TIMC-IMAG, TheREx team, 38000 Grenoble, France
[2]Novimmune S.A., Plan-les-Ouates, Switzerland

Live-attenuated bacterial vectors for antigens delivery have aroused growing interest in the field of cancer immunotherapy. Their potency to stimulate innate immunity and to promote intracellular antigen delivery into antigen-presenting cells could be exploited to elicit a strong and specific cellular immune response against tumor cells. We previously described genetically-modified and attenuated *Pseudomonas aeruginosa* vectors able to deliver *in vivo* protein antigens into antigen-presenting cells, through Type 3 secretion system of the bacteria. The latest attenuation process permits the bacteria to be metabolically active but unable to replicate so as no infection is possible (a process called "KBMA": killed but metabolically active). Using this approach, we managed to protect immunized mice against aggressive B16 melanoma development in both a prophylactic and therapeutic setting. We further investigated the antigen-specific $CD8^+$ T cell response, in terms of phenotypic and functional aspects, obtained after immunizations with a killed but metabolically active *P. aeruginosa* attenuated vector. We demonstrated that *P. aeruginosa* vaccine induces a highly functional pool of antigen-specific CD8+ T cell able to infiltrate the tumor. Furthermore, multiple immunizations allowed the development of a long-lasting immune response, represented by a pool of predominantly effector memory cells which protected mice against late tumor challenge. Overall, killed but metabolically active *P. aeruginosa* vector is a safe and promising approach for active and specific antitumor immunotherapy.

Presentation Learning Outcome

- The concept of Live Biological Products
- The main bottlenecks for active and specific immunotherapy of cancer
- The ability of bacteria to deliver tumor antigens inside antigen presenting cells
- The way to make a live bacteria safe for a clinical use

Biography

Pr Toussaint studied Biochemical Engineering at Polytechnique Institute of Toulouse (France). He received his PhD at Grenoble University in 1990. After one year post-doc supervised by Dr Vignais in Microbial Biochemistry (Grenoble) he started to learn medicine. He gets his MD in 2002. He works as practitioner in Clinical Chemistry at Grenoble University Hospital, is Professor of Medicine at University of Grenoble Alpes and is at the head of a research team called Experimental Recombinants Therapeutics at TIMC. He published 75 publications and is inventor of 5 patents.

Engineering novel selectivity into metalloantibodies germline-encoded precursor to the murine anti-S1P metalloantibody in *E.coli* and baculovirus-insect cell system

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Department or Chemistry and Biochemistry, San Diego State University, San Diego, CA, USA

The scientific aspect of this research focuses upon the use of metals by antibodies in the mammalian adaptive immune system. It is estimated that one third of all proteins are metalloproteins. However, the use of metals by antibodies to recognize and bind to antigens is still somewhat of a novelty. In recent years, antibodies that target biologically active lipids have been studied as promising therapeutic agents. Many physiological processes, such as cell growth, differentiation, survival, and pathophysiological processes, such as cancer, cardiovascular disease, multiple sclerosis, neuropathic pain, involve sphinosine-1-phosphate (S1P) signaling. LT1002 is a murine monoclonal antibody that binds to S1P with high affinity and specificity. Previously in our lab, a 1.9 Å x-ray crystal structure of humanized LT1009 Fab antibody version of the murine LT1002 anti-S1P antibody was determined. The x-ray crystal data indicates the novel finding that it employs two bridging calcium ions in binding to its lipid antigen. The two calcium interact with aspartic acid residues from the CDR-L1 and -L3 loops of the antibody variable light chain (VL) (Fig. 1). Furthermore, the amino acids involved in metal coordination are encoded in the germ-line sequences of immunoglobulin kappa light chain genes within the genomes of diverse mammalian species and are included in several antibodies that have been previously analyzed. This study is designed to identify other naturally occurring functional metalloantibodies and to test the hypothesis that the use of metal coordination chemistry by antibodies to recognize their antigens is evolutionarily conserved in the mammalian immune system.

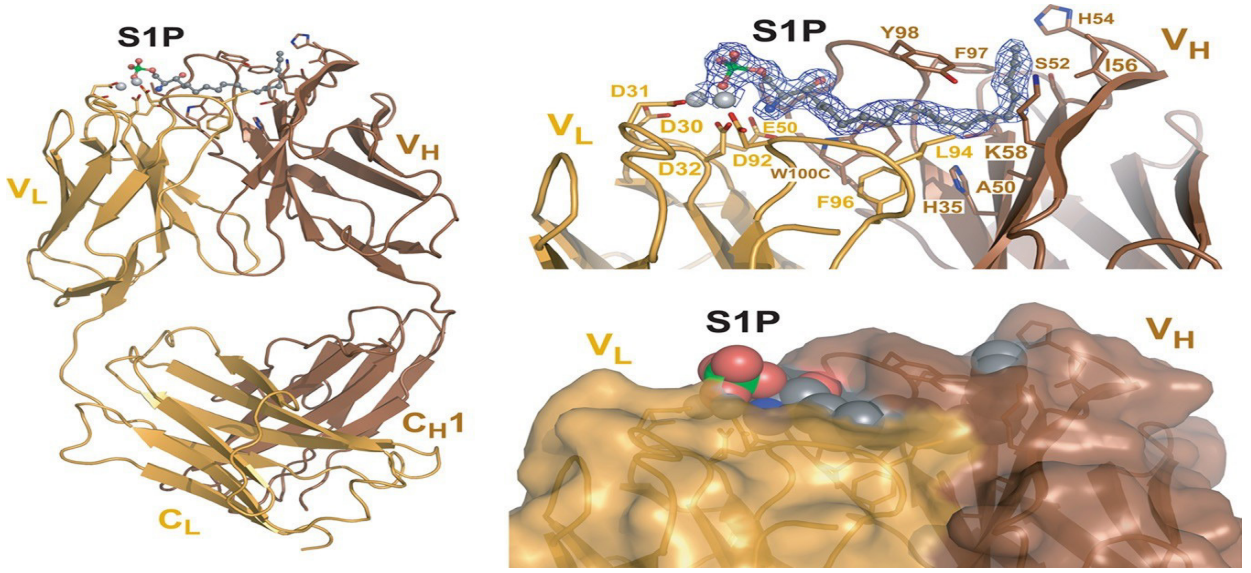

Fig. 1. X-ray crystal structure of the LT1009 Fab: S1P complex. The light chains are colored gold and the heavy chains are colored light brown. Bridging Ca ions are grey spheres and S1P antigen is depicted as a ball-and-stick model.

Inductively-coupled plasma-mass spectrometry (ICP-MS) indicates that LT1002 binds to calcium, magnesium and, to much lesser extent, barium. In order to study the chemical properties of this novel metalloantibody, I first developed methods for recombinant expression and purification. I then altered the residues observed to coordinate the Ca ionsand tested their ability to bind more biochemically active metals, such as Fe, Ni, Cu, and Zn. It is expected that thesenovel, engineered metalloantibody scaffolds might serve as substrates for further development as a class of engineered metalloantibodies with the ability to catalyze charge transfer reactions in water. In conclusion, metal binding is inherent to a class of antibodies that derive from germline light chain sequences with conserved metal coordinating residues in CDR-L1 and -L3. Also, I used Sf9 antibody expression system to test whether two additional antibodies (Q425 and 2C10) with these conserved residues function as metalloantibodies.

Presentation Learning Outcome

- Introducing novel class of antibodies that binds to metals
- Metalloantibodies as therapeutic agents
- Introducing novel high yield expression technique for antibodies in Baculovirus SF9 insect cells
- Enzymatic activity of metalloantibodies

Biography

Dr. Farokhi studied Pharmaceutical Chemistry at the University of Kansas and graduated as MS in 2014. She then joined the research group of Dr. Huxford at the Structural Biochemistry Department at San Diego State University, San Diego, CA, USA. She received her PhD degree in Chemistry and Biochemistry in 2019 at University of California-San Diego and San Diego State University. She has published more than 7 research articles in SCI(E) journals.

Discovery of novel bacterial genes encoding the enzymes acting on modified uracil/uridine derivatives and their use for gene therapy in cancer treatment

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Modified nucleotides are present in several RNA species in all Domains of Life. While the biosynthetic pathways of these nucleotides were well studied in recent years, much less attention was drawn to the degradation of different RNAs and the return of modified nucleotides or their constitutents into the metabolism. Using an *Escherichia coli* uracil auxotroph strain, we screened the metagenomic libraries for genes, which would allow the conversion of either 2-thiouracil, isocytosine' or 2'-O-methyluridine into uracil and thereby lead to the growth on a defined synthetic medium. We have demonstrated that Domain of Unknown Function 523 (DUF523) containing protein is involved in the conversion of 2-thiouracil into uracil in vivo. We have also purified several recombinant isocytosine deaminases and a nucleoside hydrolase and demonstrated their enzymatic activities in vitro. These enzymes are also capable of converting the potential prodrugs 5-fluoroisocytosine, 5-fluorouridine, 5-fluoro-2'-O-methyluridine, and 5-fluoro-2'-deoxyuridine into a well-known anticancer drug 5-fluorouracil. The human glioblastoma U87MG and colorectal adenocarcinoma Caco-2 cell lines were transfected with the recoded isocytosine deaminase genes, and their citotoxicity together with 5-fluoroisoicytosine was demonstrated. The therapeutic potential of the isocytosine deaminase/5-fluoroisocytosine pair has been demonstrated in vivo, where the co-injection of the isocytosine deaminase-encoding mesenchymal stem cells and 5-fluoroisocytosine have been shown to increase longevity of tumorized mice by 50%.

Presentation Learning Outcome

In this presentation, the audience will learn that our environment is a source of the previously undescribed enzymatic activities. It will be emphasized that the enzymes acting on the analogs of modified nucleosides and/or heterocyclic bases my act as the non-toxic prodrug activators converting them into the active drugs. The preclinical studies demonstrating relevance of the proposed gene/prodrug pair for the cancer treatment will be presented and the advantages of the proposed prodrug activation system over the existing ones will be discussed.

Biography

Dr. Jaunius Urbonavičius received a MS degree in Biochemistry at Vilnius University, Lithuania, in 1992 and Ph.D. in Microbiology at Umeå University, Sweden, in 2002. He performed his postdoctoral studies under supervision of Dr. Henri Grosjean at CNRS in Gif-sur-Yvette, France in 2003-2006. Afterwards, he worked as the Researcher at Université Libre de Bruxelles, Brussels, Belgium, between 2007 and 2012. He returned to Lithuania in 2012 where he works as Senior Researcher at Vilnius University and as Professor at Vilnius Gediminas Technical University since 2017.

Drug delivery to the skin: nanostructures for the treatment of precancerous actinic keratosis

Silvia Tampucci*, Daniela Monti, Susi Burgalassi, Patrizia Chetoni
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Actinic keratosis (AK) is a common skin disease characterized by cutaneous lesions in the sun-exposed areas of the skin; it is often asymptomatic, but if left untreated it may be the precursor of squamous cell carcinoma (SCC), a non- melanoma skin cancer. The treatment of early clinical lesions can reduce the potential for malignant trasformation that, although treatable, may potentially lead to metastasis or death.

The treatment of AK and SCC includes invasive approaches (excisional surgery, laser ablation…), and non-invasive approaches (medical and photodynamic therapy). Specifically, in case of presence of multiple lesions, topical pharmacotherapy represents an effective way of eradicating both evident and subclinical lesions. Field therapy alone, or in combination with lesion directed therapy, is able to produce high rates of sustained clearance.

Among the topical agents employed to treat AK, diclofenac, a nonsteroidal anti-inflammatory drug, is the most commonly used, due to its effectiveness, poor side effects, tolerability and low cost; side effects include pruritus, erythema, dry skin and rare photosensitivity reactions. Anyway the treatment duration of 60–90 days with twice daily applications might have an impact on practicability and lead to poor adherence.

Besides, as the link between sun exposure and AK skin lesions is well recognised, further therapeutic approaches may derive from the protection of skin keratinocytes from UV-induced damages. It has been reported that the topical use of antioxidants, that have recently showed antiproliferative activity in different types of cancer, contributes to decreasing the oxidative damage mediated by UV radiation. In this context, researchers have focused on developing new drugs and new combination of molecules, such as diclofenac and phytochemical compounds promising as anti- cancer drugs or as lead compounds in the synthesis of new drugs with suitable physicochemical properties for topical delivery (such as size, log P).

In recent years, nanocarriers have been studied to enhance drug bioavailability and reduce skin irritation by avoiding direct contact of the drug with the skin's surface. Delivery of drugs using nanotechnologies, not only can improve drug stability, but also can help overcome the stratum corneum, main barrier to penetration. Moreover, since the main target of AK treatment is the epidermis, in particular the basal layer and in a major extent the granular and cornified layers, nanotechnology-based delivery systems could be able to improve selective tissue distribution, while minimizing systemic side effects.

The assessment of the drug permeation profile and the amount of penetrated drug into the skin layers can be performed with in vitro studies on porcine ear skin, a widely accepted model for human skin.

Presentation Learning Outcome

- Design of new therapeutics approaches to deliver drugs into the skin
- Influence of nanotechnologies in overcoming skin barriers
- Techniques to investigate drug distribution into the skin

Biography

Dr. Tampucci studied Pharmaceutical Chemistry at the University of Pisa, where she received her PhD degree in Medicinal Chemistry in 2005. She is now Assistant Professor at the Department of Pharmacy of the University of Pisa. Her main research activity concerns the development of formulation strategies for improving cutaneuos, ungual and corneal delivery of drugs and the study of in vitro and in vivo models to evaluate the bioavailability of topically applied drugs. Her work includes the evaluation of citotoxicity of pharmaceutical excipients and the characterization of mucoadhesive properties of polymeric dispersions.

Liposomes as valuable drug delivery systems for siRNA and Hsp90 inhibitors to target triple negative breast tumors

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Triple Negative Breast Cancers (TNBC) are not efficiently treated by specific targeted therapy. New strategies must be envisaged and nanocarriers appear as good candidates to overcome low efficacy of drugs or resistance to treatment. CD44 is found overexpressed in many tumors, such as TNBC, making this an attractive receptor for therapeutic targeting. Besides, HSP90 inhibitors have been shown as promising molecules to treat cancer. Here we show our both drug delivery approaches to target TNBC. First, using for the first time an anti-CD44 aptamer as targeting ligand, a unique non-cationic liposome-based siRNA delivery system was evaluated for the silencing of the luciferase reporter gene (luc2) in a TNBC breast cancer model in vitro and in vivo (orthotopic model). Secondly, we succeeded to use the inhibition of the chaperone Hsp90 at the level of its C-terminal domain against breast cancer. Encapsulated in liposomes, a promising Hsp90i derived from Novobiocin (6BrCaQ) displayed a good activity on breast and prostate cancer cells in vitro and synergized with doxorubicin. In the in vivo orthotopic TNBC model we evaluated the anti-tumor activity of these liposomes. Our work gives evidences that liposomes are powerful tools to target CD44 positive cells in resistant TNBC breast tumors and to deliver not only siRNA but also an anti-tumor but poorly soluble inhibitor of HSP90.

Presentation Learning Outcome

- I will try to show the interest of liposomes in the delivery of molecules of different natures and in the selective targeting of cancer cells in vivo with a good efficacy.
- I will try to show how to highlight a new promising molecule that is difficult to administer alone due to poor water solubility as Hsp90 inhibitors.
- I will try to show how aptamers can supplant ligands conventionally found on nanovectors.

Biography

Juliette Vergnaud is associate professor. She obtained her PharmD in 2002 and her PhD in 2005 at Université de Caen-Basse-Normandie, France (Dr. Brigitte Sola's Lab). She obtained her Ability to conduct researches in 2017. In 2006, Juliette Vergnaud was recruited at Université d'Auvergne (Clermont-Ferrand, France) in the M-P Vasson's lab. Her research work focused on the immune cell functions during nutritional intervention. In 2010, she joined UMR 8612 and the Elias Fattal's team. Her main project aims to target cancer cells at the cellular and subcellular levels using liposomes encapsulating inhibitors of Hsp90 family proteins. She is the author (and co-author) of 32 publications.

A RNA producing DNA hydrogel as a platform for a high performance RNA interference system

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RNA interference (RNAi) is a mechanism in which small interfering RNA (siRNA) silences a target gene. Herein, we describe a DNA hydrogel capable of producing siRNA and interfering with protein expression. This RNAi-exhibiting gel (termed I-gel for interfering gel) consists of a plasmid carrying the gene transcribing siRNA against the target mRNA as part of the gel scaffold. The RNAi efficiency of the I-gel has been confirmed by green fluorescent protein (GFP) expression assay and RNA production quantification. The plasmid stability in the I-gel results in an 8-times higher transcription efficiency than that of the free plasmid. We further applied the I-gel to live cells and confirmed its effect in interfering with the GFP expression. The I-gel shows higher RNAi effect than plasmids in free form or complexed with Lipofectamine. This nanoscale hydrogel, which is able to produce RNA in a cell, provides a platform technology for efficient RNAi system.

Presentation Learning Outcome

- The audience will recognize a gel phase transcription shows higher efficiency than normal plasmid
- The presentation will help the audience to design a new type of gene delivery vehicle

Biography

Nokyoung Park (Ph.D.) is an associate professor of Chemistry Department in Myongji University. He got his B Sc in chemistry, M Sc in analytical chemistry, Doctor's degree in bioanalytical chemistry (Ph.D.) at Pohang University of Science and Technology, South Korea. And he moved to Cornell University to study nucleic acid engineering as postdoctoral research. And based on his research experience in academia, he served as a scientist at Samsung electronics After five years of industrial experience, he returned to academia as a faculty member and currently focusing on the development of novel DNA materials and their applications for multifunctional nanocomposites.

Metal-organic framework nanoparticles preparation of sildenafil: A new window in the treatment of pulmonary arterial hypertension

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Background: Pulmonary Arterial Hypertension (PAH) is an aggressive disease with poor prognosis, no available cure, and low survival rates. Currently, there are several classes of vasodilator drugs that are commonly used as treatment strategies for PAH, including sildenafil, a phosphodiesterase type 5-inhibitor. Despite their clinical benefits, these therapies are hindered by their short half-life and systemic side effects. This limitation could be overcome using controlled drug release with the potential for targeted drug delivery using a nanomedicine approach. In the current study, we have evaluated the use of a highly porous nano-sized preparation of iron-based metal-organic framework (MOF) commonly referred to as MIL-89 for loading with sildenafil. We have previously shown that MIL-89 is relatively non-toxic in a range of human cell types and well tolerated *in vivo.* Here, we report the use of a nano-formulation of MIL-89 (nanoMIL-89) as a drug delivery system for the phosphodiesterase type 5-inhibitor sildenafil.

Methods and Results: nanoMIL-89 was first prepared and then successfully loaded with sildenafil (Sil-nanoMIL-89). Light and confocal microscopes confirmed the cellular uptake of nanoMIL-89 and the subsequent transfer to daughter cells. The viability, toxicity, and anti-inflammatory properties of Sil-nanoMIL-89 were evaluated in a range of human cells using AlamarBlue®, LDH, and ELISA assays. Sil-nanoMIL-89 was shown to release sildenafil in a biphasic manner with an initial rapid release over 6 hours, followed by a more sustained release over 72 hours. Finally, the vasodilator effect of Sil-nanoMIL-89 was measured over 8 hours using isolated mouse aorta. Consistent with drug release kinetics, Sil-nanoMIL-89 induced vasodilation after a lag phase of 3 hours.

Conclusion: Sil-nanoMIL-89 is a promising formulation prototype for PAH drugs displaying an anti-inflammatory effect and delayed drug release and vasodilator activity. Further toxicological and pharmacological assessments of nanoMOF-89 in animal models are required and constitute the subject of ongoing investigations.

Presentation Learning Outcome

This project aims to test the potential use of nanoMIL-89 in the treatment of PAH, a devastating chronic disease with currently no effective cure. The outcomes of this study should guide therapy in the future and establish a novel nanoparticles-based drug delivery approach in the treatment of PAH. This will likely add considerable value to current prevention programs and existing conventional therapies in patients with heart diseases. Ultimately, such approach, once established, could be transferable to benefit other diseases yet incurable such as cancer, neurological disorders, and diabetes.

Biography

Dr. Haissam Abou-Saleh is an Assistant Professor at Qatar University, in the Department of Biological and Environmental Sciences. He obtained a Ph.D. degree in Biomedical Sciences from the Université de Montréal (2009) and pursued his postdoctoral training at Montreal Heart Institute-Canada and Weill Cornell Medicine-Qatar. Dr. Abou-Saleh's research interests focus on studying the pathophysiology of cardiovascular diseases such as endothelial dysfunction, atherothrombosis, vascular remodeling, and hypertension. His experimental approaches include molecular and pharmacological tools and clinically relevant animal models of cardiovascular diseases. He has more than 20 articles in his name on high-impact peer-reviewed journals.

Release and activity of the broad spectrum antibiotic Rifampicin from biodegradable polymer PLGA

Justine Fraser*, MSc; Christopher McCormick, EngD; Michelle Maclean, PhD
The University of Strathclyde, UK

Medical device infection is one of the most problematic issues associated with implanted medical devices. More than 60% of nosocomial infections are related to a medical device, with treatment being particularly challenging. Pathogenesis of infection frequently involves formation of a protective polysaccharide matrix, known as a biofilm, which acts as a barrier to both host immune response and administered antimicrobials. In order to eradicate a biofilm a significantly higher dose of antimicrobial is required when compared to the planktonic form of the same microorganism. Delivering an effective dose to the site of infection with systemic methods is extremely problematic and often cannot be achieved, meaning explant and replacement of a medical device is the only option. However these procedures are often contraindicated or high risk, with no guarantee that re-infection will not occur. As the most common causative microorganisms are *Staphylococcal* species, it is believed that initial contamination occurs during implantation. It is therefore desirable that for a time after implantation, during which there is a higher risk of infection, a medical device be resistant to infection pathogenesis.

Drug-eluting technology using a biodegradable polymer, similar to that already in use in some drug-eluting stents, may be of use in certain medical devices as a means of achieving such infection prevention. To investigate this, the polymer poly(D,L-lactic-co-glycolic acid) (PLGA) was formulated with the broad spectrum antibiotic rifampicin, and over 10 weeks both the release and antimicrobial activity against *Staphylococcus aureus* biofilm formation examined. The release study revealed that rifampicin can readily be released from PLGA, and that release is highly tunable by altering the ratio of polymer to drug. Ratios examined were PLGA:rifampicin 50:50 and 60:40, this small change in ratio produced two alternative release profiles with significantly different percentage release. However, both the 50:50 and the 60:40 PLGA:rifampicin formulations released the majority (>90%) of their respective rifampicin loads during the initial 4 weeks of release. Despite this the biofilm inhibition study, which used implantable medical grade polyester, proved the potency of rifampicin by revealing extended activity against *S. aureus* biofilm formation. After 10 weeks of rifampicin release the results showed a 99% and 90% reduction in biofilm formation when compared to material coated with PLGA alone.

What this study has demonstrated is that biodegradable polymer drug delivery technology can be used to control release of an antimicrobial, and that the antimicrobial activity can be retained for an extended period of time (≥10 weeks). This technology may therefore be of potential utility to prevention of infection in implanted medical devices.

Presentation Learning Outcome

- The potential for biodegradable polymers to be used as a drug delivery method for antimicrobials.
- Antimicrobial activity can be retained for an extended period of time by using a biodegradable polymer to control release.
- Demonstrated proof of principle, which may help inform future studies working toward *in vivo* testing of extended antimicrobial release for prevention of medical device infection.

Biography

I am a final year PhD student at The University of Strathclyde in the department of Biomedical Engineering. My research project is focused on the development of drug-eluting technologies for the prevention of medical device infections. I graduated from my MSc with distinction, also in Biomedical Engineering, from The University of Strathclyde in 2016. Previous to this I completed a BSc (hons) degree in Molecular and Cellular Biology from The University of Glasgow, which I graduated from in 2015 with a 2:1.

Role of the optimal dynamic state and stabilized catalytic complex for rational design of pharmaceutical enzymes: Engineering of streptokinase with enhanced, fibrin-dependent activity

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[4]MicrobiologyDepartment, Pasteur Institute of Iran, Tehran, Iran

Plasminogen activators (PAs), compounds that convert the blood plasminogen (Pg: inactive proenzyme) to plasmin (Pm: active enzyme) are used in the treatment of thrombotic disorders like myocardial infarction. Streptokinase (SK), the first and most utilized PA, is produced by groups A, C, and G streptococci (GAS/GCS/GGS, respectively). SKs are heterologous proteins showing different protein sequences and PA potencies. Despite several shortcomings, SK is the most cost-effective fibrinolytic drug in specially developing countries and continuous efforts are undertaken to improve its thrombolytic characteristics by protein engineering approaches.

Using conventional microbial/biochemical assays, we recently screened a GGS which was used for isolation of the gene and production of the recombinant SK protein (SKG 132). Kinetic and sequencing analyses indicated higher levels of fibrin-dependent proteolytic activities for SKG132 [Kcat/KM (min-1/μM) of 17.38 vs. 10.56] and four natural residual substitutions (Ile33Phe, Arg45Gln, Asn228Lys, Phe287Ile) compared to that of the standard SK from GCS (SKC 9542). Using computational approaches and the available crystal structure of SK.μPm complex (PDB code of 1BML at 2.9 Å resolutions), SKC.μPm complex was modeled and validated by several online servers. Subsequently, SKG132.μPm structure was constructed by altering the corresponding residual substitutions. Results of three independent molecular dynamics (MD) simulations showed increased RMSF values for SKG132.μPm, indicating the enhanced structural flexibility compared to SKC.μPm, specially in residual region of "224-229". In parallel, the average number of Hydrogen bonds especially in Asn228Lys of SKG132 compared to that of the SKC was decreased. Accordingly, residue interaction networks (RINs) analyses indicated that Asn228Lys might induce more level of structural flexibility by generation of free Lys256, while Phe287Ile and Ile33Phe enhanced the stabilization of the SKG132.μPm catalytic complex. Moreover, RINs analyses further indicated that substitution of Phe287 by a positively charged residue like "Lys" may further stabilize the SK.μPm complex. To explore if the substituted residues have a synergistic effect on the increased activity of the SKG132 or not, three other models harboring single or various combination of two replaced SK residues with Asn228Lys being maintained in both constructs (as an important substitution) were constructed, including: SK1(Asn228Lys), SK2 (Ile33Phe/Asn228Lys) and SK3 (Asn228Lys/Phe287Lys). MD and RINs analyses indicated the formation of a more stable complex for SK3.μPm compared to the other two constructs. For validation of the computational results, the corresponding SK molecules (SK1 to 3) with the specified substituted residues were produced by site-directed mutagenesis approach, confirmed by DNA sequencing analyses and produced in *E.coli* expression system as recombinant proteins and characterized. Kinetic analyses of SKs (1-3), compared with SKG132 and SKC, showed higher proteolytic activities [Kcat/Km (min-1/μM) of 12.83, 15.65 and 19.5 vs. 17.38 and 10.56, respectively] and also higher levels of fibrinogen-bond Pg activation [(x103 IU/mg) of 456.52±8.80, 723.40±8.82, 914.89±13.92 vs. 786.66±10.57 and 282.60±7.17, respectively) indicating more than three times enhancement of fibrin-dependent activity for SK3 compared to SKC. These results denoted the potential role of the optimal dynamic state and stabilized catalytic complex for increased PA potencies of SK which might be further employed for rational design of improved SK and other pharmaceutical enzymes.

Presentation Learning Outcome

The audience will be able to expand their knowledge on:

- Pharmaceutical Microbiology and Biotechnology
- Protein engineering and how such approaches will be used to improve Pharmaceutical proteins and enzymes
- Protein structure/function relations for rational design of pharmaceutical proteins
- Thrombolytic drugs in general and streptokinase in specific
- The role of the optimal dynamic state and stabilized catalytic complex for rational design of pharmaceutical enzymes
- The provided knowledge will expand the research and teaching capabilities of the audience

Biography

Farzin Roohvand received his Ph.D in Biotechnology from Middle East Technical Univ (Ankara-Turkey) in 1999. In 2002 he started Post-doctoral studies in Pasteur Institute of Paris. In 2004, he served as a guest scientist in the same institute and in 2008 as Principal investigator for ANRS (France). Since 2012, he served as an associated Prof of Biotechnology and Mol. Virology and principal investigator in Virology Dept. of Pasteur Institute of Iran. He is author of more than 60 international articles and served as invited speaker for presenting key note lectures in several international symposiums and serves in Editorial Board of several scientific Journals.

Pharmacovigilance: Aims, challenges and perspectives

Razan Ghattas Mhanna
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Drug safety and pharmacovigilance remains a dynamic clinical and scientific discipline. Pharmacovigilance is defined by the World Health Organization (WHO) as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. It receives information from spontaneous reporting of adverse reactions from healthcare professionals, clinical trials, published medical literature, pharmaceutical companies, healthcare and population statistics and information on the consumption of medicinal products. In some countries, adverse drug reactions (ADRs) rank among the top 10 leading causes of mortality. In order to prevent or to reduce harm to patients and thus improve public health, mechanisms for evaluating and monitoring the safety of medicines in clinical use are vital.

The WHO established its Program for International Drug Monitoring in response to the thalidomide disaster detected in 1961. There exist different pharmacovigilance programs around the globe. Their principal aims are to improve patient/public care and safety in relation to the use of medicines; to contribute to the assessment of effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use; to promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public.

Nowadays, pharmacovigilance is facing lots of challenges to develop better health care systems. Major challenges are globalization, web-based sales and information, broader safety concerns, public health versus pharmaceutical industry economic growth, monitoring of established products, developing and emerging countries, attitudes and perceptions to benefit and harm. In order to face these challenges all parties like public health administration, health professionals, the pharmaceutical industry, government, drug regulators, the media, consumers must strive towards the highest ethical, professional and scientific standards in protecting and promoting safe use of medicines. Policies must be regulated to describe the benefit, harm, effectiveness and risk of medicines so that governments and healthcare personnel may account for.

For future consideration, pharmacovigilance should extend knowledge of safety by encouraging adequate and balanced input of information, constructive basic training, strong collaboration among healthcare professionals and pharmaceutical companies, and clear governmental decisions. All outcomes must be employed based on pre-specified standards to promote the optimum target of 'good pharmacovigilance practice'.

Presentation Learning Outcome

The audience will be able:

- To define pharmacovigilance and recite its aims
- To highlight recent challenges faced by pharmacovigilance programs and demonstrate suggested solutions
- To recognize that the provision of good quality and safe and effective use of medicine is the responsibility of governments, healthcare personnel, pharmaceutical companies, researchers and NJOs
- To infer the need of establishing good pharmacovigilance practices

Biography

Dr. Mhanna has earned her Bachelor degree in pharmacy and pharmD degree at Lebanese Inetrnational University since 2013. She had attended many conferences (local and international), and participated through posters in the ASHP and University of Cairo, presented two lectures at two Lebanese university hospitals (AUBMC and BGUH), and published one paper in the International Journal of Pharmacy Practice about incidence of iron deficiency anemia and its risk factors in the Lebanese infants. Nowadays, she teaches at the Lebanese International University, as a clinical assistant professor, variety of courses from pre-pharmacy, therapeutics and advanced pharmacy practice experience.

Original synthesis of natural acetogenins, fattyacids and lembehynes as a potential drugs for treatment of cancer and neurodegenerative diseases

V.A.D'yakonov, L.U. Dzhemileva, A.A. Makarov, R.A. Tuktarova, S.R. Ishmukhametova, E.N. Andreev, and U.M. Dzhemilev

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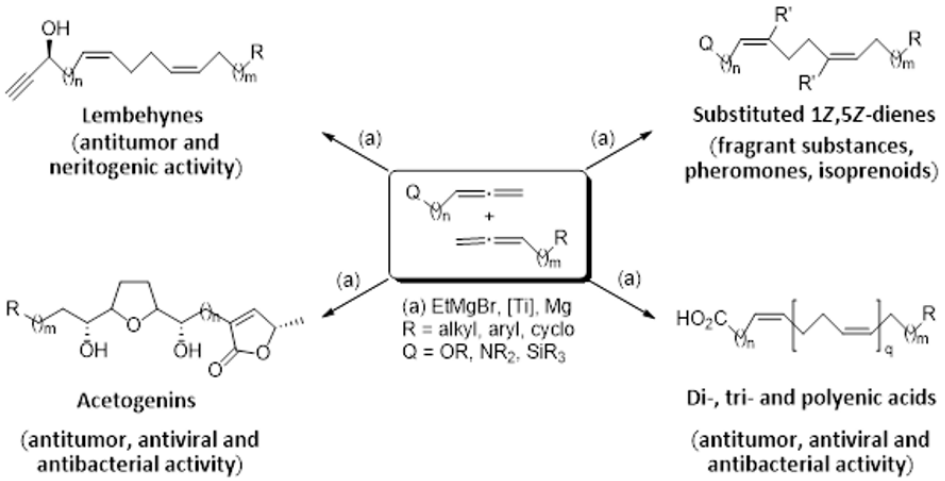
The report discusses the latest achievements of the authors in developing original methods for stereoselective synthesis of natural acetogenins, higher bis-methylene-separated(interrupted) di- and trienoic acids, lembehynes that are of interest as low-toxic target antitumor drugs, as well as compounds with neritogenic activity for treating neurodegenerative diseases.

The synthetic approaches to the above listed natural compounds are based on the use at the key stage of the synthesis, of new organometallic reactions, such as Ti-catalyzed homo- and cross-cyclomagnesiation of 1,2-dienes, discovered in the Laboratory of Catalytic Synthesis of the IPC RAS, involving available Grignard reagents.



The studies of the synthesized compounds for their antitumor and neuritogenic activities in vitro were performed withthe use of unique equipment in "Centre for Molecular Design and Biological Screening of Candidate Substances for the Pharmaceutical Industry" at the Institute of Petrochemistry and Catalysis of RAS using modern methods such as flow cytofluorometry, fluorescence microscopy, Luminex MagPlex magnetic microsphere technology and western blotting.

In silico studies into regularities of the structural influence of the synthesized compounds on their antitumor activity were fulfilled with the use of molecular docking and molecular dynamics experiments.

For compounds that showed the greatest activity, in vivo tests were performed for linear mice with grafted malignant Lewis carcinoma.

This work was financially supported by the Russian Science Foundation (Grants 16-13-10172, 18-73-10030), Russian Foundation for Basic Research (Grants 17-43-020502, 18-33-20058, 18-29-09068, 19-03-00603) and Grant of the RF President for the support of leading scientific schools(NS-5240.2018.3). The research has been carried out in accordance with the approved plans for research projects at the IPC RAS State Registration No. AAAA-A19-119022290007-9, AAAA-A19-119022290008-6 (2019-2021).

Presentation Learning Outcome

- Author's original methods for stereoselective synthesis of natural acetogenins, di- and trienoic acids, lembehynes.
- The studies of the synthesized compounds for their antitumor and neuritogenic activities in vitro, in silico and in vivo.
- Studies on the induction of apoptosis, the effect of the synthesized compounds on the cell cycle, biological effects

on mitochondria, histones and topoisomerases using modern methods such as flow cytofluorometry, fluorescence microscopy, Luminex MagPlex magnetic microsphere technology and western blotting.

Biography

Vladimir A. D'yakonov was born in 1980 in Yakutia, Siberia, Russia. He graduated from the Ufa State Petroleum Technical University (Ufa, Bashkortostan, Russia, 2002) with an honors diploma. He received his Candidate (Ph.D.) (2005) and Doctor of Science, Chemistry (2012) degrees from the Institute of Petrochemistry and Catalysis of RAS under the guidance of the Corresponding Member of RAS, professor Usein M. Dzhemilev. Since 2018, V.A. D'yakonov is the director of the Institute of Petrochemistry and Catalysis of RAS.Main scientific interests are in the field of metal complex catalysis in organic and organometallic synthesis, total synthesis of natural compounds, medicinal chemistry.

The nuclear membrane as a barrier to the action of anthracycline chemotherapeutics

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[2]Graduate School of Health Sciences, Koc University, Istanbul, Turkey
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[#]Equal contribution to the study

Anthracyclines are one of the most commonly used and most effective chemotherapeutic agents in a wide variety of cancers. Their primary mechanism of action is through binding to DNA, which leads to inhibition of DNA synthesis, DNA damage and eventually apoptosis. Since they act primarily by binding to DNA, the intra-nuclear concentration of these chemotherapeutics is a major determinant of the drug efficacy. Studies suggest that anthracyclines can enter the nucleus through both passive diffusion and an energy-dependent transport via nuclear pore complex (NPC). In sensitive cells, they have a tendency to accumulate within the nucleus. However, in chemoresistant cancer cells, anthracyclines cannot accumulate in the nucleus despite the presence of the drug within the cytoplasm. This phenomenon is known as nuclear sparing phenomenon and is thought to be an important mechanism for anthracycline resistance. Moreover, the nuclear barriers that lead to the nuclear sparing may limit the efficacy of the nanocarriers designed to overcome only the cytoplasmic membrane barriers for anthracyclines. Therefore, uncovering the molecular mechanisms of nuclear sparing is of substantial importance. The efflux pumps that were recently shown to be localized in the nuclear membrane are strong candidate proteins to explain nuclear sparing in chemoresistance cancer cells. Our studies also suggest that, an NPC protein may have an important role in controlling the active transport of anthracyclines between the cytoplasm and the nucleus. Here, we will discuss the role of nuclear efflux pumps and NPC proteins in nuclear-sparing phenomenon together with the strategies to design new carriers that can overcome the nuclear barriers against anthracycline action.

Presentation Learning Outcome

In the presentation three main topics will be discussed:

- The role of nuclear sparing phenomenon in chemoresistance to anthracycline chemotherapeutics
- Underlying mechanisms of nuclear sparing
- Strategies to overcome nuclear barriers

The findings of the study will assist the design of drug carriers that could overcome nuclear barriers against the action of anthracycline chemotherapeutics.

Biography

Dr. Ozcan received her MD degree at Hacettepe University School of Medicine in 2007. She completed her residency in Pharmacology at Ankara University School of Medicine in 2011 and investigated signaling mechanisms of G-protein coupled receptors. After residency, she was employed in the Ministry of Health, Turkish Medicines and Medical Devices Agency in the context of public service responsibility. She conducted her post-doctoral studies at University of Texas MD Anderson Cancer Center, Department of Experimental Therapeutics. Since 2016, she has been investigating the mechanisms of chemoresistance in gastric cancer and ovarian cancer at Koc University Research Center for Translational Medicine.

Global legal tools for pharmacovigilance and risk control

Eliana Silva De Moraes
Presidente of ABPVS - Brazilian Regulatory Affairs Society in Europe Paris, Ile de France - France

For those who works in the pharmaceutical sector knows that doing business globally is a challenge. The regulatory affairs profdessional needs to have a broadly view of the current trends such as risk management, pharmacovigilance, misleading, etc.

Due the divergence between regulators values of different countries and the need to meet common standars and develop efficient tools to optimize the regulatory dialogue, especially regarding risk assessment and the pharmacovigilance process, it is mandatory understand and identify common legal elements of the international regulatory enviroment. The presentation will cover the recent and relevants laws, international standards, and regulations contributing to a achievement of the essential tools to treat risks and evaluate the products benefits.

During the session, the panel on pharmacovigillance will highlight current challenges, opportunities and developements. The discussion also will creating possibilities for imporved sharing of knowledge, information and resources to supor the participant to gathered the global best perspectives in pharmacovigilance regulation and practices.

Presentation Learning Outcome

- Participants will be able to lead differents regulatory systems
- Develop better tools and capacity for effective risk/benefit assessment
- Increase measures to ensure consumers are aware of the dangers
- Gives an opportunity for participants to adresses topics of common interest which have emerge during the presentation and discussion

Biography

Eliana Silva de Moraes has her expertise in food and drug law. Twenty six years experience in international food and drug law: pharmaceutical, medical device, cosmetic, food sector. Help companies to gain presence in markets of Latin America and Europe. She has an active participation in the Global harmonization process through the organizations that she represents, ABPVS. Played an active role in setting up Brazil's Public Health Regulator (ANVISA). Partner at Silva de Moraes. Member of the Brazilian Bar Association and Portugal Bar Association. Speaks Portuguese, English, French and Spanish.

Self-propelled objects with high autonomy for transportation

Satoshi Nakata
Graduate School of Integrated Life Sciences, Hiroshima University, Higashi-Hiroshima 739-8526, Japan

Self-propelled objects have been studied as potential carriers to transport materials or themselves to a target location in a confined space, mimicking the behaviours of bacteria. Most self-propelled objects exhibit monotonous or random motion, since the direction of motion is determined by the anisotropy of the motor shape or by the external field. On the other hand, biological motors such as bacteria can flexibly change the character of their motion while responding to the physicochemical environment, and their characteristic behaviour, such as chemotaxis, is induced consequently. Designing artificial self-propelled systems that mimic biological motors, can help us to understand how the variety and autonomy of self-propelled motion seen in nature emerge. We have investigated simple self-propelled objects which indicate characteristic features of motion depending on the physicochemical environments to transport materials. The driving force of motion is the difference in the surface tension around the object. Nonlinear phenomena, such as oscillation, bifurcation, synchronization, collective motion, and pattern formation, were introduced as the characteristic features of motion based on reaction-diffusion kinetics to enhance the autonomy of the system. I would like to talk about (1) mode-bifurcation between oscillatory motion and continuous motion in couple with chemical reactions, (2) reciprocating motion depending on the chemical property of amphiphilic molecule on water, (3) memory motion depending on the trajectory of motion. I would like to discuss the relationship between these characteristic motion and physicochemical nonlinearity.

Presentation Learning Outcome

- The autonomy of the present system is enhanced by introducing nonlinear dynamics
- Utilization of nonlinear dynamics gives the audience multi-dimensional information such as spatio-temporally development
- Chemical sensing based on nonlinear dynamics
- Artificial design mimicking bacterial motion such as chemotaxis
- Basic and principle research

Biography

Satoshi Nakata is the professor of graduate school of integrated science for life in Hiroshima University, Japan. His interest is the spatio-temporal pattern formation under nonequilibrium condition, e.g., chemical oscillation, nonlinear behaviors such as oscillation, bifurcation, synchronization, collective motion, chemical sensor mimicking living organisms, by using non-living systems. He received PhD from Nagoya University, Japan.

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DAY 2

POSTERS

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JUNE
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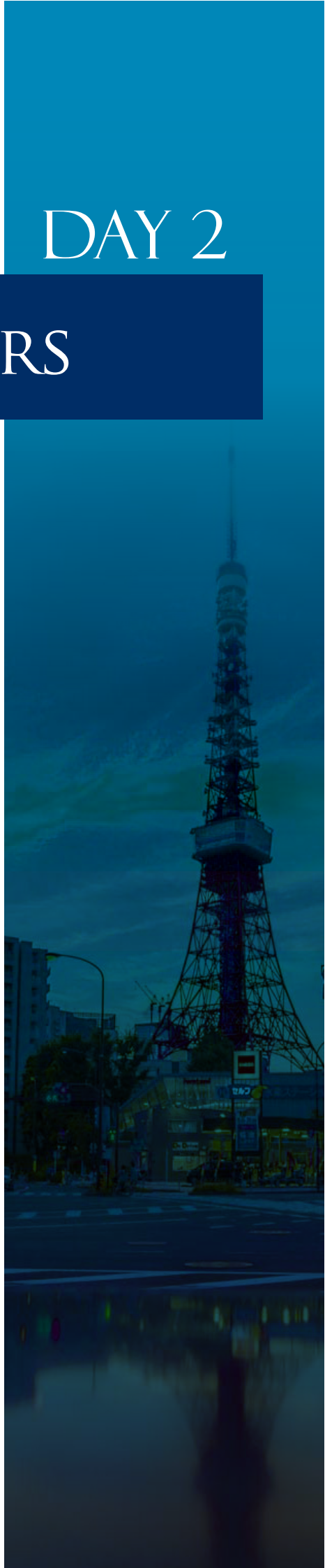

HIV-1 integrase tetramers are the antiviral target of pyridine-based allosteric integrase inhibitors

Mamuka Kvaratskhelia[1*], Pratibha C. Koneru[1], Ashwanth C. Francis[2], Nanjie Deng[3], Stephanie V. Rebensburg[1], Ashley C. Hoyte[1], Jared Lindenberger[1], Daniel Adu-Ampratwum[4], Ross C. Larue[4], Michael F. Wempe[5], Alan N. Engelman[6], Dmitry Lyumkis[7], James R. Fuchs[4], Ronald M. Levy[8], Gregory B. Melikyan[2]

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Allosteric HIV-1 integrase (IN) inhibitors (ALLINIs) are a promising new class of antiretroviral agents that disrupt proper viral maturation by inducing hyper-multimerization of IN. Here we show that lead pyridine-based ALLINI KF116 exhibits striking selectivity for IN tetramers versus lower order protein oligomers. Paradoxically, IN structural features, which are essential for its functional tetramerization and HIV-1 replication, are also critically important for KF116 mediated higher-order IN multimerization. Live cell imaging of single viral particles revealed that KF116 treatment during virion production compromises the tight association of IN with capsid cores during subsequent infection of target cells. We have synthesized the highly active (-)-KF116 enantiomer, which displayed EC_{50} of ~7 nM against wild type HIV-1 and ~10-fold higher, sub-nM activity against a clinically relevant dolutegravir resistant mutant virus suggesting potential clinical benefits for complementing dolutegravir therapy with pyridine-based ALLINIs.

Biography

Dr. Mamuka Kvaratskhelia began his independent research career at the Ohio State University in 2003 and his research has been focused on better understanding of the structure and function of HIV-1 integrase as a therapeutic target. He has recently (2017) moved to University of Colorado Denver as a Professor of Medicine (Infectious Diseases) to further extend his studies on HIV-1 integrase. By employing innovative biochemical, biophysical, structural biology, molecular biology and virology approaches, his research team has made many important contributions to the field, which include the discovery of second, non-catalytic role of integrase in HIV-1 biology and elucidating the mode of action of allosteric HIV-1 integrase inhibitors (ALLINIs), which are currently in pre-clinical trials.

Study of the capability of Chitosan-Glutathione nanoparticles to modulate redox state in human Chondrocytes

Roberto Diaz-Torres*, MS; Laura Denise López-Barrera, MS; Ambar Lopez Macay, Dr; Alberto Lopez-Reyes, Dr; Sofia Pina-Olmos, MS; Patricia Ramirez-Noguera, Dr
National University of Mexico, Mexico

The use of nanometric systems as disposal of biologically active substances is a successful tool in different areas of knowledge. In this research we studied nanometric systems with antioxidant capacity to modulate events associated with the redox state in human chondrocytes. We use nanoparticles (NPs) prepared with chitosan and glutathione (GSH), using as an *in vitro* model a primary culture of human chondrocytes extracted from hyaline cartilage. The cells were exposed to $CdCl_2$ in the presence or not of NPs. $CdCl_2$ is a widely known oxidizing agent. Fluorescence and confocal microscopy showed the location of the NPs within the cells. The results obtained showed that NPs did not affect cell viability significantly. We studied the antioxidant capacity of the NPs by estimating the content of GSH, TBARs, Cell Rox and the enzymatic activity of glutathione peroxidase (GPx). *In vitro* assays showed that glutathione (GSH) levels, as well as GPx activity and reactive oxygen species (Cell Rox), were modified with both concentrations of NPs; while lipoperoxidation (TBARs) decreased when cells exposed to $CdCl_2$ were in contact with the NPs. All these results suggest the ability of NPs to modulate the cell redox state in a dose-related response.

Presentation Learning Outcome

- The audience will have the information to know how these nanoparticles act over chondrocytes as therapy agents
- This is a very good alternative to modulate the redox balance in joints
- This presentation shows the methodologies to evaluate the effect of a toxic agent and how the nanoparticles improve the redox balance
- Provides new information in the uses of polymeric nanoparticles

Biography

Roberto Diaz-Torres, born in Mexico City, Bachelor in pharmaceutical chemistry, he worked about 10 year in the industry (Procter and Gamble, Roche and 3M), MS in physical chemistry, Dr in chemistry specifically in nanomedicine. Researcher since 2008 in the field of drug delivery systems and professor at the National University of Mexico since 2002.

The biomedical application of biogenic silver nanoparticles produced from Cotyledon orbiculata

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The biogenic synthesis of nanomaterials is considered an eco-friendly approach to nanomaterial synthesis that produces nanomaterials that is more biocompatible and therefore more suitable for biomedical applications. Several studies have shown the antibacterial properties of biogenic silver nanoparticles synthesised from plant extracts. These nanoparticles can be applied in the manufacturing of products (e.g. wound dressings, topical creams and gels) used for the treatment of wounds. South Africa and the Western Cape in particular have a rich plant biodiversity and many of these plants are used in traditional medicine to treat a whole range of human health problems, including conditions that affect the skin. In South Africa *Cotyledon orbiculata* is used in traditional medicine for the treatment of skin infections and inflammation. There are indications that biogenic nanomaterials produced from plants can integrate the inherent medicinal properties of the plant and further enhance the therapeutic efficacy. In this study silver nanoparticle synthesis using extracts of *C. orbiculata* to reduce silver nitrate was investigated. The nanoparticles were characterised using TEM, dynamic light scattering and UV-vis spectroscopy. The synthesis of the silver nanoparticles was optimised by varying the reaction time, temperature of synthesis, concentrations of the plant extract and silver nitrate. Spherical, crystalline silver nanoparticles with sizes of 20-40nm were produced using the optimal conditions. The antimicrobial activity of solvent extracts (water, methanol, chloroform) of *C. orbiculata* as well as silver nanoparticles produced from the plant was investigated against *Staphylococcus aureus, Staphylococcus epidermidis*, Methicillin resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* and *Candida albicans*. The immunomodulatory activity of the extracts and silver nanoparticles were evaluated by determining the effects on cytokine (TNF-alpha, IL-1 beta and IL-6) production in THP-1 macrophage cells. The results show that the extracts exhibited some antimicrobial activity, with the Minimum Inhibitory Concentrations of the extracts ranging from 3.13 to 50mg/ml. These extracts also exhibited anti-inflammatory properties. The same activities were observed for the silver nanoparticles. However, the bioactivities of the nanoparticles were significantly higher when compared to the extracts. The study gives credence to the traditional use of the plant and also shows that silver nanoparticles produced from this plant can be used in the production of products for the treatment of skin conditions.

Presentation Learning Outcome

- The audience will get an understanding of how indigenous South African medicinal plants are studied in our country, with a view to drug screening.
- Similar methodologies can be employed in other medicinal plant projects.
- Further research work can be proposed based on the results of this study.
- Future inter-disciplinary collaborations/ collaborative projects can be developed to continue this study, or start new projects.

Biography

Dr. Samantha Meyer did her undergraduate qualification in Medical Biosciences at the University of the Western Cape (UWC), South Africa. She then proceeded with postgraduate studies in the field of Applied Herbal Science and Medicine, and graduated with BSc Honours degree *Cum Laude*. During her Doctoral studies, she spent some time at University of Missouri-Columbia under supervision of Prof John Cannon, and obtained her PhD degree in 2009 from UWC.

She has since been employed at Cape Peninsula University of Technology, where she currently holds position of Senior Lecturer, and heads a research group (funded by South African National Research Foundation) where she conducts research on the antimicrobial potential of indigenous SA medicinal plants.

Nano-amorphous abiraterone acetate formulation with improved bioavailability and eliminated food effect

T. Jordán[1*], MSc; T. Solymosi[1], MSc; R. Angi[1], MSc; O. Basa-Dénes[1], MSc; Zs. Ötvös[1], PhD; H. Glavinas[1], PhD; G. Heltovics[2], MSc

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[2]Druggability Technologies Holdings Ltd., Regional Business Centre, University Heights, Misda MSD, 1751, Malta

Abiraterone acetate (AA) is a poorly water-soluble drug molecule indicated for patients with metastatic castration resistant prostate cancer. It is a prodrug, which is converted to abiraterone *in vivo*. The oral dose is high; 1,000 mg which is administered once daily as 4x250 mg Zytiga® tablets. The absolute bioavailability of abiraterone following the administration of Zytiga® is estimated to be below 10% in the fasted state with a 10-fold (AUC) and up to a 17-fold (C_{max}) increase following a high-fat meal. We have developed a nano-amorphous AA formulation prepared by controlled precipitation followed by lyophilization. The formulation exhibited higher apparent solubility and passive permeability when compared to either the crystalline AA or Zytiga. In beagle dog studies, this resulted in a >10-fold increase in bioavailability in the fasted state when compared to the marketed drug and the elimination of the food effect. After the preclinical investigation a first-in-human clinical trial was conducted. Based on the analysis of pharmacokinetic data~250 mg oral dose of the nano-amorphous formulation is expected to result in the same exposure as 1,000 mg Zytiga® in the fasted state. The substantial positive food effect seen for Zytiga® was eliminated. This might allow the reduction of the dose and could eliminate the requirement of taking the drug on an empty stomach. Also, the novel formulation is expected to exhibit smaller variability when compared to Zytiga®.

In conclusion we have developed a novel nano-amorphous AA formulation that significantly outperformed the marketed product in *in vitro* and *in vivo* tests. Ultimately, the formulation might allow a 75% dose reduction and negate the restriction of a food label.

Biography

Tamás Jordán has been working at NanGenex Inc for 5 years, gaining experience in the formulation of poorly water-soluble active ingredients. He holds an MSc degree in pharmaceutical engineering and currently writing his PhD thesis. He is interested in the physicochemical principles of amorphous solid dispersions and bioavailability increasing continuous technologies.

Dissolution study of drug release from biopolymer matrix tablets

Ing. Kevin Matzick*; doc. Ing. Alena Komersová, Ph.D; Ing. Václav Lochař, Ph.D.
University of Pardubice, Faculty of Chemical Technology, Department of Physical Chemistry, Czech Republic

Aim of the work is to compare chosen biopolymers and critically evaluate their ability to provide extended release of model drugs with different solubility.

Chitosan and *Alginate-natrium* are natural derivates of cellulose that are sparingly used in many fields of industry like food or pharmacy. The physico-chemical properties (solubility, toxicity, temperature of glassy transition) of these substituted carbohydrates indicates the suitability of their use as a potential excipient of solid peroral dosage forms which otherwise represent matrix tablets.

A release of well- and poor- soluble model drug from matrices containing biopolymers mentioned above with/without combination of synthetic polymer (Kollidon®) will be discussed. Next, the ability of matrices to provide extended release of the model drugs and the mechanism of their release will be compared depending on the composition of the tablets. Further, a visual observation of drug release will be shown to obtain more details about swelling and erosion.

Matrix tablets containing synthetic and natural retardants were prepared by direct compression method (compression force 8 kN). The tablets were of cylindrical shape without facets of a diameter of 13 mm and weight of 0.5 ± 0.0010 g.

All *In vitro* dissolution tests were performed according to the European Pharmacopoeia 9th edition using dissolution apparatus SOTAX AT7 Smart with paddles or baskets (37 ± 0.5 °C, 100 rpm). As a dissolution medium was used 900 mL of acidic buffer (pH 1.2). Amount of released drug was determined using UV/VIS spectroscopy. Dissolution profiles were evaluated by non-linear regression analysis.

Presentation Learning Outcome

- The audience will get information about preparation of matrix tablets containing biopolymers and their ability to provide sustained release
- The results of the study may help researchers to decide which formulations are practically usable for extended drug release
- Presented method of visualization during dissolution test also brings interesting results connected to process of the drug release from matrix tablet

Biography

My name is Kevin Matzick and I was born in Czech Republic. I am PhD student (first year) of University of Pardubice, Faculty of Chemical Technology, Department of Physical Chemistry. My specialization is kinetics of drug release (*in vitro*), especially preparation of matrix tablets, dissolution tests ant their mathematical evaluation. I also use other analytical techniques like FT-IR spectroscopy or UV/VIS spectroscopy. I'm also able to work with various software like OriginLab, GraphPad Prism or Statistica, that help us to get maximum of information.

TAA-induced liver damage in KLF10 knockout mice

Azra Memon*, Yuliya Pyao, Jung Ye Lin, Lloyds Corazon Guadilla, Woon Kyu Lee
Laboratory of Developmental Genetics Department of Biomedical Sciences, School of Medicine, Inha University, Incheon 22212, South Korea

The liver plays an important role in regulating physiological functions such as detoxification of harmful substances. Liver injuries and diseases cause necrosis and apoptosis mainly due to an imbalance in cell protection pathway or detoxification. Therefore, liver injuries and diseases are serious health problems that threaten human health. Thioacetamide (TAA), an organosulfur compound is formerly used in leather processing laboratories, textile, and paper industries. Due to its effects on protein synthesis, RNA, DNA, and Gamma-glutamyl transpeptidase activity, is commonly used as a trigger agent to make animal disease model such as cirrhosis. Krüppel-like factors 10 is a transcription factor that has been in key cellular processes including cell proliferation, apoptosis, and differentiation. When the expression of KLF10 gene is deregulated, liver disease incidence is favored. In mouse liver, KLF10 regulates the expression of genes involved in glycolysis and gluconeogenesis. However, there is no evidence on the role of KLF10 in thioacetamide (TAA) mediated hepatotoxicity and its related damage. Upon this approach, we want to verify how this gene functions along the liver damage process as follows: Hepatic injury and its related enzyme activity, gene expression pattern, oxidative damage, inflammatory cytokines, and cellular processes including cell proliferation, apoptosis, and differentiation.

Presentation Learning Outcome

- This can be helpful for researchers who are interested in liver disease area and related drug delivery.
- This study is about thioacetamide (TAA) mediated hepatotoxicity in KLF10 knockout mice.
- How KLF10 function during hepatic injury and its related enzymes activity, gene expression pattern, inflammatory cytokines and cellular processes including cell proliferation, apoptosis, and differentiation.

Biography

I Azra Memon have done Ph.D. in 2018 from Laboratory of Developmental Genetics, Biomedical sciences school of medicine, Inha University, South Korea. After then I keep going my research at the same laboratory as a Post-Doc fellow position. My research form is to develop new disease animal model and uncover gene function during disease induction with genetical engineered mouse models.

I intend to build my career as Faculty/Researcher in a well-reputed university or Research & Development organization, where I can have an opportunity to extend my research base and utilizing the acquired capabilities in emerging areas of my field of study.

Neuropeptide Y-based recombinant peptides improve bone loss in mice by regulating hematopoietic stem/progenitor cell mobilization

Hee Kyung Jin[1*], Ph.D., Jae-sung Bae[2], Ph.D.
[1]College of Veterinary Medicine, Kyungpook National University, Daegu, Korea
[2]Department of Physiology, School of Medicine, Kyungpook National University, Daegu, Korea

Hematopoietic stem/progenitor cell (HSPC) mobilization is an essential homeostatic process regulated by the interaction of cellular and molecular components in bone marrow niches. It has been shown by others that neurotransmitters released from the sympathetic nervous system regulate HSPC egress from bone marrow to peripheral blood. We have investigated the functional role of neuropeptide Y (NPY) on this process. NPY deficient mice had significantly impaired HSPC mobilization due to increased expression of HSPC maintenance factors by reduction of matrix metalloproteinase-9 (MMP-9) activity in bone marrow. Pharmacological or endogenous elevation of NPY led to decrease of HSPC maintenance factors expression by activating MMP-9 in osteoblasts, resulting in HSPC mobilization. Mice in which the Y1 receptor was deleted in osteoblasts did not exhibit HSPC mobilization by NPY. Furthermore, full-length NPY treatment in ovariectomized mice caused reduction of bone loss due to HSPC mobilization. These results suggest a new role of NPY on HSPC mobilization, as well as the potential therapeutic application of this neuropeptide for stem cell-based therapy.

Based on these concepts and findings, we were designed to search for more functional recombinant peptides from the full-length NPY with the capability to efficiently mobilize HSPCs and prevent bone loss in ovariectomized mice. Here, we demonstrate that new NPY peptides, recombined from cleavage of the full-length NPY, showed better functionality for HSPC mobilization than the full-length peptide. These recombinant peptides resulted in a greater efficiency of HSPC mobilization by decreasing HSPC maintenance factors. Furthermore, treatment with these peptides reduced the number of osteoclasts, and relieved the ovariectomy-induced bone loss in mice more effectively than did treatment with the full-length NPY. Therefore, these results suggest the useful role of new peptides recombined from full-length NPY for the treatment of osteoporosis.

Biography

Hee Kyung Jin is the Professor of the KNU Alzheimer's disease Research Institute at Kyungpook National University developing novel targets for the treatment of neurodegenerative diseases. Since 2007, she is leading a team that focuses on studying for novel pathogenesis of neurodegenerative disease by abnormal sphingolipid metabolism and developing new therapeutic and diagnostic strategies in neurodegenerative disease such as Alzheimer's disease.

Antitumor effects of retargeted AAV2 virus on ovarian cancer *in vivo*

Hyung Jun Ahn* **and Sungjin Lee**
Center for Theragnosis, Biomedical Research Institute, Korea Institute of Science and Technology, Seoul, South Korea

Adeno-associated virus (AAV) is a promising vector for systemic delivery of siRNA due to its long-term expression ability without immunogenicity and pathogenicity. However, its broad host tropism and lack of tissue specificity has limited clinical applications such as cancer therapy. Therefore, redirecting the natural tropism of AAV vectors to unique cell surface antigens is an important requirement for *in vivo* RNAi-based cancer therapy. To exploit the overexpression property of epithelial cell adhesion molecule (EpCAM) in specific cancer types, we here created anti-EpCAM anitibody-conjugated AAV serotype 2 (AAV2) vectors through a streptavidin-biotin bridge. Upon intravenous injection, anti-EpCAM-conjugated AAV2 vectors showed prominent tumor-specific accumulation in EpCAM-positive tumor-bearing mice without undesirable sequestration in liver. In addition, when loaded with transgenes to express shRNA against epidermal growth factor receptor (EGFR), systemically injected anti-EpCAM-conjugated AAV2/shEGFR vectors induced significant downregulation of EGFR expression in tumors, and eventually suppressed tumor growth even at the long dosing interval of two weeks. This *in vivo* antitumor effect represents the increased infection efficacy of tropism-modified AAV2 vectors and prolonged expression of EGFR shRNA in tumor tissues. Thus, this study suggests the great potential of anti-EpCAM-conjugated AAV2/shEGFR vectors as RNAi-based cancer therapeutics.

Presentation Learning Outcome

- We have demonstrated that anti-EpCAM-conjugated AAV2 vectors can be redirected to EpCAM-positive OVCAR3 tumors *in vivo* without undesirable accumulation in the liver.
- The *in vivo* antitumor effect represents the increased infection efficacy of tropism-modified AAV2 vectors and prolonged expression of EGFR shRNA in tumor tissues.
- This study suggests the great potential of anti-EpCAM-conjugated AAV2/shEGFR vectors as RNAi-based cancer therapeutics.

Biography

Dr. Hyung Jun Ahn is a Principal Research Scientist of Biomedical Research Institute at Korea Institute of Science and Technology (KIST). He received his BS, MS, and PhD degrees from Seoul National University (Chemistry). After postdoctoral training under the supervision of Prof. Yigong Shi at the Department of Molecular Biology, Princeton University, Dr. Ahn joined a Senior Research Scientist, KIST in 2006. Dr. Ahn has been an Adjunct Professor at the Department of Biomedical Engineering in University of Science and Technology since 2010. Dr. Ahn's research is concerned with biomaterials-based drug delivery, siRNA delivery, and molecular imaging technology.

Niosomal encapsulation of Curcumin: Characterization and its potential as a therapeutic intervention in asthma

Dinesh Kumar Chellappan[1*], Wong Jin-Ying[1], Ng Zhao Yin[1], Jithendra Panneerselvam[1], Thiagarajan Madheswaran[1], Pradeep Kumar[2], Viness Pillay[2], Nicole Hansbro[3], Peter Wark[3], Mary Bebawy[4], Alan Hsu[3], Philip Michael Hansbro[3,4,5], Kamal Dua[3,6,7]

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Asthma is a disease which occurs due to chronic inflammation in the airways. The most prominent clinical features of asthma are constriction and obstruction of the airway, which renders breathing difficult and complicated. Curcumin, a highly potent therapeutic substance, is obtained from the common turmeric, *Curcuma longa*. One of the major limitations of curcumin is that, this substance has limited or minimal solubility in water. We attempted to formulate curcumin nanoparticles that are encapsulated in a niosomal vesicular system. Characterization profile was carried out further to determine essential parameters namely, efficiency of encapsulation, particle size, analysis using FTIR, zeta potential and release profile of the formulations. In addition, we also used the human immortalized airway basal cell line, BCi-NS1.1, to quantify the expression of selected proinflammatory markers *in vitro*. Lipopolysaccharide was used to stimulate inflammation. Real-time PCR was used to study the expression pattern of the selected pro-inflammatory markers, namely, IL-6, IL-8, IL-1β and TNF-α. Our findings revealed that niosomal curcumin has an average particle size of 284.93 ± 14.27nm. The polydispersion index was found to be 0.426. The zeta potential of the nanoparticles was found to be -46.93. The formulation had an encapsulation efficacy of 99.62%. We also performed detailed molecular mechanics simulations on the nanoparticles. The interaction mechanisms that were involved between Cholesterol and Span 80 were studied. In addition, we also studied the niosomal architecture for its functional polar/non-polar alignment, and the preferential positioning of curcumin towards the hydrophobic domains. Our findings reveal that niosomal curcumin could restrict crucial pro-inflammatory markers and could be a potential therapeutic intervention in the treatment of asthma.

Presentation Learning Outcome

- We have developed and characterised a novel nanoformulation on curcumin which could be a potential intervention in asthma
- This research work could be further explored in the area of asthma, which could prove crucial in the management of asthma

Biography

Dr Dinesh Kumar Chellappan has completed PhD in Pharmaceutical Sciences, from the Manipal University, India in 2009. He has worked on several research projects especially in the field of cardiovascular diseases, diabetes and natural products. He has published more than 90 research and review articles in reputed international research journals. He has also presented a number of papers at conferences. His biography is included in the recent editions (27th – 35th) of Marquis Who's Who in the World. He has received research grants and has been on the editorial board of several research journals and is the reviewer of several journals.

Calotropis gigantea extract induces apoptosis through extrinsic/intrinsic pathways and reactive oxygen species generation in A549 and NCI-H1299 non-small cell lung cancer cells

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Background: *Calotropis gigantea* (CG), a tall and waxy flower that has been used in treating fever, indigestion, rheumatism, leprosy and leukoderma as traditional remedies. However, it has not yet been examined about the precise mechanisms of its anti-cancer effects in human non-small cell lung cancer (NSCLC) cells. In this study, we elucidated whether CG extract would exert the apoptotic effect in A549 and NCI-H1299 NSCLC cells.

Methods: Ethanol extract of CG was prepared, and apoptotic effects of CG extract in A549 and NCI-H1299 NSCLC cells were assessed using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay, annexin V-fluorescein isothiocyanate/propidium iodide (PI) staining, cell cycle analysis, polymerase chain reaction (PCR), western blotting, JC-1 staining and ROS detection assay.

Results: CG extract induced apoptosis by stimulating intrinsic and extrinsic signaling pathways in A549 and NCI-H1299 lung cancer cells. Furthermore, cell cycle arrest was occurred by CG extract in both cells. Moreover, the reactive oxygen species (ROS) which can induce cell death was also generated in a CG-treated A549 and NCI-H1299 cells.

Conclusions: These data confirmed that CG caused apoptosis by activating the extrinsic and intrinsic pathways, cell cycle arrest and generating ROS in A549 and NCI-H1299 lung cancer cells. Thus, we suggest CG as a potential agent for lung cancer prevention therapy.

Presentation Learning Outcome

- Discovery of plant anti-cancer effects
- Clarification of apoptotic mechanism in lung cancer cells
- Development of potential agent for lung cancer prevention therapy

Biography

Ms. Jiyon Lee studied biotechnology at the Konkuk University, Republic of Korea and graduated as bachelor's degree in 2018. She has joined laboratory of cell biology and immuno-biochemistry of Prof. Do-young Yoon at department of bioscience and biotechnology, Konkuk University, Republic of Korea since 2018.

Kinetics of pentoxifylline release from hydrophilic, lipophilic and dual matrix tablets

Ing. Barbora Slezáková*; Doc. Ing. Alena Komersová, Ph.D.; Ing.VáclavLochař, Ph.D.
University of Pardubice, Faculty of Chemical Technology, Department of Physical Chemistry

The aim of this study was to evaluate the possibilities of using matrix tablets and dual matrix tablets containing hydrophilic and/or lipophilic retardant for extended release of pentoxifylline.

Polyvinyl alcohol (Parteck® SRP 80) and hypromellose with different viscosity grade (Methocel® K4M, K15M a K100M) were used as hydrophilic retardants and Compritol® 888 ATO was used as a lipophilic retardant.The matrix tablets were prepared by direct compression method using Prosolv® SMCC 90 as a binder and magnesium stearate as a lubricant. The tablets were of cylindrical shape without facets of a diameter of 13 mm and weight of 0.5 ± 0.0010 g.Dissolution testing was carried outaccording to the European Pharmacopoeia 9th using dissolution apparatus SOTAX AT7 Smart. As the dissolution medium was used aqueous solution of HCl with addition of NaCl(pH 1.2). Other experimental conditions: 900 mL of the dissolution medium, temperature 37 ± 0.5°C, 100 rpm. Released amount of pentoxifylline was determined by UV/VIS spectroscopy. Obtained dissolution profiles were evaluated by non-linear regression analysis and fitted to the first order kinetic model, Weibull model, Korsmeyer-Peppas and Higuchi models. The mechanism of drug release was studied and the drug release rate constants and other kinetic parameters were evaluated.

Based on the results of fit to the Korsmeyer-Peppas model, it was found the anomal transport is major release mechanism. The higher release rate of pentoxifylline was found for tablets containing Compritol® 888 ATO in comparison with hydrophilic matrix tablets.

Presentation Learning Outcome

- The presentation brings to the audience comparison of kinetics of pentoxifylline release from different types of matrix tablets and a clear summary of kinetic parameters for different retardants used
- The audience can learn about evaluation of drug release mechanism using different mathematic models
- This study can make a designer's job more efficient because thanks to knowledge of the kinetic parameters is possible to obtain required drug dissolution profile (*in vitro*)
- Knowledge of the kinetic parameters is important for in vitro/in vivo correlation

Biography

My name is Barbora Slezáková. I am from Czech Republic and I am Ph.D. student (first year) at the University of Pardubice, Faculty of Chemical technology, Department of Physical Chemistry.My work is focused to the matrix tablets, dissolution testing and mathematical evaluation of the drug dissolution profile using non-linear regression analysis (software Origin and GraphPadPrism).

Development of rotigotine nanoparticles and its effect on haloperidol induced Parkinsonian symptoms in rats

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Rotigotine, a non-ergot dopamine agonist (D2-D5 receptors) drug used in the treatment of idiopathic Parkinson's disease (PD). Presently, its clinical use is very limited due to its poor oral bioavailability. Thus, this study was designed to develop chitosan nanoparticles (CS NPs) of rotigotine for intranasal route and further tested its efficacy in haloperidol-induced Parkinsonian symptoms in rats. Rotigotine loaded CS NPs were prepared using ionic gelation method with cross-linked tripolyphosphate. The efficacy of the nanoformulation was evaluated through akinesia, catalepsy and forced swimming behavioural test. Further, the brain samples were used for histopathological study and brain homogenates were used to estimate the lactate dehydrogenase (LDH) and catalase activity. The mean particle size and zeta potential of rotigotine loaded chitosan nanoparticles was found to be 75.37 ± 3.37 nm and 25.53 ± 0.45 mV respectively. This formulation has an entrapment efficiency of 96.08 ± 0.01%. Intranasal rotigotine CS NPs showed a reversal in cataleptic behaviour compared to haloperidol positive control rats ($P < 0.01$). Similar changes were also observed in swim test and akinesia. Rotigotine loaded CS NPs showed significant increase in catalase activity (96.45 nmol/min/ml) as compared to positive control (71.15 nmol/min/ml) ($P<0.01$). Rotigotine loaded CS NPs showed a decrease in LDH activity (111.9 ± 9.05 IU/L) as compared to positive control (147.4 ± 18.8 IU/L). Histological examination showed that haloperidol induced and rotigotine treated groups did not have any significant changes in the neuronal structure of the cerebellum. The observations in this study suggest that intranasal administration of rotigotine loaded CS NPs can be a novel nose to brain approach in the treatment of Parkinson Disease (PD).

Acknowledgment: This research project is funded by the Ministry of Science and Technology Innovation (MOSTI), Kuala Lumpur, Malaysia, grant number (02-02-09-SF0055).

Presentation Learning Outcome

- Development and optimization process of a nanoparticle that is intended to nose to brain delivery in neurodegenerative condition
- This concept is developed to deliver the CNS acting drugs those are having poor bioavailability
- This research direction can be further explored by other researchers

Biography

Dr. Subrat Kumar Bhattamisa has received his Ph.D. in Pharmacology from Banaras Hindu University, India in 2006 under fellowship obtained from Government of India. He then joined as Scientist at Torrent Research Centre, India and later shifted to academic. He joined International Medical University, Malaysia in 2014 and currently, he is involved in research areas linked to neurodegeneration and diabetes mellitus. He has published more than 40 research and review articles including patents.

Synthesis, evaluation and computational simulation of novel coumarin derivatives as potential acetylcholinesterase inhibitors

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Alzheimer's disease (AD) is characterized by a slow but progressive deterioration in cognitive performance. The decrease of acetylcholine (ACh) due to cholinergic neuronal dysfunction in the hippocampus and cortex could result in AD. Current clinical therapy for AD patients is mainly palliative treatment targeting acetylcholinesterase (AChE). Novel coumarin derivatives were designed using the fragment-based drug design. Hybridization of the acetylcholine backbone with the coumarin scaffold provides coumarin-3-carboxylates and 3-carboxamides with rigid aza(mono,bi)cyclic structures. Several coumarin derivatives exhibited much stronger AChE inhibitory activities compared to those of donepezil both *in vitro* and *in vivo*. Computational simulation studies were performed in order to gain insights into the possible binding modes of the derivatives.

Presentation Learning Outcome

- Alzheimer's disease (AD) : etiology, pathophysiology, misc
- Fragment-based drug design
- Drug discovery trends in AD
- Problems of drug development in this area (AD)
- Computational Simulation to get possible mode of bindings

Biography

Park Haeil Born in Seoul, Rep of Korea. He graduated from Seoul National University (Pharmacy, BS/MS), and done his PhD in University of Kansas (MedChem, PhD). He worked as a research scientist at pharmaceutical company for several years, Rep of Korea. He is working as a professor since 1998 in College of Pharmacy, Kangwon National University, Rep of Korea.

Characterization and validation of tumor cell-selective penetrating peptides

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**The two last authors equally contributed to this work

The aim of our project is to develop innovative tumor-specific approaches for transport of bioactive compounds in tumor cells for targeted therapy in cancer.

Tumor Penetrating Peptides (TPP) are a subclass of tumor homing peptides that penetrate extravascular tumor tissue and specifically internalize into tumor cells. TPP are defined by the presence of the C-end rule (CendR) motif. This CendR motif must be at the C-terminus of the sequence to be able to bind to the cell and tissue penetration receptor Neuropilin-1 (NRP-1), which is over-expressed in tumor vasculature and in a variety of tumor cells *in vitro* and *in vivo*. In addition, it has been shown that NRP-1 is specifically expressed in B cells from Chronic Lymphocytic Leukemia (CLL) patients.

We have tested here five different TPPs as fluorophore-labeled peptides and as nanoparticles targeting ligand for binding. The tumor specificity has been demonstrated using human primary B cells isolated from blood of healthy donors or from patients suffering from CLL. In addition, we validate also its tumoral selectivity using primary human healthy hepatocytes or tumoral hepatocytes isolated from non-viral induced hepatocarcinomas.

We observed that there is a tumoral-specific penetration of all five TPPs in B cells isolated from CLL patients. On the contrary, the TPPs are not internalized in healthy B cells. Similarly, the TPPs were also tested in healthy and tumoral hepatocytes, showing a similar result, with very week or absence of penetration in healthy hepatocytes and high level of internalization in malignant hepatocytes. Similar results were obtained when the TPP were administrated bound to the surface of nanoparticles. Finally, the TPPs did not interact with healthy human red blood cells.

These results strongly suggest that the tested TPPs specifically internalize in malignant primary B cells and hepatocytes.

Presentation Learning Outcome

Protein/protein interactions (PPIs) are well recognized as promising therapeutic targets. Consequently, interfering peptides capable of interfering PPIs are receiving increasing attention. In addition, progress on peptide administration, stability, biodelibery and safety are also encouraging the interest in peptide drug development. We consider that our results are of interest for the scientific community working on cancer, cell penetrating peptides, interfering peptides, apoptosis and new therapies against cancer.

Biography

Dr Angelita Rebollo studied Biology at the University of Leon, Spain and got her PhD in 1987. She joined the Institut Pasteur (Paris, France) for a first 6 years postdoctoral position. She was also working as postdoctoral at the MIT (Boston, USA), Ludwig Institute for Cancer Research (Brussels, Belgium) and Institut Cochin (Paris, France). She has a permanent position at Inserm (Paris, France) and CSIC (Madrid, Spain). She has published more than 100 articles and 21 patents.

Freshwater sapropel extract for use in medicine and pharmaceutics

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Sapropel is organic sediment that accumulates underwater in shallow to deep marine basins, lagoons and lakes. The sapropel forms by slow decomposition process of phytoplankton, waste material from higher plants and aquatic animals and fine-grained nonorganic particles in the sediment.

Sapropel has long been used as a remedy in medicine, having a positive health effect for skin and other organ systems. For some time there has been increasing interest in extracting of active components from the sapropel for use in skin care.

Freshwater sapropel obtained from different Latvia lakes was used in the extraction process of biologically active components. 105 samples from 5 different lakes in eastern Latvia region Latgale were collected during winter time using the frozen surface of the lakes as a platform to support the sapropel extraction device. The samples were used for the research of sapropel and for the extraction of active ingredients.

The raw sapropel samples were tested for the presence of heavy metals and pesticides and used for obtaining sapropel extracts. Sapropel extract was obtained using solid-liquid method with alkaline solution from 56 samples, mixture was stirred for 24 h, then centrifugated and filtrated; filtrate was acidified and centrifuged again. Filtrate was separated from solid particles, and both liquid extract and solid extract were stored at 4°C before use.

Sapropel extracts were characterised by organic carbon content (TOC), humic acid (HA) and Fulvic acid (FA) concentration, pH level, and antioxidant level. Total organic carbon, HA and FA were determined using spectrometric method. To determine antioxidants the following methods were used: DPPH radical method, Folin-Ciocalteu method for determination of the total phenolic content and total antioxidants status were calculated.

The yield in dried extract form was 22 -28 g of humic acids and 5 - 9 g fulvic acids from one-kilogram dried sapropel. Sapropel from different lakes gave different yields, the difference is higher for the fulvic acids where the highest and lowest values differs by more than 80%, while the total organic carbon is more uniform with the difference between lowest and highest values less being less than 30% and HA results showed dispersion within only 20%. Relative antioxidant level variations between the samples from different lakes were considerably stronger with the difference between the highest and the lowest value is almost threefold for the total antioxidant level. The antioxidant level did not correlate with the FA and HA level.

The colour of sapropel extracts is lake and sapropel strata specific ranging from light yellow to almost black due to different humification level of sapropel.

Conclusion

The raw sapropel source site should be selected differently for different active components needed in the extract in order to optimise the extraction yield. Sapropel can be standardised by defining the desired concentration corridor for the chosen parameters and specific raw sapropel location can be defined as part of the characterisation of the extract. The colour of the extract can vary and can be used for organoleptic identification of the extract from specific sapropel site.

Acknowledgments

This research was supported by "Analysis of characteristics of medical sapropel and its usage for medical purposes and elaboration of industrial extraction methods", project No. 1.1.1.1/16/A/165.

Presentation Learning Outcome

- Audience will gain knowledge about extract characterization and will learn about sapropel extract and apply this knowledge in using extracts from natural substances.
- They will gain additional experience about bulk characteristics of sapropel extract and other extracts from natural products with varying properties. Other faculties and labs can use the research results in their research. The results will simplify and make easier to use sapropel extract in drug design.
- Sapropel extract has good commercial potential for its use in cosmetics and pharmaceuticals, but methodological and technological advancements in standardization and characterization are needed for its use in industry.

Biography

Aneka Klavina studied Chemical engineering and Material science at the Riga Technical University, Latvia graduated as master in science in 2016. She joined the researcher group at the Institute of Occupation Safety and Environmental Health, Rigas Stradiņš University and work there since 2014. Now she is doing her PhD in pharmacy at Rigas Stradiņš University about natural remedies and carboxylmethylcelluloses gel systems. Now is researcher at the Institute of Occupation Safety and Environmental Health and at Laboratory of Hygiene and Occupational Diseases.

Fabrication and characterization of transdermal patch loaded with Ascorbic acid

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Ascorbic acid AA (vitamin C) has been widely used in the cosmetic field as an anti-wrinkle agent due to a variety of biological, pharmaceutical and dermatological functions. The main cause of aging is a decline in vitamin C content as a result of chronological aging and photoaging. The ability of AA to penetrate the skin is very low due to its physicochemical properties. AA is a water soluble vitamin (log p =-1.85), unstable and is not a potent drug. The aim of this study is to fabricate transdermal patch loaded with a high dose of a hydrophilic anti-aging compound (AA). The objective of using nnnanoemulsion as a vehicle in the present work is to overcome stability problems of AA since it can protect AA from degradation and promote an adequate penetration of AA into the skin for transdermal application. To the best of our knowledge, there have been no studies involving nanoemlusion loaded patch for transdermal delivery of AA. In order to fabricate patch with good mechanical properties to be used safely; number of biodegradable polymers were used. An optimized AA-loaded nanoemulsion containing 20% w/w oil phase, 60% w/w surfactant: cosurfactant and 20% water which passed visual tests for transparency, miscibility and ease of flow was selected, and then incorporated into the transdermal patch. Transdermal patches were prepared from 45% w/w hydroxypropyl methylcellulose (HPMC), 30% w/w carboxymethylcellulose sodium (NaCMC), 5% w/w polyethyleneglycol (PEG400) and 20% w/w AA-loaded nanoemulsion and then characterized for weight variation, stability and thickness. HPLC method for the quantification of AA was validated according to ICH guidelines. In addition, the *in-vitro* release of AA from these patches was determined using Franz diffusion cells. The patch with an area 1.76 cm^2 was delivered 4 mg of AA in 24 h. Further formulations will be also studied.

Biography

Dr. Ahlam Zaid Alkilani is an Assistant Professor at faculty of Pharmacy, Zarqa University, Zarqa, Jordan. Now she is the Dean of faculty of pharmacy at Zarqa University/Jordan.

She graduated from Jordan University, college of pharmacy in 2006. Then she obtained her MSc degree in pharmaceutical science from Jordan University in 2009. After that she completed my Ph.D. in drug delivery and pharmaceutical technology at the School of Pharmacy, Queen's university of Belfast, Belfast, United Kingdom in 2013.

Ahlam's research is centred on design and physicochemical characterisation of advanced polymeric drug delivery systems for transdermal drug delivery. Her research interests are transdermal drug delivery, microneedle, controlled release, pharmaceutical analysis, formulations, iontophoresis, in vitro release, sterilization and pharmaceutical industry. She has published many publications in peer reviewed and respected journals.

Nanoemulsion–laden organogels of lidocaine as lipid–based systems for topical delivery

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Conventional organogel and nanoemulsion–laden organogels (nanoemulsion organogels) were used to deliver the lipophilic drug, lidocaine, topically. Optimized formulations of lidocaine–loaded nanoemulsions of oil, water, and different ratios of surfactant to cosurfactant (Tween® 20: ethanol; 4:1 and 2:1 *v/v*) were selected based on the droplet size and physical stability of nanoemulsions. Nanoemulsions were then loaded into organogels. Lidocaine conventional organogel was prepared without the addition of nanoemulsion and was used as a reference. The rheological properties and release profiles of lidocaine organogels were investigated using a controlled-stress rheometer. The cumulative amount of lidocaine permeated through a synthetic membrane (Strat® M) and human excised SC was investigated using six vertical diffusion cells. Lidocaine organogels exhibited viscoelastic properties with more elastic behavior. Lidocaine conventional organogel exhibited the highest viscoelastic properties and lowest rate of release. Whereas, nanoemulsion organogel containing Tween® 20: ethanol (4:1 *v/v*) exhibited lower viscoelastic properties and a higher rate of release than those of nanoemulsion organogel containing Tween® 20: ethanol (2:1 *v/v*). Type and composition of organogels dictated the viscoelastic properties and rate of lidocaine release. The results obtained shed light on understanding the viscoelastic properties of organogel systems; as these mechanical factors play an important role in predicting the release behavior of drugs from these systems and their potential to enhance penetration of drugs through the skin.

Presentation Learning Outcome

- Organogels and nanoemulsion have been used separately as topical drug delivery systems
- Both delivery systems can enhance the penetration of hydrophobic drugs
- The loading of nanoemulsion into organogel has shown synergistic delivery effect topically
- The viscoelastic properties and *in vitro* and *ex vivo* release of organogels were type- and component-dependent

Biography

Rania Hamed studied Pharmacy at Jordan University of Science and technology. She received her Ph.D. in Pharmaceutical Sciences & Experimental Therapeutics from the University of Iowa in 2011. After her graduation she joined the Faculty of Pharmacy at Al-Zaytoonah University of Jordan and she is now an associate professor at the same institution. She has published 18 research articles in SCI(E) journals.

Anti-cancer effect of Tuberatolide B in MDA-MB-231 cells through induction of ROS and inhibition of STAT3 pathway

A. P*., M.S., E-A. K. Ph.D., J. K., M.S., N. K., Ph.D., S-J. H., Ph.D.
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Tuberatolide B (TTB, C27H34O4) is a diastereomeric meroterpenoid isolated from the Korean marine algae *Sargassum macrocarpum*. However, the anticancer effects of TTB remain unknown. In this study, we demonstrate that TTB inhibits tumor growth in breast, lung, colon, prostate, and cervical cancer cells. To examine the mechanism by which TTB suppresses cell growth, we determined the effect of TTB on apoptosis, ROS generation, DNA damage, and signal transduction. TTB induced ROS production in MDA-MB-231, A549, and HCT116 cells. Moreover, TTB enhanced DNA damage by inducing H2AX foci formation and the phosphorylation of DNA damage-related proteins such as Chk2 and H2AX. Furthermore, TTB selectively inhibited STAT3 activation, which resulted in a reduction in cyclin D1, MMP-9, survivin, VEGF, and IL-6. In addition, TTB-induced ROS generation caused STAT3 inhibition, DNA damage, and apoptotic cell death. Therefore, TTB suppresses cancer progression by promoting ROS-mediated inhibition of STAT3 signaling, suggesting that TTB is useful for the treatment of cancer.

Presentation Learning Outcome

- Cancer still remains a deadly disease and has a high incidence and death rate worldwide and targeted cancer therapeutic agents are developed for cancer patients for a long time
- Tuberatolide B on diverse cancer cells result from the induction of ROS-mediated apoptosis by inhibiting of STAT3 phosphorylation and enhancing of DNA damage
- Tuberatolide B might be an effective and useful chemotherapy agent against cancer

Biography

Areumi Park is a Project Based Research Scientist at Korea Institute of Ocean Science & Technology (KIOST). She received BS and MS from Jeju National University (Department of Marine Life Science). She is research in the cultivation of Marine Microalgae and analysis of functional materials of Seaweeds. In her current role, researching Anti-cancer and Anti-oxidant effect which are major ingredient of seaweed extract.

Protective effect of Bis (3-bromo-4,5-dihydroxybenzyl) ether against LPS-induced inflammatory response in RAW 264.7 macrophages through ROS-mediated ERK signaling pathway

S-J. H*., Ph.D., A. P., M.S., E-A. K. Ph.D., J. K., M.S., N. K., Ph.D.
Korea Institute of Ocean science & Technology, Republic of Korea

Inflammation is a pathophysiological defense response against various factors for maintaining homeostasis in the body. However, when continued excessive inflammation becomes chronic, various chronic diseases can develop. Therefore, effective treatment before chronic inflammation development is essential. Bis (3-bromo-4,5-dihydroxybenzyl) ether (BBDE, C14H12Br2O5) is a novel bromophenol isolated from the red alga Polysiphonia morrowii. The beneficial physiological functions of various bromophenols are known, but whether BBDE has beneficial physiological functions is unknown. Therefore, we first investigated whether BBDE exerts any anti-inflammatory effect. We demonstrated that BBDE inhibits inflammation by reducing inflammatory mediators, such as nitric oxide, prostaglandin E2, iNOS, COX2, and pro-inflammatory cytokines (tumor necrosis factor-α, interleukin-1β, and interleukin-6), in LPS-induced macrophage cells. To examine the mechanism of action by which BBDE inhibits inflammation, we confirmed its effect on signal transduction and ROS generation. BBDE selectively inhibited ERK phosphorylation in the mitogen-activated protein kinase pathways. Moreover BBDE suppressed LPS-induced ROS generation in RAW 264.7 macrophage cells. Inhibition of LPS-induced ROS generation by BBDE also caused ERK inactivation and an inflammatory reaction. Therefore, BBDE inhibits LPS-induced inflammation by inhibiting the ROS-mediated ERK signaling pathway in RAW 264.7 macrophage cells and thus can be useful for treating inflammatory diseases.

Presentation Learning Outcome

- Bis (3-bromo-4,5-dihydroxybenzyl) ether (BBDE) is a novel bromophenol isolated from the red alga *Polysiphonia morrowii*
- First confirmed the anti-inflammatory effects of BBDE
- BBDE inhibits LPS-induced inflammation by inhibiting the ROS-mediated ERK signaling pathway in RAW 264.7 macrophage cells

Biography

Dr. Soo-Jin Heo is the Principal Research Scientist of integrate use of marine biomass research group at Korea Institute of Ocean Science & Technology (KIOST). He received his PhD degree from Jeju National University in 2008. In his degree, He studied characterization and identification of valuable bioactive compounds from seaweeds and confirmed these functional activities. Recently, His research project is focused on the development of applied technology for multipurpose industry material using marine organisms to utilize functional foods, pharmaceuticals, and cosmeceuticals.

Main research interest: Identification of bioactive compounds from marine organisms, functional evaluation (anti-oxidant, anti-inflammatory, anti-cancer, anti-diabetes, anti-obesity, anti-hypertensive, anti-wrinkle, and whitening activities).

Saringosterol acetate suppressed hepatocelluar carcinoma growth and metastasis in a zebrafish xenograft model

E-A. K*. Ph.D., J. K., M.S., N. K., Ph.D., A. P., M.S., S-J. H., Ph.D.
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Saringosterol acetate (SSA) can be isolated from an edible brown alga, *Hizikia fusiforme*. In this study, we developed an adult zebrafish human hepatocellular carcinoma (HCC) xenograft model to confirm our previous finding that SSA inhibits tumor growth and metastasis. The zebrafish is one of the most widely used model organisms for drug discovery, molecular genetics, and the screening of human diseases. Established Hep3B cells labeled with the fluorescent tracker CM-Dil were xenografted into the abdominal cavities of zebrafish once every three days for one month. Compared with the control group, the fish injected with Hep3B showed a significant increase in α-fetoprotein (AFP) and factors related to tumor growth and metastasis (IL-6, TNF-α, TGFβ, MMP2, and MMP9). Using the zebrafish xenograft model, we then showed that SSA affected survival rate, AFP production, and the levels of factors related to tumor growth and metastasis via the PI3K/AKT/mTOR and TGFβ/Smad pathways. In conclusion, this HCC model can be used for in vivo experiments to investigate the inhibition of cancer, and SSA isolated from *H. fusiforme* may be useful for the treatment of cancer.

Presentation Learning Outcome

- Saringosterol acetate which is the marine natural product possess anti-cancer properties
- An adult zebrafish human hepatocellular carcinoma (HCC) xenograft model can be used for in vivo experiments to investigate the inhibition of cancer
- Saringosterol acetate may be used as a pharmaceuticals and nutraceuticals

Biography

Dr. Eun-A Kim is the post-doctoral scientist at Korea Institute of Ocean Science & Technology (KIOST). She received her MS and PhD degree from Jeju National University in 2016. She studied functional evaluation such as anti-oxidant, anti-inflammatory, anti-cancer, anti-diabetes, and whitening and safety assessment both in vitro cell lines and in vivo zebrafish model. Recently, she is concerned with development of an evaluation model for functional evaluation using zebrafish model.

Molecular weight characterization of sodium carboxymethyl cellulose by advance polymer chromatography

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Advanced polymer chromatography (APC) is a size exclusion chromatography (SEC) designed by Waters for fast, efficient, and robust polymer characterization. The molecular weight (Mw) separation range is from 100 Da to 2000 kDa and quick switch from one solvent to another solvent is possible. APC shows high reproducibility. By combination of columns with different pore sizes in a single column set, it is possible to adjust the molecular weight separation range for the measured polymer. This poster demonstrates the application of APC for the determination of relative molecular weight distribution (MWD) of Sodium Carboxymethylcellulose (NaCMC), a commonly used pharmaceutical excipient. NaCMC is a linear cellulose derivate functionalized with the sodium acetate groups which make the polymer soluble in water. Depending on the cellulose material source and the degree of the substitution, the NaCMC can vary in MWD which can cause variability in the properties like viscosity, thickening, emulsifying, and suspending-ability in solution.

Firstly, we investigated the elution behaviour of NaCMC and Pullulan standards in several buffers and choose the best eluent for SEC separation on the APC. Secondly, the relative MWD of the NaCMC samples was determined and compared to their viscosity data. Different grades of NaCMC samples were obtained from two vendors. For the calibration for the relative MWD determination the narrow Pullulan standards (peak molecular weight in range 180 – 1 200 000 Da) were chosen. Pullulan as calibration standard was used because its chemical structure is similar to NaCMC, and also high molecular weight Pullulan standards are commercially available. The SEC separations were run on the APC (Waters corp.) equipped with IR-detector.

NaCMC is a polyelectrolyte and showed different elution behavior dependent on the mobile phase. After testing several eluents on the APC column set, it was found that $NaNO_3/NaH_2PO_4$ pH=7 was the most suitable buffer for the separation. The NaCMC samples eluted as a broad peak with a main peak in the high molecular weight range and a tail which combined the middle and low molecular weight range. It is shown that APC is a very fast, reproducible, and powerful tool for the relative MWD determination of the derivates of cellulosic polymers. Variations in MWD of the NaCMC samples could be easily detected with the APC and the results compared with viscosity data.

DISCLOSURE

All authors are employees of AbbVie and may own AbbVie stock. AbbVie sponsored and funded the study; contributed to the design; participated in the collection, analysis, and interpretation of data, and in writing, reviewing, and approval of the final publication.

Presentation Learning Outcome

The application of the novel Advanced Polymer Chromatography (APC) for the aqueous-based SEC separation is shown. APC is a very fast, reproducible, and powerful tool for the relative MWD determination of the NaCMC. Variations in MWD of the NaCMC samples could be easily detected with the APC and the results compared with viscosity data.

Biography

Ekaterina Sobich studied Chemical Biology at the Karlsruhe Institute of Technology, Germany and graduated as Master of Science in 2015. She then joined GGPD NCE Formulation Sciences at AbbVie Deutschland GmbH & Co. KG and has focused on the implementation and application of Advanced Polymer Chromatography for the researches on the polymers and pharmaceutical formulations.

Strategies to increase the passage of large molecules through the blood brain barrier

C. Lombardi[1*], M. Debiossat[1], N. S. Bacot[1], M. Ahmadi[1], N. De Leiris[1], J.L. Lenormand[2], C. Ghezzi[1], M. Moulin[1]
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The diagnosis of Alzheimer's disease (AD), a neurodegenerative disease that affects cognitive functions, remains difficult and the first noticeable symptoms, as well as the detection of current biomarkers, means that brain lesions have already occurred and often for several years. Intensive efforts for the development and the validation of new diagnostic methods to identify early phase of AD, before irreversible brain damage or mental decline, are being conducted. Biomarkers like protein tau oligomers, the toxic form which is present in abnormally large quantities in the brains of people with AD is particularly suitable.

In order to develop a new nuclear radiotracer, the Radiopharmaceutiques Bioclinique Laboratory (LRB UMR UGA INSERM U1039) in Grenoble, France, is interested in the passage of the blood brain barrier (BBB) by large molecules (several kiloDaltons). First of all, several Cell Penetrating Peptides (CPP) have been selected for their potential ability to improve the BBB crossing and to increase their brain availability. A synthetic CPP have also been design to combine and optimize the properties of the previous CPP. A second strategy has been to take the advantage of the trans-epithelial cerebral transport by using a nanobody (Nb), which consists of the unique variable domain of naturally occurring heavy-chain antibodies (Abs) of *camelidae,* binding the transferrin with a high affinity and selectivity. Thus, transferrin will act as a trojan horse.

After the production in *E.coli* and purification, the brain entrance has been followed by different approaches. *In vitro*, cellular models of BBB developed by the BIP facility (Lyon, France) have been used to evaluate the cytotoxicity on endothelial cells with specialized tight junctions as at the front line of the BBB. The molecules able to cross from blood to brain synthetic compartment have been detected by western blot and ELISA assay. *In vivo*, radiolabelling with 99mTc followed by pharmacokinetics and biodistribution experiments, have been carried out in mice as well as brain nuclear imaging by SPECT.

Presentation Learning Outcome

- A synthetic model of Blood Brain Barrier and sensitive methods to follow the passage of molecules are proposed offering new possibility to test rapidly and with high sensitivity the effect of new molecules on the BBB
- This study highlights new issues to improve brain availability of large molecules
- Early stage AD diagnostic is within reach for fundamental research & drug development

Biography

Dr. Charlotte Lombardi studied Biochemistry at the Paris 7 University, France and Structural Biology at the Paris XI University. She received her PhD degree in 2011 after several years of research on viral replication in the team of Dr. Bressanelli at the Molecular and Structural Virology laboratory, France. She then joined the research group of Dr. Dessen at the Institute of Structural Biology (IBS), France, where she studied the type III secretion system of *P. aeruginosa*, at a molecular level to developed new drugs. After four years postdoctoral fellowship at IBS, she finally join the Radiopharmaceutiques Biocliniques Laboratory, France and develop new strategies to deliver large molecules through the BBB.

Peptide functionalized nanoparticles for the selective induction of apoptosis in target cells

Prof Mervin Meyer[1*], Dr Nicole Sibuyi[1], Ms Miché Meyer[1], Dr Ntevheleni Thovhogi[2], Prof Martin Onani[1], Dr Amanda Skepu[3] and Prof Abram Madiehe[1]
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[3]Mintek, South Africa

The unique optical properties of gold nanoparticles (AuNP) can facilitate the development of ultrasensitive imaging-based therapeutic systems. Several studies have demonstrated the application of AuNPs for targeted drug delivery and photothermal therapy (PTT). Consequently, a number of gold nanoparticle-based therapies are currently in clinical trials. In this study we demonstrate the application of AuNPs as multimodal drug delivery systems for the targeted destruction of cells as a treatment for obesity. The multimodal functionality of the AuNPs was achieved by conjugating the AuNPs with two peptides, a pro-apoptotic therapeutic peptide and a receptor targeting peptide. Prohibitin (PHB) is a multifunctional protein, which is over expressed on the surface of the endothelial cells in the White Adipose Tissue (WAT) vasculature of obese individuals. Adipose Homing Peptide (AHP) is a PHB targeting peptide that binds to PHB with high specificity. We previously demonstrated that AuNPs functionalized with AHP accumulated in the WAT of animal models of obesity. We evaluated the selective targeting and toxicity of AuNPs that were bi-functionalised with AHP and a pro-apoptotic peptide (KLAKLAK). We used 3 human cancer cell lines (Caco-2, MCF7 and HT29), of which only one (Caco-2) express PHB. Toxicity was evaluated using the WST-1 and the APOPercentage assays, while the uptake of the nanoparticles was confirmed by ICP-OES and TEM analysis. The cytotoxic activity of the receptor targeted AuNPs was more pronounced in the cells ex-pressing the receptor for AHP. The AuNPs induced significant levels of apoptosis Caco-2 cells, but not MCF7 and HT29 cells. We applied these AuNPs in an animal study and demonstrated anti-obesity effects, which resulted in reduced body weight and reduced adipose tissue mass. This study shows receptor mediated targeting, and the selective destruction of cells expressing the receptor through the induction of apoptosis and the potential for the development of targeted anti-angiogenic strategy.

Presentation Learning Outcome

My presentation will focus on design and application of multimodal drug delivery systems, peptide targeted drug delivery and the therapeutic potential of gold nanoparticles. It will describe preclinical in vitro and in vivo research towards a treatment for obesity.

Biography

Mervin Meyer is a Professor of Biotechnology and Director of the DST/Mintek Nanotechnology Innovation Centre Biolabels Research Unit at the University of the Western Cape (Cape Town, South Africa). His research is focused on the application of nanotechnology to develop nanostructured materials for applications in therapeutics and disease diagnostics. His work in nanotherapeutics involves the development of nanomaterials for the targeted removal of diseased cells through the selective induction of cell death. Prof Meyer also has an interest in the development of nanotechnology-based rapid diagnostic tests for infectious diseases.

Cell-free expression of a membrane antigen for vaccine uses

Géraldine Mayeux[1*], Landry Gayet[1], Lavinia Liguoria[1,2], Marine Odier[1,3], Donald K. Martin[1,8], Sandra Cortès[4], Béatrice Schaack[1,5] , Jean-Luc Lenormand[1]
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Pseudomonas aeruginosa is an opportunistic bacterium and is the second-leading cause of nosocomial infections and pneumonia in hospitals, which are mainly acquired in intensive care units. The pathogen is also responsible for the chronic colonization of the respiratory tract that is a major cause of morbidity and mortality in patients with cystic fibrosis.

Different vaccine strategies such as multivalent DNA vaccines, recombinant fusion proteins, viral vector expressing bacterial proteins or bioengineered bacterial pathogens have been proposed to induce a protection against *P. aeruginosa* infections. However, even though some of these vaccines are still in clinical phases, most of them failed to achieve some specific primary goals and are no longer in trials.

Here, we overexpressed a porin, a well conserved membrane antigen from clinical isolates, in a cell-free protein synthesis system in the presence of liposomes. We used different biochemical and biophysical approaches to demonstrate that this membrane protein is mainly inserted in a correct orientation into the lipid bilayer and harbors a porin activity and native conformation. This expression system produced monomer and oligomer of the protein resulting in the formation of pores of large size and containing a large proportion of the porin into an open channel conformer. Using these recombinant proteoliposomes, we demonstrated that immunization of mice resulted in total protection of these mice against a lethal dose of *P. aeruginosa*. Administration of sera from immunized animals into infected mice was also capable of fully protecting them against lethal infection. These results demonstrate that by using the bacterial cell-free expression system, a production of a fully functional recombinant vaccine against *P. aeruginosa* is feasible.

Presentation Learning Outcome

- Cell-free expression systems represent an attractive alternative to the classical overexpression systems for producing membrane proteins. Limitations in the production of folded membrane proteins for functional and structural studies can be easily overcome by such approaches.
- The production of a bacterial membrane antigen in a cell-free system in the presence of liposomes results in the insertion into the liposome of a fully active protein harboring conformational epitopes which are not present in the composition of the other recombinant vaccines developed so far.
- Immunizations of mice with this recombinant proteoliposome result in a total protection of these mice against a lethal dose of *P. aeruginosa.*
- The vaccine response after administration of the proteoliposome is higher than vaccine platforms developed by other groups or in clinical trials.
- Producing recombinant proteoliposomes in a cell-free system for vaccine use is feasible and easy.

Biography

Géraldine Mayeux is a post-doctoral fellow at TIMC-IMAG laboratory in Grenoble. Her work focuses on the development of neutralizing monoclonal antibodies to an outer membrane protein of *pseudomonas aeruginosa*. She gained a PhD in structural biology and nanobiology at University Grenoble Alpes (UGA) as well as two Master's degrees, one in biomedical sciences obtained at University of Liège (Belgium) and another one in biochemistry and structural biology obtained at UGA. It is during her PhD dedicated to the biochemical and structural characterization of an antiviral restriction factor of the innate immune system that she learned how to deal with membrane proteins.

Thermoresponsive *in situ* Gelling systems for ophthalmic drug delivery

Concepción Renedo* and José Ignacio Perez
Pharmacy and Pharmaceutical Technology, Pharmacy Faculty, University of Seville, Seville, Spain

The administration of drugs through the ocular topical route supposes a considerable reduction of its bioavailability (naso-lacrimal drainage, protection mechanisms of the eye such as blinking and loss towards systemic circulation), which translates into a short therapeutic effect.

Currently, *in situ* gelling systems are being studied as a new alternative for the ocular topical route. They are drug controlled release systems that are in a solution phase before their administration in the eye, and which are transformed into gel after instillation. These systems are based on the use of polymers called "intelligent polymers", which its chain-structure depends on the physicochemical conditions of the environment. The principal stimuli of this mechanism are environmental parameters such as temperature, presence of ions or alteration of pH.

This presentation consists of a detailed bibliographic review of the main polymers used in these systems, focusing in thermoresponsive polymers. The mechanism of action of this type of response to temperature can be explained as follows: The temperature at which the transition from sol to gel occurs is known as gelation temperature.

When the environmental temperature (in this case, physiological temperature of the eye) is higher than the GT, the hydrogen bonds are altered and as a consequence the hydrophobic interactions increase enabling the transition between the sol and gel phases.

The most used and studied thermoresponsive polymers are: Methyl cellulose, Xyloglucan, N isopropylacrylamide and

Poloxamer. Information has been gathered about the optimal concentrations of each polymer in the formula of eye drops.

Likewise, it has been observed how several authors prefer the association of different polymeric materials in order to improve their rheological properties and how this synergistic effect is translated into different commercial preparations.

The gelation involves an increase in viscosity and, therefore, an increase in resistance to naso-lacrimal drainage. This converts them into controlled release systems that prolongs the local action of drugs.

Compared with conventional delivery systems, they have the following advantages: lower frequency of dose administration and greater therapeutic adherence to the patient.

Presentation Learning Outcome

- This presentation is a detailed bibliographic review of what has been researched for now in this area of ocular drug administration.
- Topical ophthalmic drug delivery is a wide field of research and very promising. This research will help others to expand their research or/and teaching.
- This research could simplify the job of other researchers interested in this field and specialists of pharmaceutical technology who work improving the formula of eye drops in Research and Development Departments.

Biography

Miss Concepción Renedo Laguna studied the Double Degree in Pharmacy and Optics and Optometry at the University of Seville, Spain. She obtained Merit with distinction in her Final Degree Project: "Novel in situ gelling systems in ophthalmic preparations", so she was invited to present a poster about her research in "IPAP 18: Innovations in Pharmacy, advances and perspectives" last September in Salamanca, Spain. After that, she was invited to deliver a lecture at the "Andalusian Optometry Conferences" last October in Granada. Then, she studied a master's degree in Pharmaceutical Industry. While she was studying she collaborated with the research group of Dr. José Ignacio Pérez at the University of Seville.

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DAY 3

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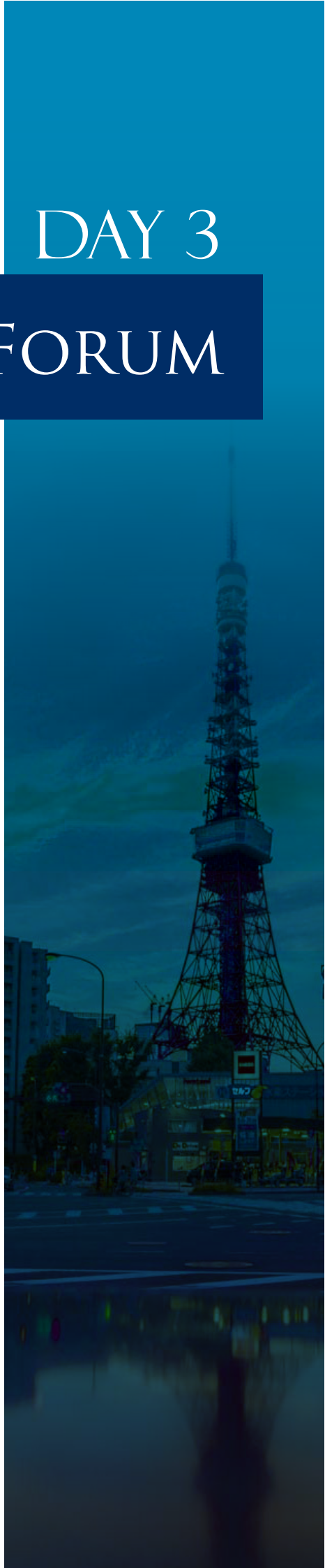
JUNE
24-26, 2019

PARIS, FRANCE



PDDS 2019

Biography

Ülo Langel is a Professor at the Department of Biochemistry and Biophysics, Stockholm University, and at the Institute of Technology, Tartu University. Prof. Langel graduated from Tartu University, Tartu, Estonia, as bioorganic chemist in 1974; he has received his PhD degree twice: in 1980 from Tartu University, Tartu, Estonia (bioorganic chemistry), and in 1993 from Tartu University/Stockholm University (biochemistry/neurochemistry). He is a Honorary Professor at Ljubljana University, Slovenia. He was elected a member of Academia Europaea and foreign member of the Estonian Academy of Sciences.

Cell-penetrating peptides and delivery of oligonucleotides

Ülo Langel

Stockholm University, Sweden

PepFect delivery technology for oligonucleotide transfection by transportan based cell-penetrating peptides *in vitro* and *in vivo* is described. Recent data on mechanisms and applications of PepFect strategies are summarized on the variety of different cargoes including plasmid, antisense and siRNA oligonucleotides. Nanomaterials, including graphene oxides (GOs), and cell penetrating peptides (CPPs) in combination are presented and are shown promising as non-viral vectors for gene delivery. The GO-CPPs serve as an effective platform for gene delivery with high cell transfection efficiency. The protocol is simple, offers high cell transfection compared to the CPPs-ONs complexes and can be used for further improvements using external stimuli.Possible mechanisms of oligonucleotide delivery by PepFects is discussed and novel data on genome analysis involved in these mechanisms are discussed. Further improvement of these technologies of the modulation of gene expression and identification of novel intracellular interactions in tumors after i.v. administration is discussed, aiming to find novel drug targets, and defining New Chemical Entities for drug development.

Presentation Learning Outcome

- PepFect delivery technology for oligonucleotide transfection
- Cell-penetrating peptides

Biography

Dr Larhrib was educated at the University of Sciences and Technology, Lille I and the faculty of Pharmacy, Lille II, France where he obtained an MSc Biochem, DU Pharm, DESS Pharm. Tech., a certificate in Pharm. Chemistry. He moved to the UK to do a PhD in Pharmaceutical technology at Liverpool John Moores University (1994-1998). Following his PhD, Dr Larhrib worked for 4 years (1998-2002) as Senior Research Fellow in Pharmaceutics at the Department of Pharmacy, King's College London. He worked at Liverpool John Moores University as a Senior lecturer in Pharmaceutics for 6 years (2002-2007) before joining the industry; Solid Solution Limited, Liverpool (2007-2010). He was involved in cosmetic products development and manufacture. He moved to Medway school of Pharmacy before joining the University of Huddersfield as a Senior lecturer in Pharmaceutics in July 2011. Dr. Larhrib is a regular reviewer for many international Pharmaceutical journals and member of editorial board of journal of International Research in Medical and Pharmaceutical Sciences, British Journal of Pharmaceutical Research and Journal of Biomedical Research and Practice. He is an academic member of Royal Pharmaceutical Society of Great Britain and Fellow of HEA. He has published more than 30 peer reviewed publications, 30 national and international conferences, four patents and book chapter.

Strategies to improve drug delivery to the lungs from dry powder inhalers

El Hassane Larhrib
University of Huddersfield, United Kingdom

The respiratory route has been used to deliver drugs into the human body for centuries. However, the airways and lungs have a complex physio-anatomical architecture, thus making drug delivery to the lungs more challenging and most current inhalers still suffer from poor drug delivery. The presentation will focus on the progress made to the inhaled formulations and devices to improve drug delivery to the lungs with more focus on dry powder inhalers.

Presentation Learning Outcome

- For asthma alone, the number of people with asthma in the world may be as high as 334 million (The Global Asthma Report (GINA), 2014). And in the UK about 5.4 million people suffer from asthma, of which 1.1 million are children. Despite improvements made in inhaler devices and formulations, drug delivery to the lungs is still low. In this talk we will discuss the formulations and devices which will of interest to the formulation scientists, engineers and patients affected by asthma or chronic obstructive disease.
- Particle engineering and formulations can be applied to areas outside inhalation. Those researchers starting in the inhalation can learn some skills which can use in their research. Those with experience in the field can enhance their knowledge in the area and those working in other dosage forms can apply the knowledge to their specific area.
- The information gained from the talk or discussion group can be used for both teaching undergraduates students and research. The talk will help the engineers improving design of their inhaler devices, formulation scientists will learn different ways making formulations for inhalers. Such knowledge is transferable to other pharmaceutical formulations areas.

Pharmaceutical applications of graphene-based nanomaterials in cancer theranostics

Marlene Lúcio
CF-UM-UP, Portugal

After its astonishing and unexpected discovery in 2004, graphene, a two-dimensional nanomaterial made of single-layered carbon molecules organized in a honeycomb cross section, has been broadly investigated for an incredible number of uses including quantum material science, nanoelectronics, energy storage and chemical processes. Since the first reported study on the utilization of graphene as a drug delivery system for cancer chemotherapy in 2008, graphene and graphene-based nanomaterials (GBNs) have likewise enraptured the excitement of specialists for its promising biomedical applications, translatable in an expanding number of published studies. GBNs include graphene derivatives, such as graphene oxide (GO), nanographene oxide (NGO); reduced graphene oxide (rGO) and graphene quantum dots (GQDs). GBNs show unique chemical nanosheet-like structure and remarkable physical and optical properties that lead to numerous potential pharmaceutical applications. Among different pharmaceutical applications, theranostic uses of graphene in cancer treatment and diagnosis have pulled in consistently expanding interests throughout the most recent years. In this talk, the optical properties of GBNs and the advantages of these emerging luminescent nanomaterials are explored, namely their large surface area that enable the conjugation with a large diversity of functional groups. Further advantages comprise excellent biocompatibility, high near infrared absorption capabilities and its inherent fluorescent properties that allows monitoring the cellular uptake of these nanocarrier systems. After presenting the unique photophysical and physical-chemical characteristics of GBNs I will offer an outline of recent progresses and pitfalls in uses of graphene in pharmaceutical applications with spotlight on cancer therapy and diagnosis. Finally, a critical comment on the difficulties and points of view for future research and clinical translation in this field will be provided.

Biography

Marlene Lúcio graduated in Pharmaceutical Sciences at Faculdade de Farmácia da Universidade do Porto, Portugal in 1999 and received a PhD degree in 2006 at the same institution. In 2008 she was awarded for her research after a selection of leading young scientists of the EuChems Award competition. Since 2013 she has been working as Associate Researcher at Centre of Physics of Universities of Minho and Porto (CF-UM-UP) and as Invited Associate Professor of Department of Physics of UM (from 2015). She has a publication record of 62 papers in SCI journals, 5 book chapters, and over 1400 citations (h-index=22).

Presentation Learning Outcome

- This talk will provide audience with the capacity to understand the physical-chemical properties of different GBNs, being able to distinguish the different GBNs types, main preparation methods and advantages or disadvantages of each GBN type.
- Audience will learn the inherent advantages and limitations of therapeutic strategies (drug and gene therapy, phototherapy (PTT), magnetic hyperthermia (MHT), photodynamic therapy (PDT)) and diagnostic strategies (therapy guiding by fluorescence imaging (FI), two photon fluorescence imaging (2PFI), infrared thermal imaging (IR-TI), Raman imaging, magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), computed tomography (CT), photoacoustic imaging (PAI) and ultrasound imaging (USI)) that are being used in nanotheranostic systems for cancer. Audience will also learn how the combination of complementary strategies can result in a synergic theranostic effect.
- The promises and the pitfalls of GBNs translation to clinics will be presented together with a short tutorial of guidelines that should be followed by those that are developing or wish to develop GBNs systems for pharmaceutical applications. The aim is to provide a more rational and standardized design strategy of the nanotherapeutic systems.

Biography

Amanda Silva obtained a degree in Pharmacy in 2005 and a PhD in Pharmaceutical Technology in 2008 both from UFRN, Natal, Brazil and a second PhD in Cellular and Molecular Biology in 2010 concerning polysaccharides for thermo-controlled cell culture at Université d'Evry/Université Paris V. She worked as a postdoctoral fellow on drug-loaded magnetic EVs for image-guided therapy. She is currently a tenured CNRS researcher and works on EVs engineered with nanoparticles and drugs as drug delivery vectors for cancer therapy and regenerative medicine. She has 47 publications, 2 book chapters, 6 pending patents, >1000 citations and a H-factor of 19.

Designing extracellular vesicles for bio-camouflaged drug delivery and cell-free regenerative medicine

Amanda Silva Brun
CNRS, Université Paris-Diderot, France

Extracellular vesicles (EVs) are multifaceted subcellular entities that may represent a new generation of bio-camouflaged drug/nanoparticle delivery system and regenerative medicine effectors. In a top-down procedure, our group has engineered nanoparticle/drug-loaded EVs from precursor cells previously loaded with this cargo. EVs from HUVEC cells and THP1 macrophages were tested for anti-tumor therapy. Concerning regenerative medicine, EVs were obtained from adipose stem cells and tested in a fistula model. By using our method, EVs could encapsulate a set of nanoparticles regardless their chemistry or shape. These hybrid vesicles were able to generate heat when submitted to an alternating magnetic field and could be monitored by fluorescence imaging or MRI. Dual drug/nanoparticle EV loading was also feasible by this method. We demonstrated that vesicles from THP-1 cells could be loaded with iron oxide nanoparticles and different therapeutic agents irrespective to their molecular weight, hydrophobic, hydrophilic and amphiphilic character. The theranostic potential of mTHPC-loaded magnetic EVs was tested *in vivo* in a murine tumoral model. Vesicles could be tracked *in vivo* by dual-mode imaging, combining optical imaging and MRI. The engineered EVs were found to induce an efficient photodynamic action, as evidenced by tumor growth curves and histological analysis. The regenerative properties of EVs obtained from adipose stem cells was demonstrated in a fistula model. In brief, we succeeded in customizing EV by engineering them to display several nanoparticle/drug cargoes featuring therapeutic and imaging properties both *in vitro* and *in vivo*. EV regenerative effect was for the first time demonstrated for fistula therapy.

Presentation Learning Outcome

- How we can convert biological messengers into a bio-camouflaged delivery system
- About production and engineering methods to do so
- In vitro and In vivo properties of the designed extracellular vesicles

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DAY 3

SPEAKERS

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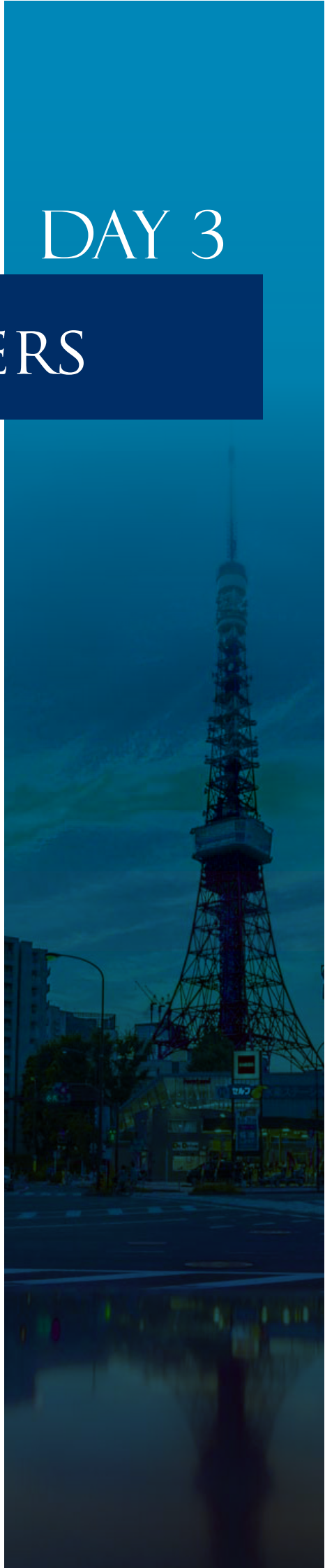

Antibody-guided discovery of potent small-molecule fusion inhibitors of influenza virus

Maria van Dongen
Discovery Sciences, Janssen Research & Development, The Janssen Pharmaceutical Companies of Johnson & Johnson, Beerse, Belgium

Influenza therapeutics with new targets and mechanisms of action are urgently needed to combat potential new pandemics, emerging viruses, and constantly mutating circulating strains. We report here on discovery and structural characterization of potent peptidic and non-peptidic small-molecule inhibitors against influenza hemagglutinin (HA). Guided by structural knowledge of the interactions and mechanism of anti-stem broadly neutralizing antibodies (bnAbs) CR6261, CR9114 and FI6v3, we selected and optimized molecules that effectively mimic the bnAb functionality. Our lead compound neutralizes influenza A group 1 viruses by inhibiting HA-mediated fusion in vitro, protects mice against lethal and sublethal influenza challenge after oral administration, and effectively neutralizes virus infection in reconstituted 3D-cell culture of fully differentiated human bronchial epithelial cells. Co-crystal structures with H1 and H5 HAs reveal that the lead compound recapitulates the bnAb hotspot interactions.

Presentation Learning Outcome

- We present proof-of-concept for antibody-guided, small molecule discovery. Starting from a well-characterized antibody with a desired activity profile, we selected and further improved a small molecule 'antibody mimetic' that recapitulates the antibody features *in vitro* and *in vivo.*
- The approach addresses the common challenge of effective targeting biologically validated molecular targets by pharmaceutically relevant modalities. The success of this approach demonstrates the advantage of rigorously considering the targeted epitope-specific binding activity in close combination with the associated functional activity and mechanism of action, instead of focusing on potency alone. The strategy allows for the generation of robust structure-activity relationships, thereby yielding a great level of control over the pharmacodynamic and pharmacokinetic properties of the selected ligand classes.

Biography

Maria was appointed Director, Discovery Sciences in Janssen Research & Development in 2016, to lead multiple early drug discovery programs, and where she presently leads the Discovery Sciences' External Innovation team. Before her current role, she served as member of the Jansen Prevention Management Team, Head of Preventive Interventions and led global teams working to deliver preclinical proof of concept for innovative products, focusing on small molecule drugs and B-cell vaccines. During her tenure, she brought distinguished small molecule discovery expertise to the specific needs related to preventive interventions and played a pivotal role in research that resulted in innovative antibody-guided drug discovery. Prior to joining Janssen, Maria held scientific positions in pharmaceutical research organizations, including Abbott, Solvay Pharmaceuticals, Biovitrum, Pharmacia Corporation and Pharmacia & Upjohn. She holds a Ph.D. in biophysical chemistry from the Radboud University Nijmegen, the Netherlands.

Targeting liver function to circumvent neuronal and cardiac dysfunctions linked to hyperhomocysteinemia

Nathalie Janel*, YuChen Gu
Univ Paris Diderot, Sorbonne Paris Cité, Unité de Biologie Fonctionnelle et Adaptative (BFA), UMR 8251 CNRS, F-75205 Paris, France

Hyperhomocysteinemia is well recognized as an independent risk factor for cardiovascular diseases and is associated with diverse dysfunction. It's the second most common amino acid metabolic disorder. If it is not treated, the life expectancy of these patients is greatly reduced, and cardiovascular events are the leading cause of death. However, all patients suffering from severe hyperhomocysteinemia do not respond favorably to drug treatments currently given. In order to protect the cardiovascular system from hyperhomocysteinemia, new substances with protective properties on both the vascular system and the cardiac system are sought. Our research program meets this need and find its originality by an innovative approach to biotherapy which could be considered a definitive and curative treatment, unlike a pharmacological approach. Plasma homocysteine level is an important reflection of hepatic methionine metabolism and the rate of processes modified by B vitamins as well as different enzyme activity. Reduction of homocysteine levels is the key objective in treatment of hyperhomocysteinemia. The liver is a central organ of metabolism and many metabolic diseases have their origin in the liver, although the clinical manifestations are extrahepatic. We recently found a negative correlation between plasma homocysteine level and the hepatic expression of an anti-inflammatory protein, Dyrk1A. Many studies indicated that overexpression of Dyrk1A, a serine/thronine kinase involved in diverse functions ranging from development and growth to apoptosis, not only causes developmental defects with life-long structural and functional consequences, but also contributes to neurodegeneration, neuronal death and loss of function observed in multiple neurodegenerative diseases. The proof of concept has already been obtained in mice by the use of an adenovirus adapted to murine model. It is now necessary to transfer technology to a vector applicable in humans that also will serve for preclinical studies. To do this, we decided to use a gene transfer strategy with a specific hepatic adeno-associated viral (AAV) serotype 8 vector expressing Dyrk1A to analyze the effect of this selective homocysteine lowering therapy upon molecular mechanisms linked to Dyrk1A overexpression in brain and heart of hyperhomocysteinemic mice. We conclude that specific hepatic Dyrk1A gene transfer restores the molecular mechanisms altered in brain and heart of hyperhomocysteinemic mice. The positive effect on plasma homocysteine and brain and heart signaling pathways demonstrates that this gene therapy can constitute a useful approach for prevention of cardiovascular diseases and neurodegenerative processes linked to hyperhomocysteinemia.

Biography

Nathalie Janel is professor at the university Paris Diderot in the research unit of functional and adaptive biology. She is currently director of the bachelor's degree in Biology. She has a long-standing interest in the study of biochemical and physiological consequences of genetic alterations which lead to functional alterations affecting liver, vessels and brain. Her group is focusing on studying dysregulated signaling pathways in metabolic and cognitive diseases and develops a translational research to establish blood biomarkers. She is currently working on finding therapeutical strategies with viral vectors in order to specifically modulate these dysregulated pathways at the cellulal level. She has published more than 80 research articles in SCI(E) journals.

Detection of "Hidden" Drug Resistance by the EZMTT assay

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Drug resistance has become a serious public health problem in cancer therapeutics and bacterial infections. The main issue is that with the current cell proliferation assays, such as Cell-Titer Glow, MTT and turbidity assays, it is not simple to monitor minor changes in growth. Therefore, we have optimized an EZMTT-dye based detection method, that can continuously measure time-dependent growth after drug treatment and reliably detect partial drug resistance (5-20% growth) for, M. tuberculosis, other bacteria and cancer cells. The assay provides facile measurement of the doubling time and cell density required for exponential growth. Importantly, tracking time-dependent growth after drug treatment demonstrates that KGA allosteric inhibitors alone failed to completely inhibit cancer cell growth, but drug combinations are able to provide complete inhibition *in vitro* that translate well *in vivo*. In conclusion, this simple EZMTT method provides a rapid and precise determination of drug efficacy and has great potential to be developed for medical diagnosis and drug screening to help meet the unmet medical need against drug resistance.

Presentation Learning Outcome

- The EZMTT-based cell viability assay is a true continuous assay that may be used to generate cell growth curves easily and precisely under various conditions. Its sensitivity is 10-30 times better than that of the bacterial turbidity assay, so that minor drug resistance can be detected reliably. Researchers (Scientists, doctors, students) can use the EZMTT method to investigate the growth condition-induced changes in cell proliferation, and applications in biomedicine, including cancer, aging, drug resistance, drug discovery, environment contamination, material bio-compatibility, fermentation, immunology, etc.
- The EZMTT method is simple, reliable and precise. With one step addition of the reagent, scientists can follow cell growth from a single well for hours, days, or weeks. The method is high throughput and makes the measurement of doubling time and drug induced proliferation rate very easy. The EZMTT method is a great tool to help "visualize" the effect of growth conditions and to obtain data for cutting-edge research or teaching. The high sensitivity reveals "hidden" drug resistance and facilitates drug discovery and clinical diagnosis.

Biography

Dr. Benfang (Bennie) H. Ruan holds a doctorate in Biochemistry and Bioanalytical Chemistry from Rice University and completed post-doctoral research in Molecular Biology and Biophysics at Yale University. From 2005 to 2013, she actively worked as a scientist/project leader in therapeutic area of drug discovery at Wyeth/Pfizer and then at Forma Therapeutics. In 2013, she won the Distinguish Global Expert Award from Zhejiang Province and accepted a full professor position at Zhejiang University of Technology. Now she has published 50 research articles and leads a 20-member research team working on tumor metabolism and drug discovery.

New indications for FDA-approved drugs: Selective inhibition of the growth of *Helicobacter pylori* by covalent allosteric regulation of urease

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To date, little attempt has been made to develop new treatments for *Helicobacter pylori (H. pylori)*, although the community is aware of the shortage of treatments for *H. pylori* and the increase in drug resistance of gram-negative bacteria. Thus, there is an unmet need to identify new potent inhibitors with a safe profile to control *H. pylori.* In this study, we developed a high-throughput assay for urease, an enzyme that is a known virulence factor of *H. pylori*. The assay is established on a previously-reported 192-tandem-well plate for gas-releasing enzymes. After executing a high-throughput screening of 1,563 clinically approved drugs with this assay, we identified three drugs that could potently inhibit the urease of jack bean, *H. pylori* and *Ochrobactrum anthropic.* The newly identified inhibitors, have an IC_{50} of 0.4 μM and 2.3 μM, and are ~400 and 70-fold more potent than acetohydroxamic acid (AHA), a well-known urease inhibitor and clinically used drug for the treatment of bacterial infection. Interestingly, a consistently new mode of action was found to rely on covalently and allosterically modifying the non-active-site Cys residue. These drugs as well as its newly synthesized derivatives could inhibit the growth of *H. pylori* much more efficiently than AHA, without affecting the growth of the urease-negative *E. coli* strain, and prevent *H. pylori* infection of human gastric cells. This study offers several bases for repurposing the old drugs to develop new treatments for urease-containing pathogens and to study the mechanism responsible for the regulation of urease activity.

Presentation Learning Outcome

- Cutting-edge technology and knowledge on assay development and high-throughput screening
- A newly developed tandem-well-based assay for NH_3-producing enzymes
- New indications of two clinically used drugs on inhibiting the growth and infection of *H. pylori*

Biography

Dr. Fang Wu obtained PhD degree from the Department of Biochemistry, University of Zurich (UZH) in 2007. He became a postdoctoral scientist in the Department of Organic Chemistry, University of Basel and in the Brain Mind Institute, Swiss Federal Institute of Technology (EPFL) during 2008-2010. He starts to carry out his independent research at the Shanghai Center for Systems Biomedicine, Shanghai Jiao Tong University since 2011.

His current research focuses on the development of new drug leads targeting enzymes and studying their underlying mechanism in the related diseases (ysl.sjtu.edu.cn). He has identified several novel inhibitors for enzyme targets involved in various diseases, e.g. cancer, neurodegenerative diseases by using novel high-throughput bioassays, and uncovers few underlying mechanisms for drug resistance and the regulation of amyloid beta generation with the pharmacological probes. The research work has been published in FASEB J, Chemical Communications, J. Med. Chem., Cell Death and Disease, ACS Chemical Biology, JBC or ChemBioChem. Dr. Fang Wu is currently serving as an Editorial Board Member of Chemical Biology field for Scientific Reports.

Chimeric antigen receptor(CAR)-T CELL; a biodrug as cancer therapeutic agent

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A class of fastest growing therapeutic agents, biodrugs are the complex molecules derived from living organism or its products, used in the prevention diagnosis and treatment of cancer or other diseases. These biodrugs include a vast variety of molecules including antibodies, cells, interleukins, vaccines and various proteins. The therapeutic molecules have revolutionized the treatment of many serious and chronic illnesses and have nudged the traditional drugs. Rheumatic arthritis, certain cancers, and diabetes are the diseases having greatest number of dedicated biologic treatment drugs.

Crossing through threshold in clinical activity, chimeric antigen receptor modified T cells have emerged as a new effective therapeutic regimen against various types of cancer both in adults and pediatric oncology. Currently available CARs are designed in a manner so as to be capable of MHC independent antigen recognition and incorporate costimulatory signal, converting the transduced T cells with potent T cell activity. There are three generations of CAR-T cells depending upon intracellular signalling domain number. They have higher efficacy than monoclonal antibody and antibody-drug conjugate. CAR therapy maintained especial status as cancer immunotherapeutic agent, after targeting the CD19 cell surface molecules expressed in a various types of cancers and, successfully transforming in clinic practice. Standing on the pillars of genetic engineering, T cell biology, molecular biology, tumor biology, target identification, CAR-T therapy holds great promise as off the shelf cancer therapeutic agent. But several unresolved concerns are still prevailing. Various issues with regard to safety, efficacy and their preparation, quality control issues, are still stucking the way. Cytokine release syndrome, neurological toxicities are few major side effects of the therapy blocking the successful development of CAR-T cells in the clinical trials. Our presentation shall be dealing with structural aspects of CAR T cells, target and signalling, their toxicity perspectives and current status.

Presentation Learning Outcome

- In the present lecture an extensive analysis of one of the most efficient anticancer biodrug, the chimeric antigen receptors and its current status has been done. From this we can surely gain insight into the successful strategies so far available to bring this innovative biodrug in the market.
- Well many challenges still persist for the researchers working in the area. The way is not likely to be straightforward due to on/off tumor targeting and toxicity and hostile microenvironment of the cancer cells leading to less efficacious response. Cost and complexity of these product is another issue to be taken into consideration to further execute the studies in this direction to come up with the solution.

Biography

Dr. Preeti Sharma is currently working as Associate Professor, Department of Biochemistry, Santosh Medical University, Ghaziabad, deeply involved in teaching and research. Her area of research includes drug metabolism and inflammatory markers. She did her doctorate research from renowned world class institute 'Central Drug Research Institute',Lucknow, under the aegis of CSIR, New Delhi India, in the Department of Medicinal Chemistry and awarded Research Fellowship. She has more than 75 publications (research and review articles) and few in phase of communications with high citation. She also wrote 2 books on bioorganic chemistry and immunology. She is credited with a number of ICMR-STS funded projects and guided and co-guided a number of Ph.D and MD students.

Freshwater Sapropel as raw material in medicine and pharmaceutical production

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Sapropel is natural remedy that has been applied externally via different topical applications or as a base for mud bath in skin care and health improvement procedures and can be classified as traditional remedy. Sapropel forms over long period of time in shallow waters by slowly decomposing organic sediment and has different compositions depending on the location of the lake, its surroundings, the water regime and the location of the sample in the sediment strata.

There is a revived interest in sapropel during the last decades and a steady growth in its use and popularity in medicine, rehabilitation and skincare. There are reports about the extraction of active ingredients from the sapropel for the use in cosmetic and pharmacological products. According to modern practice raw material control and quality assurance are essential and have to be developed for sapropel as raw material in medicine and pharmacology.

This work attempts to test and standardize freshwater sapropel from 5 different lakes in Latgale, eastern Latvia, for the use in medicine and pharmaceutical industry. Official geological survey of Latvia lakes from Latvian lake database *(ezeri.lv)*, were used in the selection of lakes. The main selection criteria were sapropel deposits depth, hydrological regime, the history of agriculture next to lake and the potential exposure to industrial waste. 105 sapropel samples were obtained from 5 lakes during the winter time.

The following factors were identified for standardizing and describing sapropel: organoleptic testing (look, consistence and smell, coarse composition test), test for heavy metal residue, test for pesticide residue, bacteriological test) and pH.

Pb, Cd, Co, Ni, Cu were present in all samples none of the metals exceeded maximum acceptable level. Some samples showed the presence of DDT pesticide. Sapropel is still a living material with its specific biome and microbiological flora that is not yet identified in details. Coarse testing of the samples is ongoing; results will be available at the end of our study. pH level is between 7 – 8.

Humic, fulvic acid content - The concentration of humic and fulvic acids in samples are different in various mining sites, and sapropel strata levels.

Several storage temperatures ranging from room temperature to -20C were tested. 4C without exposure to light and oxygen were sufficient for preserving sapropel. In detail studies of the microbiological flora can give further insight in this issue.

Conclusion:

Once the sapropel site has been tested by grid of samples from different positions in the lake and different depth and the site is certified, sapropel from the site can be used as a quality assured raw material for medicine and pharmacology. Each batch has to be tested organoleptically and by pH to ensure that sapropel corresponds to the certified site. Extended tests for the certification of the site should consist of organoleptic testing, heavy metal residue testing and pesticide testing and bacteriological testing for presence of harmful bacteria. Analytical testing for humic/fulvic content as well as other analytical can be included in the site characteristic.

The research was co-financed by project "Analysis of characteristics of medical sapropel and its usage for medical purposes and elaboration of industrial extraction methods", No.1.1.1.1/16/A/165

Presentation Learning Outcome

- Audience will learn about sapropel as a traditional remedy that can be standardized according to modern requirements in the health and pharmaceutical industries. Audience will gain better understanding what sapropel is and how to characterize it.
- Audience will be able to apply the results and methods in the evaluation and use of sapropel as raw material in medicine and pharmacy and what potential usage in pharmacy and medicine it has as raw material.
- Our study gives guidelines how to characterize raw sapropel for medical and pharmaceutical purposes thus it can be used in teaching and courses on the use of natural and traditional remedies and give useful information for developing medical and pharmaceutical applications based on sapropel and its active ingredients.

Biography

Dr. Agris Auce, studied physics in the University of Latvia, graduated in 1989. PhD in Nuclear Physics in 2004 from the Uppsala University, Sweden for the experimental work with the Gustaf Werner Cyclotron in the The Svedberg Laboratory, Sweden and iThemba medical and isotope production cyclotron in South Africa. In 2006-2008 was scientific leader for Latvia cyclotron project intended for the production of medical isotopes. In 2000 -2013 with partners developed SIA Silvanols, the most successful pharmaceutical startup company in Latvia specializing in natural remedies based products. Now leading researcher at Riga Stradins University and University of Latvia.

P-selectin targeted nanocarriers are efficient drug delivery systems to activated endothelium

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Inflammation is a common process associated with numerous vascular pathologies. During the vascular inflammation process, endothelial cells (EC) express both the receptors for advanced glycation end products (RAGE) and the cell adhesion molecule P-selectin that initiate and perpetuate inflammation by promoting leukocyte infiltration into the vascular wall. We questioned whether P-selectin could be employed as a target for nanotherapeutic intervention. We hypothesized that targeting the inflamed endothelium by coupling a peptide with high affinity for P-selectin to the surface of nanocarriers entrapping anti-inflammatory agents will highly increase their specific binding to activated EC and reduce the cell activation. Therefore, our aim was to develop suitable nanocarriers to perform specific and effective delivery of therapeutic agents to dysfunctional EC. We developed and characterized lipid-based nanoparticles directed towards P-selectin and used them as vectors for specific delivery of dexamethasone or small interfering (si) RNA/short hairpin (sh) RNA for RAGE and monitored their anti-inflammatory effects in vitro using cultured endothelial cells and in vivo using mouse models. Our results showed that nanocarriers directed to P-selectin bind specifically to activated endothelium and are functional in delivering the cargo (dexamethasone and RAGE-siRNA/shRNA) to EC, reducing the expression of proinflammatory genes and preventing the monocyte adhesion and transmigration to/through activated EC. The distribution of P-selectin targeted nanocarriers in different organs was assessed by an IVIS Imaging System at 1 hour after intravenous (i.v.) injection of fluorescently-labelled nanocarriers into a mouse model of acute inflammation (lipopolysaccharides (LPS) i.v. administered in C57BL/6 mice) and ApoE-deficient mice. Given i.v. in mice with acute inflammation, dexamethasone-loaded lipid nanoemulsions directed towards P-selectin accumulated at a significant high level in the lungs (compared to nontargeted nanoemulsions) and significantly reduced mRNA expression level of key proinflammatory cytokines such as IL-1ß, IL-6, and MCP-1. To silence the expression of RAGE, a mixture of five plasmids that contain different RAGE-shRNA sequences was used to obtain lipoplexes with P-selectin targeted cationic liposomes (Psel-lipo/RAGE-shRNA) that were i.v. injected 2 times/week for 4 weeks in ApoE-deficient mice. The treatment with Psel-lipo/RAGE-shRNA specifically downregulated RAGE in the aorta and liver of mice and did not significantly alter the weight and the liver and kidney function. In conclusion, nanocarriers directed to P-selectin are efficient vectors for delivery of various therapeutic agents to activated endothelium. Acknowledgments. The work was supported by UEFISCDI, 13PCCDI/ 2018 (INTERA) and PN II-RU-TE-2014-4-1837 (NANORAGE) projects.

Presentation Learning Outcome

- Vascular endothelium is an ideal target for therapeutic interference in chronic inflammation
- P-selectin is an appropriate target for nanotherapy
- Design of targeted lipid-based nanoparticles to carry small molecules or nucleic acids to vascular endothelium

Biography

Dr. Călin studied Physics at the University of Bucharest and graduated as MS in Biophysics in 1996. She then joined the research group of Institute of Cellular Biology and Pathology "N. Simionescu", Bucharest where she received her PhD degree in Biological Sciences in 2005 under supervision of Dr. Maya Simionescu. Then she performed a 3-year post-doc in "Biomaterials: nanocarriers with controlled drug release" at the Institute of Macromolecular Chemistry "Petru Poni", Iasi, Romania. In present, she is principal investigator, head of "Medical and Pharmaceutical BioNanoTechnologies" laboratory and member of the Scientific Council of the ICBP "N. Simionescu". She received 10 national and international prizes, and published 44 papers in ISI journals, cited >1080 times (as per Google Scholar).

Development of novel leads for triple-negative breast cancer immunotherapy

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Breast cancer ranks first of all cancers among women in the world in incidence and mortality. It is still on the rise year by year. Triple negative breast cancer (TNBC) comprises around 15~20% of breast cancers. It is characterized by a poor prognosis, high rates of proliferation and metastases. However, no FDA-approved targeted therapies are currently available for TNBC.

CCL5 and CCR5 are highly expressed by breast tumor cells, and involved in the disease progression, relapse and metastasis, particularly in TNBC. Our previous work from a mouse TNBC model indicates that CCL5 induces immunosuppression principally by promoting the generation of myeloid-derived suppressor cells (MDSCs, $CD11b^+$, $Gr\text{-}1^+$), which accumulate in many cancer patients and exert a variety of immunosuppressive mechanisms. In addition, systemically blocking of CCL5 with a murine monoclonal antibody profoundly suppresses the primary mammary tumor growth. Our recent work has further conceptually demonstrated that the CCL5/CCR5 signaling axis in MDSCs represents an excellent target for TNBC immunotherapy. Inhibition of the CCL5/CCR5 axis in a mouse model of TNBC resulted in strong reductions of MDSCs and regulatory T cells, while increasing tumor-infiltrating $CD8^+$ T cells and improving their cytotoxic potency. Moreover, we have developed a high-throughput screening assay for discovering novel antagonists of CCL5-CCR5 signaling. Through the screening of about 2,200 clinically approved drug, three drugs were identified. The new finding provides us the potential mechanism for these drugs in TNBC immunotherapy.

Presentation Learning Outcome

- The new targets for TNBC immunotherapy
- The novel antagonists of CCL5-CCR5 signaling
- New indications of three clinically used drugs on inhibiting the CCL5-CCR5 signaling

Biography

Dr. Jing Yu received her PhD degree in drug discovery from the University of Basel (Switzerland) in 2008, and then she commenced her two-year postdoctoral work in drug delivery for delivery of large molecules (including cells & antibodies) at the University of Geneva (Switzerland). Now she is an Associate Professor at the Shanghai Jiao Tong University, China. Her research focuses on the drug discovery and mechanism studies of lead compounds for novel drug targets, as well as drug delivery. Her original research works have been published in the top journals of these fields. In addition, she has applied for 5 patents and all of them have been authorized from China and the United Kingdom now.

Screening of new peptidomimetics based on kinase-inhibitory region of suppressors of cytokine signaling 1 as anti-inflammatory agents

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SOCS (Suppressor Of Cytokine Signalling) proteins are negative feedback regulators of the JAK (Janus kinase)/STAT (Signal Transducer And Activator Of Transcription) pathway. Their expression levels are low under physiological conditions, but they are up-regulated in response to cytokine stimulation in many immune and inflammatory processes. Unlike the other SOCS proteins, SOCS1 and SOCS3 show a small kinase inhibitory region (KIR) involved in the inhibition of JAK kinases. Drug discovery processes of compounds based on KIR sequence developed a peptidomimetic called PS5, as lead compound resulting promising in functional *in vitro* and in inflammatory animal models. On the basis of this lead compound, several peptidomimetics have been designed bearing new structural constraints that were analyzed in both affinities toward JAK2 (through different biochemical assays) and conformational features through Circular Dichroism and NMR spectroscopies. To shed light on the anti-inflammatory actions of PS5, these compounds have been tested in the most abundant cells of blood vessels involved in inflammatory vascular diseases, VSMCs. These experiments revealed the specificity of action of PS5 as mimetic of the entire SOCS1, since it demonstrated able to reduce STAT1 and STAT3 phosphorylation and their nuclear translocation. Among these mimetics, several cyclic analogues of PS5 showed better anti-inflammatory functions suggesting that the presence of a steric hindrance and aromatic group, as naphthyl group, improves proteases' resistance. Overall data prompted us to generate more constrained peptides with increased rigidity to build up a model of the pharmacophore, also with the help of docking studies, to design suitable modifications to achieve selective inhibition of JAK2's activity. As preliminary results, new analogues containing different intramolecular cycles have been designed and tested as new and more potent peptidomimetic of KIR-SOCS1.

Presentation Learning Outcome

- The audience will greatly appreciate this simple low-cost strategy for developing lead compounds with high affinities towards targets
- The audience will be able to understand the benefits in multidisciplinary approaches to the screening of new active molecules

Biography

Dr. Scognamiglio studied Pharmaceutical Chemistry and Technologies at the University of Naples "Federico II", Italy and graduated as MS in 2008. She received her PhD degree (Drug's science) in 2011 at the same institution. During the PhD program, she joined the research group of Dr. Oren Scherman at the Department of Chemistry in Cambridge (UK). After one year postdoctoral fellowship supervised by Dr Marasco at the University of Naples "Federico II" Italy, she joined the research group of Prof. Paolo Netti at the Center for Advanced Biomaterials for Health Care, Istituto Italiano di Tecnologia, Naples, Italy. She has published more than 30 research articles in peer-reviewed journals.

Novel small molecules for PPARs modulation and their potential use for treatment of metabolic disorders

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Peroxisome Proliferator-Activated Receptors (PPARs) are ligand-activated transcription factors that play a pivotal role in the regulation of glucose homeostasis and lipid metabolism and so they are considered as suitable targets for the treatment of metabolic disorders. These receptors have also been shown to be implicated in cellular proliferation, differentiation, tumor promotion, apoptosis and immune reaction/inflammation. Most recently, it has been highlighted that they also may be involved in the pathogenesis of various disorders of the central nervous system including multiple sclerosis, Alzheimer's and Parkinson's disease.

The search for synthetic ligands towards the different PPAR subtypes (α, γ, δ) has been therefore very extensive and led to the identification of a large number of powerful and selective ligands some of which are currently in therapy as hypolipidemic (PPARα agonists) and antidiabetic (PPARγ agonists) agents. However, subsequent studies have highlighted the important side effects linked to the use of selective and powerful PPAR full agonists, effects that can nullify their therapeutic utility. Therefore, current lines of research focus on the modulation of these receptors as well as the simultaneous activation of different subtypes that seem to be more beneficial for the dissociation of therapeutic activity from adverse side effects.

In this context, for many years our research group has been interested in the synthesis and biological activity of new compounds showing multiple activity towards PPAR receptors. In particular, we identified the lead compound LT175, a dual PPARα/γ ligand with a partial agonism profile toward the γ subtype, that showed an improved therapeutic profile and reduced side effects compared with standard PPARα and PPARγ ligands.

Here we report a novel series of LT175 analogs among which we identified a new ligand whose biological activity was assessed by transactivation assay, gene expression analysis and glucose uptake, inhibition of Cdk5-mediated phosphorylation of PPARγ, and coactivator recruitment assays.

Interestingly, X-ray studies of the complex with PPARγ showed the possibility for this ligand to bind an alternative site besides the canonical one. Although the pharmacological utility of the PPARγ alternative site remains unclear, it is possible that ligands binding this site might favor a correct balance of coactivator and corepressor binding or synergize with endogenous canonical ligands to provide a unique functional activity profile.

Thus, the development of a new generation of PPARγ drugs as alternative modulators targeting non-canonical sites of the ligand binding domain could be a promising approach to address safety concerns and therapeutic profile.

Presentation Learning Outcome

- Synthetic methods and characterization of chiral compounds
- Use of small molecules to treat metabolic diseases
- Novel applications for PPAR ligands in therapy

Biography

Dr. Antonio Laghezza graduated summa cum laude in "Chimica e Tecnologia Farmaceutiche" at the University of Bari (Italy) in 2000. He defended his Ph.D. in Medicinal Chemistry in 2004 and worked as a research fellow until 2006 at the Medicinal Chemistry Department of the same University. He has been Lecturer since 2006. His research activities deal with the preparation and biological in vitro evaluation of new PPARs ligands, useful for the treatment of pathologies such as obesity, type II diabetes, heart failure, and cancer. He is co-author of more than 50 publications in peer-reviewed journals.

Caloric restriction and longevity

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Caloric restriction (CR) in normal human bodies means to maintain a low-caloric diet, balanced in nutrients, vitamins and catalytic mineral ions (ca. 1750 Kcal/day), in order to benefit aging in good health, an active longevity preventing emerging diseases, and avoiding not genetic but certain kinds of obesity.

A correct caloric intake for the energy needs of the human body for normal activity is necessary. Every organism has a particular metabolism that depends on its genetic and epigenetic characteristics, diet and habits (activity, stress, and toxics). We must adapt its diet, hoping to enjoy good health and achieve an active longevity. Food that we consume our body metabolizes, excreted or accumulated. If it is too much can be stored in the form of fat. The excess of diet leads to cell damage and shortening of life. The mitochondria is like a metabolic turbine of energy production, and eliminates the last steps of nutrients as CO_2 and H_2O. Its functioning and its good physiological condition is cause of longevity. In humans, caloric restriction (CR) is beneficial, and prevents a long list of diseases of the elderly, which we quote in the text. It protects against the causes of aging, prevents production of free radicals, glycation of proteins, the accumulation of fat and other disturbances with damage.

The researcher Guarente discovered that caloric restriction activated the transcription of a gene called Sirtuin2 (SIR2), with capacity to delay aging. Nowadays, as will be mentioned the Spanish researcher Maria Blasco, whose work focuses on the loss of the protective telomere of chromosome ends, which kept young the cells. Telomeres become worn down during cell division, while the enzyme *telomerase* repairs and lengthens the telomeres and obtains, according to the mentioned research in mouse and rats, increasing active longevity.

The circadian rhythm *day-night activity* is important in the regulation of psychic, physical activity and obesity. The light of the sun which control our hormonal rhythms (circadian rhythm) determines that the evening rises several hormones (growth hormone (HGH), melatonin and serotonin). HGH uses our fat reserves as fuel. Everyone's rhythm is different. Melatonin helps maintain the body's circadian rhythm, and there are reciprocal connections of the serotonin and circadian systems likely have importance for neurobehavioral disorders.

The mitohormetic hypothesis of CR, proposes a mitochondrial organic defense response to the genetic level that induces a new epigenome, which has led several scientist to propose that *"we are what we eat"*. A fact that has opened a new scientific discipline, Nutrigenomics, which studies the effect of the diet on the expression of the genome of our cells.

Biography

Bartolome Ribas Ozonas Born in Palma de Mallorca (Balearic Islands, Spain), Doctor In Pharmacy and extraordinary Price. License and Graduate in Medicine and Surgery by the Complutense Univ. Madrid. Ex scholarsip of frensh Government, France. Humboldt Researcher in Max Planck Institute of Biochemistry, Munich, Germany. Head Area of Toxicology, Institute of Health Carlos III; and Associated Professor, Faculty of Medicine, Complutense University Madrid. Invited Professor in Clinical Chemistry Department, Connecticut University, USA. European Unión Expert. Published more than 200 articles amd more than 100 scientific communications. Introduce the courses of Neurochemistry in the Faculties of Pharmacy and Medicine, and of the Biochemical Toxicology to the Fac. of Pharmacy, Complutense University, Madrid.

Synactix Inc and academic case studies of targeted therapy

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Synactix Pharmaceuticals, Inc. is a biotechnology company established to help decrease the catastrophic burden cancer has placed on global health. Instead of looking at cancer as a whole, Synactix identifies unique, malignant pathways that are amenable to therapeutic intervention. Using bioinformatics, cooperating, interdependent pathways are identified and a single-agent is created to block both pathways at the same therapeutic dose. In oncology, resistance is the major limitation for successful treatment of cancers and Synactix has invented an effective strategy to block multiple, malignant pathways to decrease the frequency of resistant disease and to enhance treatment response. Synactix is revolutionizing precision medicine through the strategic targeting of multiple-disease pathways with a single-agent. This is a breakthrough therapeutic strategy and will lead to treatments that can safely and effectively combat cancers, while simultaneously lowering its burden on global health. In line with this approach, a drug discovery campaign was initiated to inhibit the RET or TRK tyrosine kinases in conjunction with VEGFR2. Through development, a clinical candidate was discovered, which is a RET/VEGFR2 dual inhibitor that can block driving oncogenes while simultaneously starving the tumor by inhibiting VEGFR2 mediated angiogenesis. The clinical candidate represents a new archetype for targeted therapy displaying that the strategic inhibition of multiple, disease pathways is well tolerated and highly efficacious compared to mono-targeted or broadly-targeted agents. This presentation will also highlight how academic research can impact the translation outcomes from laboratory to the bed-side.

Presentation Learning Outcome

- In the clinical setting, this clinical candidate can be a more efficient drug.
- This approach can translate the targeted therapeutics into drugs with more efficacy and less toxicity.

Biography

Hong-yu Li is a Professor of Medicinal Chemistry at the University of Arkansas for Medical Sciences (UAMS). He is also an Arkansas Research Alliance (ARA) Scholar, the Helen Adams & ARA endowed chair in drug discovery, and co-director for the Therapeutics Science Program, Winthrop P Rockefeller Cancer Institute. He received his Ph.D. degree from the University of Tokyo and did postdoctoral training at Columbia University and Harvard University. He previously worked at Eli Lilly and the University of Arizona where he focused on oncology drug discovery. His current research interests are in chemical biology and drug discovery, especially for oncology related targets and phenotypes. In his lab at UAMS, a robust oncology pipeline is under development exploiting single agent polypharmacology and synergistic medicinal chemistry approaches.

Liposomal encapsulation of silver nanoparticles suppresses nanoparticle-induced ROS and inflammation, and induces caspase-dependent apoptosis

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Nanolab research group, Technical University Dublin, Ireland

High concentrations of silver nanoparticles (AgNP) are increasingly present as active ingredient in everyday consumable products for antibacterial purposes causing increased human exposure and high risk of adverse effect development. In this study, AgNP were encapsulated dipalmitoylphosphatyidyl choline (DPPC) based liposome, to enhance intracellular delivery, associated cytotoxicity and suppress AgNP induced inflammation. It was noted that as a result of the encapsulation, 0.625 µg/ml liposomal-AgNP (Lipo-AgNP) at induced significant cell death in THP1 cell lines at a notably lower dose than that of the uncoated AgNP induced cytotoxicity. The induced cytotoxicity was shown to result in an increased level of DNA fragmentation resulting in a cell cycle interruption at the S phase of the cell cycle. The predominate form of cell death upon exposure to both uncoated and Lipo-AgNP was found to be caspase dependent and ROS independent apoptosis.

In THP1 monocytes and THP1 differentiated macrophages (TDM), it was found that AgNP induced release of IL-1β. IL-6, IL-8 and TNF-α in THP1 monocytes all of which were suppressed by Lipo-AgNP exposure. AgNP was also found to induce release of IL-1β, IL-6 and TNF-α in TDMs while Lipo-AgNP suppressed these cytokine releases. However, both AgNP and Lipo-AgNP suppressed IL-1β and TNF-α release in LPS-stimulated THP1 monocytes and TDM respectively. Lastly, we showed that AgNP may induce uncontrolled inflammation through induction of STAT3 protein expression in LPS stimulated THP1 monocytes and TDMs whether they are stimulated with LPS or not. This data showed that Lipo-AgNP suppressed AgNP induced inflammation and thus Lipo-AgNP may be particularly useful in treatment of bacteria induced inflammatory diseases.

These findings showed that encapsulation of AgNP enhance AgNP cytotoxicity and mediates a ROS-independent induction of apoptosis.in addition, Lipo-AgNP suppressed AgNP induced inflammation which may be linked to the suppressed ROS. this immunosuppression may be important in application of Lipo-AgNP in treatment of inflammatory diseases like Crohn's disease, ulcerative colitis and inflammatory breast cancer.

Presentation Learning Outcome

- Encapsulation of AgNP in liposome can be carried out by a cost-effective method through extrusion
- Encapsulation of AgNP in liposome help enhance intracellular delivery of AgNP into cancer cell without induction of ROS
- The encapsulation also aids suppression of associated inflammatory response due to AgNP exposure
- Encapsulation of AgNP is a potential therapeutic strategy for treatment of inflammatory diseases

Biography

Azeez is a final year PhD scholar at the Technical University Dublin Ireland. His research thesis is on surface modification of silver nanoparticle to enhance nanoparticle delivery and suppress the associated inflammatory response of the nanoparticle. He is a Master's degree holder in molecular medicine form the University of Sheffield UK and had his Bachelor's degree in Biochemistry at Lagos State University in Nigeria. He has worked as research assistant and project support in a career spanning over 4 years. He is currently a senior tutor at Technical University Dublin.

Development of substances with biological and pharmacological activity based on structural nucleus hybrids from phytochemical compounds like secondary metabolites

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The treatment of different diseases is currently associated with the pharmacokinetics of chemical substances which are supplied to certain patients where there are, for example, enzymatic inhibitions, and this is directly related to the molecules interactions presents in the human body with the external chemical compounds. That's why it's important to keep in mind these molecules must possess some physicochemical properties to be able to enter the different biological systems. The many of these substances problem is their biological origin, as for example, those that come from plants or bacteria, where their synthetic production is costly enough so that the average world population can't access to them. In contrast, there are some substances that are more economical but their effect is less than the initially substances mentioned.

For this reason, it's necessary to find molecules that are accessible to people with an average global economy, although this means they are not as effective as the compounds obtained by biological matrices. This implies designing for example drugs that can fuse different set of substances properties which are accessible and for this reason is a good idea synthesize hybrids of molecules supposing the physicochemical properties and the effect as a drug would potentially increase. An example for this is related to orphan diseases where people suffering from these diseases don't even have access to health insurance because they are endemic to very little inhabited areas or where the poverty level is high. Some examples are cutaneous leishmaniasis, trypanosomiasis and malaria which affects the less developed areas of Colombia, where it's proposed to design some medicines so people can take an adequate treatment of these diseases. In this way it's proposed the design, synthesis and evaluation of two groups of fused phytochemicals: chalcones and coumarins, where both they have shown separately, evaluated by recent studies, being alternatives for these diseases' treatment; so different hybrid derivatives were synthesized and that were named like chalco-coumarins.

Presentation Learning Outcome

- New forms to design dugs connecting two different chemical structures with pharmacological – biological activity
- How to synthesize some secondary metabolites and hybrids from secondary metabolites
- Design of some synthetic drugs from Natural Products
- Propose economic substances to treat orphan diseases base on Natural Products

Biography

Mr. Cuéllar studies Chemical Engineering in the Process and Energy Department in *Facultad de Minas* at Universidad Nacional de Colombia, Medellín – Colombia. He actually is with Prof. Diego Luis Durango in the research group QUIPRONAL *(Química de los Productos Naturales y los Alimentos)* in the Chemistry school, in *Facultad de Ciencias* at Universidad Nacional de Colombia. His research lines are phytochemistry, chemical synthesis with pharmacological and biological applications.

Aspects of controlled-release dosage forms in veterinary medicine with emphasis on GRDF (Gastro retentive dosage forms)

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Early development of controlled-release drug delivery systems was aimed at serving the challenges of human medicine. Around the mid-1970s the technology of controlled-release dosage form (CRDF) was started to be applied for veterinary medicine purposes.

The development of CRDF is highly desirable, both from a convenience and a compliance perspective. One of the biggest advantages of such formulations over the conventional ones is the ability to release a drug at a pre-prescribed rate, leading to relatively constant and stable serum concentrations. Another benefit is the ability to administer medications in infrequent. The use of CRDFs reduces adverse effects and thereby assists in optimizing therapy.

During recent years our team developed and evaluated several kinds of CRDFs based on a drug delivery system producing a polymeric matrix for various indications in animals.

These include parenteral controlled release antibiotic formulation model in goats, pigs, calves, dogs, pigeons, and parrots; a topical sustained release varnish for treatment of dental disorders in dogs and kangaroos and a topical sustained release formulation for udder health in dairy cows. Other formulations which have potential application in human medicine included gastro-retentive dosage form (GRDF) in dogs and coated catheters with a sustained release varnish for prevention of urinary tract infections in dogs. In many of these trials, we achieved the ability to provide a constant serum drug level that is higher than the MIC for several days, by using a single administration.

In conclusion, it appears to be an enormous potential for controlled release drugs for many indications in various species of animals.

Biography

Eran Lavy is an Associate Professor for Veterinary Medicine at the Koret School of Veterinary Medicine Robert H. Smith Faculty of Agriculture, Food and Environment of the Hebrew University of Jerusalem (HUJI). He received BSc. in agriculture (animal husbandry) HUJI at 1984, MSc. in pharmaceutical sciences HUJI at 1986 and his DVM degree HUJI at 1989. He was certified as specialist in clinical medicine of companion animals by the Israeli Veterinary Services at 1995 and as specialist in veterinary pharmacology by the Israeli Veterinary Services at 1997. He was certified as specialist Diplomate in Veterinary Pharmacology and Toxicology (Dip. ECVPT), by the European College of Veterinary Pharmacology and Toxicology at 1999. Since 1989 he is a faculty member at the HUJI and is working at the Hebrew University Teaching Hospital in the Internal Medicine Department with special interest in gastroenterology. His research interests are mainly in clinical pharmacology especially aspects related to controlled release drug delivery systems (CRDDS). Since 2011 He is Associate Professor in Veterinary Medicine. He is teaching in several Veterinary Medicine courses. Professor Lavy supervised M.Sc., Ph.D. and final DVM thesis students, published over 60 scientific papers and hold 8 patents in the field of CRDDS. He is a member of several comities at the Veterinary Medicine School as well as the Agriculture Faculty and several organizations around the world.

The impact of inspiratory parameters on the performance of marketed dry powder inhalers using patients' inhalation profiles

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Dry powder inhalers (DPIs) are passive devices used to administer inhaled medication for the management of asthma and chronic obstructive pulmonary disease (COPD). DPIs require patients to generate a sufficient internal turbulent airflow force during each inhalation to deaggregate the powdered drug formulation into an emitted dose containing particles with the greatest likelihood of lung deposition. This internal force is generated by the interaction between the user's inhalation flow and the resistance of the DPI. Traditional compendial *in vitro* methods of measuring dose emission use a vacuum pump to simulate inhalation. We have adapted this *in vitro* method by replacing the square wave inhalation profile generated by a vacuum pump with the inhalation profiles of patients using an empty DPI. This method enables accurate assessment of the actual dose they would have inhaled. Effective use of DPIs depends on adequate powder deaggregation to aerosolize the drug with a high fine particle fraction (FPF), which facilitates adequate deposition of the drug in the lungs. Deaggregation of the drug depends on many factors, including the aerodynamic particle behavior of the formulation and the design of the inhaler. A typical patient's inhalation profile (IP) generates a flow-versus-time profile that can be characterized by parameters such as the peak inhalation flow (PIF), the inhaled volume (V_{in}), and the initial acceleration of the inhalation maneuver (ACIM).The compendial method using vacuum pump exaggerate the acceleration rate and therefore is not representing the actual inhalation manoeuvre patients would receive in real life use. The results of our study on indacaterol Breezhaler® showed that the quantity and the quality of the emitted dose from the indacaterol Breezhaler® are dependent on the capability of a patient generating an optimal inhalation profile. Therefore, when using the device patients should be encouraged to inhale as fast as they can from the start of their inhalation and for as long as possible. The inspiratory parameters PIF, V_{in} and ACIM were acting together and it was difficult to distinguish the dominant factor in the overall dose emission from Indacaterol Breezhaler®. Recently, we altered the patients' inhalation profiles by fixing two parameters and changing one at a time, the results showed that all inhalation parameters had an impact on the dose emission, dose emptying from the capsule/device in the order of PIF >V_{in}>ACIM. ACIM and V_{in} have almost an equal effect on the delivered dose (DD) and the fine particle dose FPD but the impact of the PIF was the most pronounced. This *ex-vivo* methodology provides a more realistic representation to the way patients use their inhalers and the type and quality of the dose they would receive in real life use.

Presentation Learning Outcome

- The presentation will provide the audience with an understanding on the correct use of dry powder inhalers to optimize drug delivery to the lungs
- The audience will gain an insight of the three important patient's inhalation manoeuvre parameters to master the use of a dry powder inhaler
- Importance of the patients' profiles generated in-vivo and replayed using a breath simulator to assess the dose that patients would receive when using the inhaler

Biography

Dr. Abadelah has completed his degree in Pharmacy in 2010, before joining the University of Huddersfield in 2011 to study for a Master degree in the pharmaceutical and analytical science. After completing his master degree with distinction and awarded the Queen Elizabeth II diamond Jubilee Prize for his outstanding achievement, he decided to pursue his Ph.D. in the inhalation field. He has presented his research nationally and internationally at different conferences including UK Pharm.Sci, AAPS, DDL, PDDS and ERS. He has a track record of publishing in leading peer- reviewed international journals EJP and AAPs Pharm.Sci. In December 2017, He has been awarded his PhD in pharmaceutical science from the University of Huddersfield. He has worked as Lecturer in pharmaceutics at the University of Tobruk - Libya in 2018. Recently, He has started his Postdoctoral position at the University of Huddersfield with Dr. El Hassane Larhrib.

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