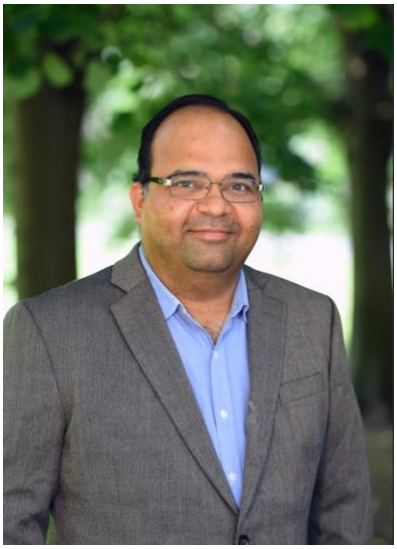
American Association of Pharmaceutical Scientists
Northeast Regional Discussion Group
25th Annual Conference
Friday, March 31, 2023

St. John's University – Queens Campus
D'Angelo Center (DAC)
8000 Utopia Parkway
Queens, New York

http://aaps-nerdg.org

Message from the Chair

Dear Conference Attendees,



Welcome to the 25th Annual American Association of Pharmaceutical Scientists Northeast Regional Discussion Group (AAPS-NERDG) Meeting. This year marks the first ever time when the conference is being organized in New York City. In coming years, we aim to transition AAPS-NERDG meeting in a traveling conference, so that we are able to include scientific community across the entire northeast US.

This year's comprehensive program includes several well-known speakers and presentations from young scientists. The conference features 2 keynote presentations. The morning presentation will be delivered by Dr Naresh K Jain, CEO and Founder of NJ Bio. Dr Jain is a veteran in the pharmaceutical industry and will share his vision on proteins as site-specific drug delivery tools for improving efficacy of therapeutics. The afternoon keynote address will be presented by Dr Giovanni Traverso of Massachusetts Institute of Technology (MIT) and a founder of multiple biotech companies including Lyndra Therapeutics, who will discuss recent developments and innovations in oral delivery of therapeutics.

The morning agenda has three sessions of Short Topic Presentation with talks on a range of pharmaceutical research areas. For the Academic Research Award (ARA), six students will present their research to compete for awards. Winners will be announced in the Awards ceremony later in the day. We will also have a vendor presentation from Simulations Plus.

Following lunch, afternoon events are equally exciting, with exclusive poster session hour (new this year), and 4 Round Table Discussion sessions: In poster sessions, all attendees will have an opportunity to interact with poster presenters and choose award winners in various categories. Round Table Discussion sessions include panelists discussing various topics in areas of Long-acting Drug Delivery, Targeted Drug Delivery, Process Scale-up and Manufacturing, and Regenerative Medicine. The conference will conclude with an awards ceremony, and a networking reception in the evening.

The conference also features a vendor exhibition. Participants that visit vendor booths will have a chance to win a prize. We are grateful to Insmed, JRS Pharma, Croda and Distek who sponsored the ARA and Poster Awards. We also appreciate all our sponsors who support this event. Please take some time to visit their exhibition tables and listen to their technical talks.

I would also like to thank the incredible group of volunteers who have tirelessly worked to organize this year's conference. Putting together an event of national recognition requires a lot of commitment, planning, and flexibility. It would not be possible without their hard work and dedication to AAPS-NERDG.

Please enjoy the conference!

Sincerely,
Vivek Gupta, PhD
AAPS-NERDG Chair 2022-2023
St. John's University

Schedule of Events - Morning

8:00 – 8:30 am

Registration, Breakfast, Vendor & Poster Set-up

416AB Ballroom, 416C, 412 Foyer

8:30 – 9:30 am

Keynote Presentation: *Proteins as site-specific drug delivery tools*

Naresh K Jain, PhD; President & CEO, NJ Bio

416AB Ballroom

9:30 – 9:45 am

Vendor Presentation

Dan O'Connor, Simulations Plus

416AB Ballroom

9:45 – 10:00 am

Break, Vendors, Posters

412 Foyer, 416C

10:00 am – 12:00 pm

Academic Research Awards (ARA) Presentations

416AB Ballroom

10:00 am – 12:00 pm

Short Topic Presentations (STP)

STP Session 1	STP Session 2	STP Session 3
DAC 401	*DAC 311*	*DAC 312*

12:00 – 12:45 pm

Lunch

412 Foyer, 416AB Ballroom, 416C

Schedule of Events - Afternoon

12:45 – 1:15 pm

Hot Topic Presentation
Daniel Heller, PhD; Memorial Sloan Kettering Cancer Center
416AB Ballroom

1:15 – 2:15 pm

Posters (Authors Present), Vendors, Break
416AB Ballroom, 412 Foyer, 416C

2:15 – 3:45 pm

Roundtable Discussion
(2:00 – 3:45 pm for Roundtable 1)

Roundtable 1
DAC 416AB
Long-Acting Drug Delivery

Manish Gupta, PhD; *GSK*

Ashley Johnson, PhD; *Merck & Co., Inc.*

Cameron Lee, PhD; *Novartis*

Jaymin Shah, PhD; *Pfizer, Inc*

Roundtable 2
DAC 308
Targeted Drug Delivery

Debra Auguste, PhD. *Northeastern University*

Liping Zhou, PhD. *AstraZeneca*

Himanshu Bhattacharjee, PhD. *GSK*

Roundtable 3
DAC 309
Process Scale-up

Bing-Shiou Yang, PhD; *Boehringer Ingelheim*

Carmen Popescu, PhD; *Roquette*

Adam Gormley, PhD; *Rutgers University*

Roundtable 4
DAC 401
Regenerative Medicine

Vijay S Gorantla, MD. PhD; *Wake Forest Institute*

Phillip G Campbell, PhD. *Carnegie Mellon University*

Andrew J Shephard, B.Sc. Ph.D. *MD Anderson Cancer Center*

Schedule of Events - Afternoon Cont'd

3:45 – 4:30 pm

Keynote Presentation: *Developments in Oral Drug Delivery*
Giovanni Traverso, MD, PhD; MIT
416AB Ballroom

4:30 – 4:45 pm

Awards & Closing Ceremony
416AB Ballroom

4:45 – 5:30 pm

Networking Reception
416AB Ballroom, 412 Foyer, 416C

Available Through the Day

Posters on Display
416C

Vendors Present
412 Foyer

Coffee and Water
412 Foyer

Event Photography

Photographs will be taken throughout the day by Tina Berardi Photography. Please note that the photographs taken at this event may appear on our website and/or LinkedIn page. If you would prefer not to be photographed, please let the photographer know.

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Md. Asrarul Islam, Rhema Khairnar, Sravani Ravula, Dhwani Mehta, and Vasudha Prithipaul

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St. John's University

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GSK, Plc

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Keynote Speaker 1:
Proteins as site-specific drug delivery tools to improve the therapeutics index

Naresh K Jain, PhD
President & CEO, NJ Bio

Dr. Jain is a scientist, mentor, and entrepreneur with a passion for finding innovative solutions to challenging chemistry problems. He is the Founder, President, and CEO of NJ Bio, Inc. (NJ Bio) and co-founder of Amar Chemistry Pvt. Ltd., which specialize in bioconjugation, oligonucleotide conjugations for immuno-oncology applications, complex molecule synthesis, and flow chemistry. At NJ Bio and Amar Chemistry, Dr. Jain has hired, trained, and developed more than 60 scientists in the last three years, and plans to double the number by the end of 2023. Under his leadership, NJ Bio has, two years in a row, won the distinguished global World ADC Award for Best Contract Research Provider and one for Runner Up. Dr. Jain is also an alumni member of Robin Hood Ventures, a leading Mid-Atlantic investment group for the pharma sector.

Prior to starting NJ Bio, in 2009, Dr. Jain founded a chemistry based CRO, The Chemistry Research Solution LLC (TCRS), serving for 6 years as Managing Director. During that time, he grew the company to 50 employees, worked with more than 200 leading biopharmaceutical clients, and secured long-term contracts with the National Cancer Institute (NCI). In 2015, Abzena PLC acquired TCRS, with Dr. Jain serving as Senior Vice President and Global Head of Chemistry.

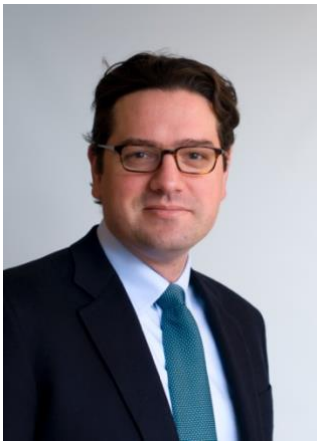
Dr. Jain started his pharma industry career at Johnson & Johnson, where he gained about 10 years of medicinal chemistry experience while advancing new drug molecules from hits to leads and into clinical trials. Among his notable chemistry achievements are the total syntheses of the complex antibiotic natural products vancomycin and rutamycin. Over the past three decades, Dr. Jain has co-authored more than 60 publications, patents, and book chapters in medicinal and synthetic chemistry. His work has been cited more than 2,700 times, and his publications have an overall h-index of 27.

Dr. Jain received his Ph.D. from Boston University and was a Post-Doctoral Research Fellow at The Scripps Research Institute in La Jolla, California. In 2017, Dr. Jain graduated from the Advanced Management Program at The Wharton School of the University of Pennsylvania. He recently received the Distinguished Alumnus Award from ICT (formally UDCT) in Mumbai.

Keynote Speaker 2:
Developments in Oral Drug Delivery

Giovanni Traverso, MB, BChir, PhD

Assistant Professor, Department of Mechanical Engineering, Massachusetts Institute of Technology
Assistant Professor of Medicine (part-time), Division of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School



Dr. Traverso is an Assistant Professor in the Department of Mechanical Engineering at the Massachusetts Institute of Technology and in the Division of Gastroenterology, Brigham and Women's Hospital (BWH), Harvard Medical School. Dr. Traverso grew up in Peru, Canada and the United Kingdom. He received his BA from Trinity College, University of Cambridge, UK, and his PhD from the lab of Prof. Bert Vogelstein at Johns Hopkins University. He subsequently completed medical school at the University of Cambridge, internal medicine residency at the Brigham and Women's Hospital and his gastroenterology fellowship training at Massachusetts General Hospital, both at Harvard Medical School. Dr. Traverso's previous work focused on the development of novel molecular tests for the early detection of colon cancer which was published in the New England Journal of Medicine and The Lancet. This work was licensed to Exact Sciences and informed the development of the FDA-approved non-invasive test Cologuard for colon cancer screening. For his post-doctoral research, he worked in the laboratory of Professor Robert Langer at the Massachusetts Institute of Technology (MIT) where he developed a series of novel technologies for drug delivery as well as physiological sensing via the gastrointestinal tract.

Dr. Traverso's contributions have been recognized through several awards including, the Grand Prize of the Collegiate Inventors Competition, a Research Fellowship from Trinity College (Cambridge, UK), being recognized on the MIT Tech Review's TR 35 list and receiving the 2023 Acta Biomaterials Silver Medal. Additionally, Dr. Traverso has been elected to the American Society for Clinical Investigation, the National Academy (NAM) Emerging Leaders in Health and Medicine Scholars program, the College of Fellows of the Controlled Release Society, and most recently the National Academy of Inventors.

His current research program is focused on developing the next generation of drug delivery systems to enable efficient delivery of therapeutics through the gastrointestinal tract as well developing novel ingestible electronic devices for sensing a broad array of physiologic and pathophysiologic parameters.

Hot Topic Presentation:
Nanomedicines for the Research, Detection, and Treatment of Cancer and Allied Diseases

Daniel A. Heller, PhD

Head, Cancer Nanomedicine Laboratory
Member, Memorial Sloan Kettering Cancer Center
Professor, Weill Cornell Medicine, Cornell University

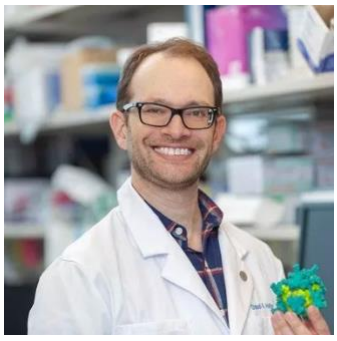
Abstract

We develop nanotechnologies to accelerate the research, diagnosis, and treatment of cancer and allied diseases. We focus on nanoparticle drug delivery systems and nanosensor-based diagnostics and drug discovery tools.

To build better cancer therapeutics, we investigate the potential to improve the therapeutic index of precision medicines via nanomedicine-based strategies to localize drugs to tumors using vascular targets. We developed machine learning processes to facilitate the encapsulation of diverse drug classes into these nanoparticles, based on drug molecular structure, resulting in the rapid synthesis of many, diverse, targeted nanotherapeutics. We found that P-selectin, expressed endogenously on activated endothelium in tumors, can be used as a nanotherapeutic target to improve the efficacy of kinase inhibitors and abrogate dose-limiting toxicities, to improve therapeutic index. P-selectin can also be induced via ionizing radiation, enabling the enhancement of the target. We also found that endothelial targeting can improve delivery across intact blood-brain barrier for the treatment of intracranial tumors and metastases, via activating transendothelial transport.

We also develop optical nanosensor technologies using carbon nanotubes to facilitate longitudinal detection of cancer biomarkers, and to build new assays for cancer drug development. These technologies employ the bandgap fluorescence of single-walled carbon nanotubes (SWCNTs) which emit in the near-infrared "tissue transparent" window and can respond to analytes down to the single-molecule level. We have developed new sensors for the detection of metabolic changes in live cells and tissues, disease biomarkers in situ via implants, and overall disease states, aided by machine learning processes.

Speaker Biography



Dr. Daniel A. Heller, PhD, is Head of the Cancer Nanomedicine Laboratory, Member of the Molecular Pharmacology Program in the Sloan Kettering Institute at Memorial Sloan-Kettering Cancer Center, Professor in the Department of Pharmacology at Weill Cornell Medicine, and a member of the Graduate Field Faculty in the Meinig School of Biomedical Engineering at Cornell University. His work focuses on the development of nanoscale technologies for the treatment, diagnosis, and research of cancer. Dr. Heller obtained his PhD in chemistry from the University of Illinois at Urbana-Champaign in 2010, working in the laboratory of Michael Strano. He completed a Damon Runyon Cancer Research Foundation Postdoctoral Fellowship in the laboratory of Robert Langer at the David H. Koch Institute for Integrative Cancer Research at MIT in 2012. He is a 2012 recipient of the National Institutes of Health Director's New Innovator Award, a 2015 Kavli Fellow, a 2017 recipient of the Pershing Square Sohn Prize for Young Investigators in Cancer Research, a 2018 American Cancer Society Research Scholar, a 2018 recipient of the CRS Nanomedicine and Nanoscale Drug Delivery Focus Group Junior Faculty Award, a 2018 NSF CAREER Awardee, a 2020 awardee of the Weill Cornell Graduate School Pharmacology Teaching and Mentoring Award, and a 2021 American Institute for Medical and Biological Engineering (AIMBE) Fellow.

Vendor Presentation

Daniel J. O'Connor,
Senior Director, Business Development
Simulations Plus, Inc.

Abstract

In 2004, an FDA publication discussed the low productivity and escalating costs of drug research. The paper highlighted the promise that *in silico* Model Based Drug Development might offer to help speed discovery & development, increase safety and efficacy while potentially reducing costs. We will explore a bit of the 26-year history of Simulations Plus and highlight several new technologies that are helping scientists to achieve that goal!

Speaker Biography

Dan O'Connor, has been Senior Director of Business Development with Simulations Plus for the last seven years. He is responsible for sales, marketing and support for GastroPlus which is a software platform for insilico mechanistic PBPK modeling and simulation. Dan has spent his corporate career at the intersection of business and science with companies that include Agilent, Hitachi and Perkin Elmer, spanning technologies from HPLC to PET/SPECT preclinical imaging.

Dan holds a degree in Chemistry & Computers from Trinity College in Hartford, CT, and in his free time…for the last 14 years, Dan has been serving as an ordained Deacon in the Catholic Church.

Short Topic Presentations (STP)

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	10:30 – 11:00	Comparative tissue proteomics reveals unique action mechanisms of vaccine adjuvants	Yibo Li	University of Rhode Island	20
	11:00 – 11:30	The Role of CXCL1 In Crosstalk Between Endocrine Resistant Breast Cancer and Fibroblast	Ahone Akume	Albany College of Pharmacy and Health Sciences	21
	11:30 – 12:00	Scale-up study for low dose powder filling using vacuum drum filler	Tanu Mehta	University of Connecticut	22
Room B Moderator: Sameera Sansare	10:00 – 10:30	Exploring the Potential of Inhaled Nano Therapy for Malignant Pleural Mesothelioma	Mimansa Goyal	St. John's University	23
	10:30 – 11:00	Enhancing oil solubility of BCS Class II drug phenytoin through hydrophobic ion pairing	Dimple Modi	GSK	24
	11:00 – 11:30	Development of Inhalable Clofazimine Loaded Microparticles for Tuberculosis Infection	Druvasarika Barji	St. John's University	25
	11:30 – 12:00	Improving mRNA-lipid nanoparticle stability by lyophilization	Zimeng Wang	AstraZeneca	26
Room C Moderator: Jelena Janjic	10:00 – 10:30	A novel therapeutic approach for neuroblastoma - direct targeting of the cell cycle regulator *WEE1*	Parul Suri	St. John's University	27
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	11:00 – 11:20	Pharmacokinetics and Pharmacodynamics of a Novel Iron Chelator in Rodents	Mitchell Lobo	MCPHS	34
	11:20 – 11:40	Osimertinib immunoliposomes as inhaled therapy for non-small cell lung cancer treatment	Apoorva Daram	St. John's University	35
	11:40 – 12:00	Fabrication of Novel Adapter for *In-Vitro* Release Testing and IVIVC Development of Long-Acting Injectable Suspensions	Nileshkumar Malavia	University of Connecticut	36

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	Ashley Johnson (Merck & Co., Inc.)	Formulation and Biopharmaceutics Considerations in the Development of Long-acting Injectable Suspensions	72
	Cameron Lee (Novartis)	Long-Acting Technologies for Biologics to Treat Ocular Diseases	73
	Jaymin Shah (Pfizer, Inc)	Back to Basics: Model for Long-Acting Parenteral Delivery Systems	74
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	Liping Zhou (Astrazeneca)	The industrial design, translation, and development strategies for long-acting peptide delivery	76
	Himanshi Bhattacharjee (GSK)	Targeted Drug Delivery: Design of Delivery	77
Process Scale Up DAC 309 Moderator: Ka Ning Yip/Gautam Chauhan	Bing-Shiou Yang (BI)	Drug Substance Property Controls in Scale Up	78
	Carmen Popescu (Roquette)	Tablet Development Support (TaDeS) in direct compression process	79
	Adam Gormley (Rutgers)	AI and Automation to Accelerate the Scale of Drug Discovery and Development	80
Regenerative Medicine DAC 401 Moderator: Jelena Janjic	Vijay S. Gorantla (Wake Forest Institute for Regenerative Medicine)	Drug Delivery, Biosensors, and Imaging – The Trifecta of Regenerative Surgery	81
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	Andrew J. Shepherd (Anderson Cancer Center)	Using Nanoemulsions and Hydrogel Formulations to Target Neuro-Immune Interactions in Chronic Pain	83

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5	Shrey Shah	Development of a Flow-based *in*-vitro Multicellular Tumor Spheroid Model for Testing Anti-Cancer Therapeutics	MCPHS	41
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34	Sweta Mishra	A Disintegrant Extracted from Banana Peel Waste	NIMS	70

Virtual Polymorph Screening and Targeted Crystallization of a Drug Candidate

Dedong Wu[1]*, Sten Nilsson Lill[1], James McCabe[1], Emma Eriksson[1], Christoph Bauer[1], Michelle Lamb[2]

[1]*Advanced Drug Delivery, PharmSci, R&D, AstraZeneca, Boston US,*
[2] *Data Science and Modelling, PharmSci, R&D, AstraZeneca, Macclesfield US,*
[3] *Early Pharmaceutical Development, PharmSci, R&D, AstraZeneca, Macclesfield UK,*
[2] *Early Oncology Chemistry, Oncology R&D, AstraZeneca, Boston US*

Correspondence: dedong.wu@astrazeneca.com

Purpose:
It is critical to select an appropriate solid form, usually the most thermodynamically stable one, for pharmaceutical development of a drug candidate. Usually, it requires a significant amount of sample and a long period of time for an experimental polymorph study to select an optimal solid form. Nevertheless, the experimental polymorph study itself does not ensure that the selected form is the most stable one. There is always a risk of missing a more stable form early on and discovering it during further crystallization experiments. *In silico* solid-state modeling provides an opportunity to mitigate the risk in drug substance form selection.

Methods:
By employing emerging technology of crystal structure prediction (CSP), polymorph energy landscape of a drug candidate was calculated. Essentially, "virtual polymorph screening" was established by the comparison of simulated powder X-ray diffraction (XRD) patterns of predicted structures with experimental XRD patterns, allowing to confirm whether the identified crystalline form is the most stable one. When the predicted most stable form was not observed experimentally, predictions of 'conformer weighting in solution' based COSMO-RS method (Conductor like Screening Model for Real Solvents) highlighted solvent systems to increase the likelihood of the most stable form's conformation in solution environment, making it possible for a "targeted crystallization" process to produce the desired solid form.

Results:
A workflow based on 'virtual polymorph screening" and "targeted crystallization" allows to access the most stable form of a drug candidate. A rational crystallization process was achieved to obtain the desired crystalline form of a drug candidate by using a minimal amount of sample within a shortened time period in the early stage of drug development.

Conclusions:
This workflow for "virtual polymorph screening" and "targeted crystallization" not only minimizes the costs for experimental polymorph studies but also provides scientific rational to ensure the most stable form is selected in early stage in order to lower the risks for future pharmaceutical development.

Keywords:
In silico Prediction, Polymorph, Form selection, Crystallization

Comparative tissue proteomics reveals unique action mechanisms of vaccine adjuvants

Yibo Li [1], Zhuofan Li [1], Xinyuan Chen [1] *

[1] *Biomedical & Pharmaceutical Sciences, College of Pharmacy, University of Rhode Island*

Correspondence: Xinyuan Chen, Email: xchen14@uri.edu

Purpose:
Radiofrequency adjuvant (RFA) was recently developed to boost influenza vaccination without the safety concerns of chemical adjuvants due to its physical nature. Yet, the action mechanisms of RFA remain largely unknown. Omics techniques offer new opportunities to identify molecular mechanisms of RFA. This study utilized comparative tissue proteomics to explore molecular mechanisms of the physical RFA.

Methods:
This study utilized sequential windowed acquisition of all theoretical fragment ion mass spectra (SWATH-MS) proteomics to explore RFA-induced tissue proteome change to identify novel signatures crucial for RFA effects.

Results:
Comparison of RFA and chemical adjuvant (Alum, AddaVax, MPL, MPL/Alum)-induced tissue proteome changes identified 14 exclusively induced proteins by RFA, among which heat shock protein (HSP) 70 was selected for further analysis due to its known immune-modulating effects. RFA showed much weakened ability to boost ovalbumin and pandemic influenza vaccination in HSP70 knockout than in wild type mice, hinting crucial roles of HSP70 in RFA effects.

Conclusions:
This study supports comparative tissue proteomics to be an effective tool to study molecular mechanisms of vaccine adjuvants.

Keywords:
Radiofrequency adjuvant, physical adjuvant, chemical adjuvant, adjuvant mechanism, HSP70

The Role of CXCL1 In Crosstalk Between Endocrine Resistant Breast Cancer and Fibroblast

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Purpose: ER positive breast cancer is currently targeted using various endocrine therapies. Despite the proven therapeutic efficacy, resistance to the drug and reoccurrence of tumor appears to be a complication that many patients deal with. Molecular pathways underlying the development of resistance are being widely studied.

Methods: We utilized a human cytokine array to identify secreted factors in crosstalk between endocrine resistant breast cancer (ERBC) cells and fibroblast. Real-time qRT-PCR and U-Plex assay were performed to validate factors. Cell viability assay and migration assay were performed to assess the function of CXCL1.

Results: In this study, using four established endocrine resistant breast cancer (ERBC) cell lines, we characterized CXCL1 as a secreted factor in crosstalk between ERBC cells and fibroblasts. Protein array revealed upreguation of CXCL1 and we confirmed the CXCL1 expression by real-time qRT-PCR and U-Plex assay. Co-culturing ERBC cells with fibroblasts enhanced the cell growth and migration compared to monoculture. The crosstalk of ERBC cells with fibroblasts significantly activates ERK/MAPK signaling pathway while reparixin, CXCR1/2 receptor inhibitor, attenuates the activity. Reparixin displayed the ERBC cell growth inhibition and the combination treatment with reparixin and CDK4/6 inhibitor (palbociclib and ribociclib).

Conclusions: Taken together, our study implicates CXCL1 as a critical role in ERBC growth and metastasis via crosstalk with fibroblast and cotargeting CXCR1/2 and CDK4/6 could potentially overcome endocrine resistant breast cancer.

Keywords:
Breast cancer, Endocrine resistance, CXCL1, and reparixin

Scale-up study for low dose powder filling using vacuum drum filler

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Purpose:
Dry powder inhaler (DPI) manufacturing involves handling of low dose formulations. Multiple methods exist for low dose DPI filling but powder filling in milligram fill weight is still a challenge. As most of the pharmaceutical powders are poor flowing and show unpredictable flow behavior, this filling process becomes even more difficult when the process is transferred from lab to pilot scale. In this study, we have evaluated lab scale (DrumLab) and pilot scale (ModuC LS) vacuum drum filling system by Harro Hofliger to understand the impact of scale up on overall filling performance.

Methods:
For this study, powders with different properties were selected and filled in size 3 HPMC capsules using ModuC LS and DrumLab. The selected materials were Lactohale 300/LH300 (poor flow with D50 5µm), Inhalac 230 (fair flow with D50 90µm) and in-house formulation A (very poor flow). The selected powders were filled using both the equipment at different vacuum levels, using different types of stirrers and drum sizes. At the end, the capsule fill weight and %RSD was recorded. The data obtained from DrumLab was compared with the ModuC LS results to understand the scalability.

Results:
The fill weights obtained using ModuC LS were higher than fill weights achieved using DrumLab. For example, with LH300, using ModuC LS and standard stirrer at 200 mbar, 400 mbar and 600 mbar vacuum levels the fill weight was 12.23mg, 14.24mg, and 15.17mg respectively. With DrumLab and standard stirrer at 200 mbar, 400 mbar and 600 mbar vacuum levels the fill weight obtained was 11.031mg, 13.531mg, and 14.486mg respectively. Additionally, we observed higher %RSD with DrumLab in comparison to ModuC LS. The variation in fill weights and %RSD could be attributed to the difference in hopper geometries, powder feeding mechanism and stirrer size.

Conclusions:
The scale up study for vacuum drum filling was conducted using lab scale DrumLab and pilot scale ModuC LS for powders with different properties. Vacuum drum filing system is an efficient method for low dose powder filling and can be easily scaled from laboratory to pilot scale.

Keywords:
Low-dose filling, DrumLab, ModuC LS, Drum filler

Exploring the Potential of Inhaled Nano Therapy for Malignant Pleural Mesothelioma

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Purpose:
Malignant Pleural Mesothelioma (MPM) is a rare cancer of pleura, lining the lungs. Multiple small molecule therapies have been clinically tested but none of the molecules have transitioned to the market. This high failure rate can be attributed to the lack of efficacy of molecules against this complex rare disorder. Carmofur, an anti-neoplastic agent, has been in clinical trials since 1981 for colorectal cancer. Recent discovery shows carmofur irreversibly binds to acid ceramidase (AC), an enzyme which indirectly catalyzes sphingosine into sphingosine-1 phosphate (regulates angiogenesis and cell proliferation). Carmofur-AC binding leads to tumor suppression and promotes cancer cell death. However, Carmofur requires high oral dose which further causes severe neurotoxicity. Therefore, in this project, we aim to develop inhaled nano formulation which will enable local delivery of carmofur to the lungs, thereby reducing the dose/dosing frequency.

Methods:
Polymeric nanoparticles containing carmofur were prepared using double emulsion technique. Nanoparticles were tested with phenotypic assays such as preliminary cytotoxicity on immortalized and patient-derived cell lines and efficacy against 3D-cell based models. Deep lung deposition of particles was evaluated using Next Gen Impactor (NGI).

Results:
Prepared nanoparticles exhibited particle size of 186.0±6.5 nm with a PDI of 0.1 ±0.05 and zeta potential -21.7±1.8 mV. The entrapment efficiency was 26.4±3.5% corresponding to a drug loading of 2.0±0.3 mM The mass median aerodynamic diameter (MMAD) of the nanoparticles was determined to be 2.6±0.1 µm with a fine particle fraction of 76.8±2.0%, thus highlighting excellent inhalation and deep lung deposition potential. Cell viability assay revealed IC_{50} values; 14.8±1.2 µM (Carmofur) and 1.8±0.6 µM (Carmofur Nanoparticles) in immortalized cell line.

Conclusions:
This study demonstrates the efficacy of inhaled carmofur loaded nanoparticles through extensive phenotypic and mechanistic assays. Fabricated nano systems enhanced carmofur's efficacy, achieved deep lung deposition, thereby concentrating the drug in the lungs (at the target site). These studies represent the relevance of inhalable therapy as a novel treatment for mesothelioma.

Keywords: Malignant Pleural Mesothelioma, Carmofur, Acid Ceramidase, Inhalation

Enhancing oil solubility of BCS Class II drug phenytoin through hydrophobic ion pairing

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Purpose:
This work investigates the micellar titration of phenytoin (a weakly acidic drug) with quaternary ammonium counterion, cetyltrimethylammonium hydroxide (CTAH) to form a hydrophobic ion-pair to potentially enhance oil solubility of phenytoin.

Methods:
pH solubility study of Phenytoin in presence of CTAH counterion was investigated. Mathematical modeling of pH-solubility data indicated that ionization and micellization were the dominant mechanisms for the solubilization of the titration. X-Ray Powder Diffraction (XRPD), Fourier Transform Infrared Spectroscopy (FTIR), and Nuclear Magnetic Resonance (NMR) were analyzed to understand phase transition and formation of ion pair. Dynamic light scattering and quantitative analysis of CTAH using high-performance liquid chromatography (HPLC) throughout the titration were investigated to understand micellization and potential ionization effects. Ion pair was characterized using Hot stage microscopy to understand melting point behavior. Aqueous/oil solubility was performed to understand the lipophilicity of ion pair.

Results:
The pH solubility analysis confirmed the conversion of phenytoin into an ionized state and its subsequent ionic interaction with CTAH forming a hydrophobic ion-pair complex (HIP). XRPD and FTIR data of undissolved solids showed the complete ion pair formation evident at pH_{max} (8.8 to 9.2), and its 1:1 stoichiometry was confirmed using HPLC and H^1 NMR, hence could also be called as salt. The ion-pair (salt) was practically insoluble in water and showed very high partitioning (log P) in octanol/water. The solubility of the ion pair in castor oil increased approximately eight-fold compared to the free acid form. As characterized by hot-stage microscopy, the melting point of the ion-pair complex was lowered to 150.8ºC compared to the free acid (> 300^{o}C). The high miscibility in castor oil and suppressed melting point make the ion pair suitable to formulate in a high drug load injectable dispersed system.

Conclusions:
This study showed the potential of lipophilic ion-pair formation of BCS Class II drug and its oil solubility enhancement, thereby providing a pathway to further explore injectable nano-emulsion formulations that could enhance drug loading and alleviate a typical phlebitis issue associated with the injectable phenytoin solution administration at physiological pH.

Keywords:
equilibrium, pH-solubility, ion-pairing, phenytoin, counterion, micellization, complexation

Development of Inhalable Clofazimine Loaded Microparticles for Tuberculosis Infection

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Tuberculosis (TB) is responsible for causing approximately 1.5 million deaths in 2020 worldwide. Moreover, an ongoing rise in drug-resistant TB strains is a particular concern globally. Therefore, there is a need to develop antibacterial formulations with improved specificity and shorter regimens that would enable the treatment of TB infection. Inhalation drug delivery provides high drug concentrations at site of disease thereby limiting potential systemic adverse effects. Clofazimine (CFZ) is an iminophenazine antibiotic drug approved for treatment of tuberculosis. However, oral administration of CFZ is limited by severe systemic side effects, such as discoloration of the skin, cardiotoxicity and poor aqueous solubility. Therefore, we intend to formulate CFZ loaded inhalable microparticles as a promising strategy to provide sustained drug release and overcome the limitations.

Here, clofazimine poly (lactic acid-co-glycolic acid) (PLGA) microparticles (CFZ MPs) were prepared by a single emulsion solvent evaporation technique followed by spray drying of MPs suspension to yield dry powder formulation (CFZ SD MP). The clofazimine microparticles demonstrated a particle size of ~1 µm with zeta-potential of -31.42 ± 5.30 mV. The entrapment efficiency and drug loading of clofazimine in microparticles were 66.40 ± 2.22 %w/w and 33.06 ± 1.45 µg/mg respectively. Clofazimine spray dried microparticles (CFZ SD MP) prepared using spray drying process resulted in a yield of 71.01 ± 3.67 %w/w. The formulation exhibited an initial burst release of 44.34% in 12 h followed by a complete release. Moreover, the optimized formulation also exhibited good aerosolization properties with fine particle fraction (FPF) of about 86.45 ± 0.21% and mass median aerodynamic diameter (MMAD) of 1.56 ± 0.11 µm. Additional stability studies confirmed the stability of dry powder formulation after 12 weeks of storage at 4˚ C and 25 ˚C. The in vitro anti-bacterial studies revealed improved therapeutic efficacy of spray dried formulation as compared to free drug resulting in almost 8-fold reduction in minimum inhibitory concentration (MIC). Hence, clofazimine dry powder formulation presents immense potential for the treatment of tuberculosis with localized pulmonary delivery with improved patient compliance**.**

Keywords: Microparticles, fine particle fraction, median aerodynamic diameter, minimum inhibitory concentration**.**

Improving mRNA-lipid nanoparticle stability by lyophilization

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Purpose:
Messenger RNA (mRNA) based vaccines delivered by lipid nanoparticle (LNP) have been widely applied in the fight against COVID-19 pandemic with proven success. Both mRNA-LNP based vaccines currently approved require cold chain storage due to drug product stability concerns. Lyophilized dry powder provides a promising way to improve the long-term stability of mRNA vaccines in non-freezing conditions. Many studies have been published on the optimization of lyophilization processes; however, few of them take the LNP fabrication into consideration. In this research, we performed a comprehensive study to improve LNP stability at 4 °C by investigating the fabrication and lyophilization parameters together, which could offer a more flexible and effective lyophilization method for different LNP formulations.

Methods:
eGFP mRNA-LNPs are prepared by Nanoassemblr microfluidic system, purified by dialysis, condensed by centrifuge filtration and lyophilized to achieve dry powder. The process parameters are optimized by Box-Behnken experimental design (DOE) using Design-Expert ® Software. The nanoparticles are characterized prior and after storage under different conditions. Particle size, PDI, and Zeta potential are measured by Malvern Zetasizer. Encapsulation efficiency is measured using Ribogreen Assay. LNP morphology is studied using Cryo-EM. In vitro efficacy of LNP is evaluated using ELISA assay in Hela, Huh7, and HepG2 cell lines.

Results:
Our data has shown that having higher amount of PEG lipid and using acidic dialysis pH with low salt concentration are essential to prevent reduction of efficiency in lyophilization. A mixture of disaccharide and oligosaccharides as lyoprotectant facilitates maintaining good LNP dispersity in reconstitution. The evaluation of in vitro efficacy of lyophilized LNP is ongoing.

Conclusions:
The mRNA-LNP stability various at different pH conditions, temperatures and under different physical states. While the solution-based mRNA-LNP has simpler compositions but require low temperature for long term storage. An optimal process to form dry powder LNP can significantly improve the situation. Such a process can be identified by a comprehensive study on both LNP fabrication and lyophilization under different conditions, potentially offering a method to improve LNP long term stability at 4 °C and maybe even under ambient condition.

Keywords:
mRNA-LNP, Lyophilization, Stability, DOE

A novel therapeutic approach for neuroblastoma – direct targeting of the cell cycle regulator *WEE1*

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Purpose:
High-risk neuroblastoma (NB) is a solid pediatric tumor that develops from the extracranial sympathetic nervous system. Despite recent advances in therapeutic regimens of dose-intensive chemotherapies, radiation, and surgery NB often relapses as a metastatic and drug-resistant tumor. These issues further mandate the identification and development of novel therapeutic approaches for NB treatment. Cell cycle regulator Wee1 regulates the activation of Cdk1 and Cdk2 to inhibit the DNA damage response of the cell cycle and promote cancer growth. In the present study, we hypothesized that direct targeting of Wee1 with a specific small molecule inhibitor adavosertib will block the NB proliferation and growth.

Methods:
We analyzed multiple NB patient datasets using R2 Genomic Database platform. The effect of adavosertib on NB cell proliferation was determined using different 2D and 3D growth assays. Apoptosis and cell cycle assays were performed using respective kits and analyzed using Attune Flow cytometer. Gene expression analysis and Western Immunoblotting were performed to determine the effects of adavosertib using standard methods.

Results:
We found that Wee1 expression is strongly correlated with poor overall survival of NB patients and associated with an overall poor NB prognosis. Further, Wee1 inhibition using adavosertib significantly and in a dose-dependent manner inhibits NB proliferation and colony formation capacity in both MYCN-amplified and MYCN non-amplified NB cells. Adavosertib significantly induces apoptosis up to 3-fold and inhibits NB cell cycle progression by inhibiting the S phase and blocking the G2/M transition in different NB cell lines in contrast to controls. Further, the Wee1 inhibition significantly inhibits the expression levels of different cell cycle-related genes and proteins in NB cells. Furthermore, the NB 3D spheroid tumor model that mimics the in vivo growth of NB tumors showed that adavosertib significantly and in a dose-dependent manner inhibits spheroidal growth and volume in contrast to control treatments.

Conclusions:
Overall, our data suggest that inhibition of the cell cycle regulator Wee1 is an effective therapeutic approach for NB. Further combining Wee1 inhibitors with current therapies will pave the way for developing effective targeted therapeutic approaches for NB patients.

Keywords:
Neuroblastoma; adavosertib; cell cycle; Wee1; pediatric tumor

Direct targeting of survivin inhibits neuroblastoma growth in a xenograft mouse model

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Purpose:
The 5-year survival of neuroblastoma (NB) patients is only 40-50%, which signifies the limited effectiveness of current therapeutic modalities for high-risk NB. Therefore, the need for innovative NB therapies is optimal. This present study elucidates the effects of the small molecule survivin inhibitor as a novel therapeutic approach for NB.

Methods:
NB patient datasets were analyzed using R2 Genomic analysis and visualization platform. *In vitro* studies were performed using six NB cell lines: SH-SY5Y, SK-N-AS, CHLA-255, NGP, IMR-32, and LAN-5. Cell proliferation studies were performed using MTT assays. Apoptosis and cell cycle assays were performed using an Apoptosis Detection Kit and Click-iT EdU Alexa Fluor 488 Kit respectively with Attune NxT Flow Cytometer. *In vitro* tumorigenic studies were performed using Corning 3D-spheroid microplate system, and *in vivo* studies were executed using a xenograft mouse model developed using athymic immunocompromised mice.

Results:
In the present study, genomic datasets of 1135 NB patients revealed that poor overall and event-free survival of NB patients strongly correlated with high expression of survivin coding gene *BIRC5*. Significantly higher *BIRC5* levels were analogous with more aggressive NB malignancies. Evaluation of survivin inhibition on NB growth was performed using a specific small molecule inhibitor via cell proliferation and clonogenic assays, which revealed significant and dose-dependent inhibition of NB proliferation and colony formation *in vitro*. Additionally, survivin inhibition significantly induced apoptosis and blocked the cell cycle progression in different NB cells in contrast to control treatments. Moreover, *in vitro* 3D-spheroid formation assay revealed significant inhibition of spheroid growth and live cells in response to survivin inhibition. Furthermore, *in vivo* xenograft model showed that survivin inhibition significantly inhibits NB tumor growth and tumor weight without exerting any toxic effects in contrast to the control treatment cohort.

Conclusions:
Overall, our results suggest that survivin potentiates NB activity and the inhibition of survivin significantly inhibits NB growth *in vivo* and *in vitr*o. In our future efforts, we will combine the survivin inhibitor with chemotherapeutics *in vivo* to develop a dual therapeutic approach for NB.

Keywords:
Neuroblastoma, Survivin, Cancer Therapy, Repurposing, Xenografts

Osmotic Capsules for Preclinical Assessment of Extended-Release Drug Delivery Feasibility

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Purpose:
Compound X was developed using an oral immediate release dosage form for bid dosing. A qd product is desired to reduce dosing frequency and decrease side effects by blunting the C_{max}. Multiple OzmoCAP® formulations were developed and dosed into dogs to understand the absorption of Compound X throughout the GI tract and to determine the feasibility of developing an oral extended-release dosage form.

Methods:
One osmotic capsule formulation was prepared incorporating FreeThink's proprietary OzmoCAP® products. In the fed state, three dogs were dosed with a fast release formulation ($t_{80\%}$ of 6 hours). Blood samples were analyzed up to 24 hours after dosing.

Results:
Plasma data for Compound X showed the fast release OzmoCAP® formulation extended the t_{max} from 4 hours for the immediate release dosage form to 12 hours. Pharmacokinetic data suggest that there is still absorption in the colon, although at decreased levels.

Conclusions:
Based upon these data, it was determined that extended-release delivery of Compound X is feasible, and further development was progressed. OzmoCAP® enables rapid development and *in vivo* dosing for quick assessment of extended-release drug delivery viability.

Keywords:
Extended release, Capsules, OzmoCAP®, oral dosage

Design, Evaluation, and Optimization of Immune Stimulating Antibody-drug Conjugates for Cancer Therapy

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Purpose:
Immune-regulating antibody-drug conjugates (ADCs) have been considered as a novel solution for cancer immunotherapy. Use of highly potent immunostimulants, such as TLR7 agonists, have been hampered by potent off-target toxicity when dosed systemically, such as a cytokine storm. We describe the use of ADC technology to help overcome this limitation. We have designed, conjugated, and optimized ADCs carrying TLR7 agonists that target cancer cells and activate immune cells in the tumor microenvironment, leading to regression of tumors.

Methods:
In this research, TLR7 agonists were conjugated to lymphocyte targeting and tumor targeting monoclonal antibodies via a variety of linkers. We evaluated the efficacy of the immune stimulating ADCs in several in vitro models as well as an in vivo xenograft mouse model.

Results:
In an in vitro lymphocyte reporter assay, lymphocyte targeted TLR7 agonist ADCs successfully induced NF kappa B activation, while analogous control ADCs exhibited no activation. In cancer cell/immune cell co-culture assays, our TLR7 agonist ADCs selectively activated the mouse macrophage reporter line Raw-Dual as well as human peripheral mononuclear cells (hPBMCs). We further co-cultured GFP-transduced cancer cells with hPBMCs. Our targeted ADCs were able to activate effector immune cells and induce cytotoxic effect towards the cancer cells, while the naked antibody demonstrated no efficacy. Finally, our ADCs induced tumor shrinkage in a mouse xenograft tumor model in an antigen-dependent manner.

Conclusions:
We developed multiple immune-stimulating ADCs carrying TLR7 agonist as payloads. The ADCs were able to activate immune cells, thus eliminating the targeted cancer cells in both in vitro and in vivo models. This research helps to pave the way for the design of immune-stimulating ADCs for use in anti-cancer therapy.

Keywords:
Cancer immunotherapy, Antibody-drug conjugates, Targeted delivery, TLR7 agonist.

Enhanced nuclear delivery for targeting chromosomal DNA for cancer therapy

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Purpose:
Targeting oncogenes at the chromosomal DNA level can open new avenues for precision medicine. Significant efforts are ongoing to target oncogenes using platforms like proteolysis-targeting chimeras or antisense drugs, but no progress has been made to target chromosomal DNA for cancer therapy. Targeting the chromosomal DNA to downregulate the transcription of oncogenes is a promising approach to treating cancers. We aimed to utilize gamma peptide nucleic acid (gPNA) to inhibit the transcription and cause the silencing of oncogenes. The main hurdle to this approach is the delivery of gPNAs to the nucleus. We have covalently conjugated the gPNA to a nuclear localization signal (NLS) to achieve nuclear delivery. We evaluated the use of gPNA-NLS for nuclear delivery *in vitro* and *in vivo*. We conducted proof-of-concept studies to inhibit *c-Myc* oncogene in lymphoma, which can further imply targeting other oncogenes like *KRAS*, or *HER2*, dysregulated in cancers.

Methods:
We used confocal microscopy and flow cytometry to study the cellular uptake of gPNA-NLS. We quantified the c-Myc levels and their downstream targets using gene expression assays and western blots. We tested the effect on cell viability in multiple lymphoma cell lines. We tested the biodistribution, pharmacokinetic and *in vivo* efficacy of gPNA-NLS in transgenic, cell line-derived, and patient-derived xenograft mouse models.

Results:
We confirmed the uptake of gPNA-NLS in the nucleus. We established the downregulation of c-Myc and its downstream targets using gene expression and western blots. We demonstrated that administering gPNA-NLS improved survival in multiple mice models without toxic side effects. Further, combining gPNA-NLS with histone deacetylase inhibitors results in high and robust anti-cancer activity *in vivo.*

Conclusions:
We identified a novel treatment platform to repress the expression of oncogenes in the nucleus at the DNA level. The gPNA-NLS undergoes nuclear uptake, invades the genomic DNA and inhibits the transcription both *in vitro* and *in vivo.* Results presented in this study evaluated the preclinical efficacy of gPNA-NLS based technology to repress the transcription of oncogenes for cancer therapy.

Keywords:
Peptide nucleic acid, transcription inhibition, *c-Myc*, lymphoma, cancer therapy

Lipid nanoparticles for combinatorial delivery of PTEN plasmid and BRD4 PROTAC in BRAFi-resistant melanoma

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Purpose:
BRAF inhibitors (BRAFi) provide initial regression in mutated melanoma but rapidly develop resistance. Molecular pathways for resistance converge to oncogenic Myc activation. We targeted upregulation of BRD4 oncoprotein and loss of PTEN tumor suppressor gene as MYC-dependent vulnerabilities of resistant melanoma. Co-delivery of PTEN plasmid synergistically enhanced the cytotoxicity of BRD4 PROTAC, ARV-825 (ARV), in BRAFi-resistant melanoma. Objectives of our research were to; (a) develop and characterize PTEN plasmid and ARV co-loaded ionizable lipid nanoparticles (PAL-NANO) using microfluidics and (b) evaluate anticancer efficacy of PAL-NANO in 2D and 3D spheroids models of BRAFi-resistant melanoma.

Methods:
PTEN plasmid and ARV-loaded lipid nanoparticles were fabricated using microfluidic mixing at flow rate ratio of 4:1 (aqueous: organic) and total flow rate of 5 mL/min to attain a concentration of 50 µg/mL for PTEN (PL-NANO) and 1 mg/mL for ARV (AL-NANO) alone and in combination (PAL-NANO). Anti-proliferative effects of nanoformulations were evaluated in BRAFi-resistant (SK-MEL-28R, A375R, RPMI-7951) melanoma cell lines using *in vitro* assays including MTT, migration, vasculogenic mimicry and apoptosis. Lipid nanoformulations were analyzed for tumor growth inhibition and apoptosis in resistant 3D spheroids. Nuclease protection, serum stability and hemolysis assays were preformed to identify systemic safety of PAL-NANO. ELISA was carried out to confirm expression of target protein PTEN in resistant melanoma cells.

Results:
Microfluidic mixing resulted in particle size of <100 nm, unimodal size distribution, neutral surface charge and >99% entrapment efficiency for PTEN plasmid and ARV in all 3 lipid nanoformulations with FDA approved ionizable lipid. PAL-NANO depicted strong synergism between tumor suppressor PTEN plasmid and ARV by significantly reducing the IC_{50} of ARV by ~5-fold to as low as 20 nM in resistant melanoma cells. PAL-NANO demonstrated inhibition in migration and vasculogenic mimicry of A375R cells while inducing significant apoptosis with sustained growth inhibition in 3D spheroids. PAL-NANO protected PTEN plasmid against DNase or in presence of serum and showed negligible hemolysis. Significantly higher expression of PTEN was observed following transfection of lipid nanoparticles in A375R cells.

Conclusions:
Lipid nanocarrier delivering lethal combination of oncoprotein degrader and tumor suppressor gene is a "one-of-a-kind" approach for BRAFi-resistant melanoma therapy.

Keywords:
BRD4 PROTAC, PTEN, Myc, Resistant melanoma, Lipid nanoparticles.

Targeted kidney delivery using covalent glycoconjugates

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Purpose:
Kidneys have remained elusive for targeted delivery in the clinic despite numerous strategies attempted in the past. We developed a novel glycoconjugate for selective, *in vivo* targeting of the kidneys. As proof of concept, we evaluated the systemic delivery of an antisense oligonucleotide covalently conjugated to a carbohydrate-based ligand to target microRNA-21, which is upregulated in kidney fibrosis. Further, we evaluated its efficacy in an *in vivo* kidney fibrosis mouse model.

Methods:
We first synthesized the peptide nucleic acid-based oligonucleotides by solid phase synthesis and conjugated them covalently to a carbohydrate ligand by solution phase synthesis. Further, we did quality control analysis by high-performance liquid chromatography and mass. We confirmed the *in vitro* uptake of conjugated and unconjugated oligonucleotides in the human embryonic kidney (HEK-293T) and human proximal tubular kidney (HK-2) cell lines. We investigated *in vivo* biodistribution and pharmacokinetics of the fluorophore-tagged conjugates using the *in vivo* Imaging System, flow cytometry, and fluorescence microscopy. Finally, using a folic acid-induced *in vivo* model of kidney fibrosis, we tested the efficacy of the conjugates by gene expression analysis, western blot, and histological staining-based techniques.

Results:
We achieved a scalable synthesis of covalent oligonucleotide glycoconjugates. Conjugates show higher *in vitro* uptake in HK-2 cells compared to unconjugated oligonucleotides. Pharmacokinetics of the conjugates demonstrated prolonged retention in the kidney for up to 72 hours with a 5 mg/kg dose. Preliminary efficacy data indicate fewer fibrotic areas in mice treated with conjugated oligonucleotides and reduced smooth muscle actin protein level as a fibrotic marker without toxicities.

Conclusions:
We demonstrate a scalable synthesis of covalent glycoconjugates for selective and extended kidney targeting. Initial *in vivo* efficacy evaluation indicates improvement in kidney fibrosis. This platform is a reliable strategy to explore targeting various kidney diseases such as fibrosis and polycystic kidney disease using molecules ranging from small to macromolecules.

Keywords:
Glycoconjugate, antisense, peptide nucleic acid, targeted kidney delivery, kidney fibrosis

Pharmacokinetics and Pharmacodynamics of a Novel Iron Chelator in Rodents

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Purpose:
Secondary iron overload occurs from prolonged iron therapy typically in patients with impaired erythropoiesis (e.g., thalassemia, sickle cell anemia). Iron chelation therapy represents a critically important strategy to remove excess iron, but the existing iron chelators have displayed incomplete efficacy and poor pharmacokinetics. Hinokitiol, a naturally occurring tropolone derivative, isolated from essential oil of the *Chamaecyparis taiwanesis* tree is a newly characterized lipophilic iron chelator. Our goal is to evaluate the pharmacokinetics and efficacy of hinokitiol in alleviating aberrant iron accumulation using an animal model of iron overload.

Methods:
To evaluate single-dose pharmacokinetics, hinokitiol was administered as 50 mg/Kg orally to CD-1 mice and samples were taken for up to 24 hours. The samples were analyzed via derivatization using a LC-MS/MS method. Compartmental PK analysis was performed with Phoenix WinNonlin®. For mass balance study, Fisher rats were dosed intravenously (15 mg/Kg) and orally (50 mg/Kg) to collect urine and feces for 24 hours using metabolic cages. For Pharmacodynamic study, CD-1 mice were fed high iron diet (10,000 ppm) for a week, followed by IP dosing with 10 mg/Kg hinokitiol twice daily for one week. Animals were sacrificed after the last dose and tissues were analyzed for non-heme iron and ferritin.

Results:
Hinokitiol exhibited a biphasic concentration time profile after an oral dose with a terminal half-life ($t_{½}\beta$) of 4h, distribution half-life ($t_{½}\alpha$) of 0.3 h, volume of distribution (V/F) of 18.7 L/Kg and clearance (CL/F) of 7.4 L/h/Kg. It displays extensive tissue distribution and limited urinary excretion of parent drug (10%). Non-heme iron analysis revealed that hinokitiol significantly decreased serum and liver iron levels by 70% ($p<0.01$) and 69% ($p<0.05$), respectively. Hinokitiol restored serum iron levels close to normal levels. Furthermore, levels of ferritin, the major iron storage protein, in serum and liver were decreased by 43% ($p<0.05$) and 69% ($p<0.05$), respectively as compared to saline-control.

Conclusions:
Hinokitiol displays a rapid distribution, moderate half-life and ameliorates abnormal iron buildup in iron-overload condition. The findings of this study may guide in planning the dosage regimen of anemic iron overload disorders in future.

Keywords:
(Pharmacokinetics, Pharmacodynamics, Iron overload)

Osimertinib immunoliposomes as inhaled therapy for non-small cell lung cancer treatment

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Purpose: Lung cancer is a prevalent cause of cancer mortalities globally, of which non-small cell lung cancer (NSCLC) accounts for >85% of those cases. Tyrosine Kinase Inhibitors (TKI) have been extensively used for treatment of NSCLC with epidermal growth factor receptor (EGFR) overexpression. Osimertinib (OB), a third-generation irreversible TKI, is an approved therapy for NSCLC patients bearing the EGFR T790M mutation. Eventually, resistance to EGFR-TKI therapy due to triple mutations (sensitizing mutations, T790M and C797S) will become a significant challenge. Therefore, there is a need to overcome the resistance, which can be effectively achieved by targeting the EGFR with anti-EGFR monoclonal antibodies. In this study, osimertinib was encapsulated in liposomes, and the surface of the liposomes was modified for conjugation with cetuximab (CTX), an anti-EGFR monoclonal antibody to enhance drug delivery and anti-tumor efficacy. Further, pulmonary administration of liposomes was utilized for safe and efficacious delivery of the drug to the target site, limiting systemic toxicity.

Methods: In the present study, osimertinib liposomes were prepared using thin film hydration method followed by a conjugation reaction between the N-terminal of the antibody and the carboxylic group present on the liposomal surface to obtain immunoliposomes (CTX-OB-LPs) for pulmonary administration.

Results: These immunoliposomes exhibited a particle size of around 150 nm with a zeta potential of -2.69±0.98mV and a protein conjugation efficiency of 87.53±2.84%. The conjugated liposomes demonstrated an initial burst release of 53.42% in 10h followed by complete release within 48h. Additionally, in-vitro aerosolization studies demonstrated a mass median aerodynamic diameter of 3.22±0.12µm and a high fine particle fraction of 88.43±0.38%. Further stability studies on the immunoliposomes proved their stability when stored at 4˚C for 4 weeks. In-vitro studies of immunoliposomes on H1975 cells displayed higher cytotoxicity with ~1.7 and ~1.2-fold reduction in IC_{50} values compared to free drug and unconjugated osimertinib liposomes, respectively. Furthermore, the immunoliposomes displayed significant suppression in tumor cell migration over 48h compared to free drug and unconjugated osimertinib liposomes.

Conclusion: Hence, EGFR-targeting inhalable immunoliposomes can potentially contribute to greater anti-tumor efficacy for non-small cell lung cancer treatment.

Keywords: Non-small cell lung cancer, Osimertinib, Cetuximab, Immunoliposomes, Inhalation therapy**.**

Fabrication of Novel Adapter for *In-Vitro* Release Testing and IVIVC Development of Long-Acting Injectable Suspensions

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Purpose:
Long-acting injectable suspensions form depots for slow release of drug following subcutaneous or intramuscular administration. To ensure product quality, it is necessary to develop robust and reproducible *in vitro* release testing methods. The FDA recommended testing methods are short in duration. However, release testing methods with longer duration that adequately mimic the *in vivo* release profiles are necessary for the purpose of *in vitro-in vivo* correlations (IVIVCs).

Methods:
Medroxy Progesterone Acetate (MPA) suspensions were selected as a model. Particle size and excipient source were considered as possible critical parameters in the preparation Q1/Q2 formulations. Two suspending media (Media 1 and Media 2) with the only difference being the PEG3350 source were prepared to assess the impact of polymer source on MPA release. Formulations F1 and F3 were prepared by dispersing MPA as received in media 1 and 2. Whereas, in formulation F2 the API was recrystallized using an anti-solvent (acetone) method and then suspended in media 1. The MPA suspensions were prepared *via* a simple mixing method. The formulations along with the reference listed drug were then tested for physicochemical properties such as viscosity, F-value, particle size and morphology. The *in vitro* release behavior was investigated using a novel adapter in USP Type IV apparatus.

Results:
Formulations prepared using different polymer sources and MPA of different particle sizes had significantly different release behavior. Since F2 had the largest particle size it showed the slowest release which was attributed to poor dissolution of larger particles or closed packing of irregular shaped particles. The difference in the release behavior of F1 and F3 suggested that polymer source affected MPA release. The *in vitro* data generated using the novel adapter achieved a good correlation with the *in vivo* data. A good Level A correlation was established using this method.

Conclusions:
The developed novel adapter showed good discriminatory ability and reproducibility for the Q1/Q2 formulations and the reference listed drug. The relatively longer release duration was critical in the successful development of a Level A *In-vitro-In-vivo* correlation

Keywords:

Long-acting parenteral suspensions; Medroxy Progesterone acetate; Novel adapter; USP type IV apparatus, *In-vitro-In-vivo* correlation.

Development of Thermo-Responsive Drug-Loaded Hydrogels for Treatment of Diabetic Neuropathy

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Purpose:
A major and irreversible complication of diabetes is diabetic peripheral neuropathy (DPN), which can lead to significant disability and decreased quality of life. The current treatments achieve DPN pain relief in only half of the patients affected. An additional challenge is that current therapies do not necessarily support nerve repair, which is critical for restoration of function and reduced pain. Our prior and ongoing work confirms that DPN is associated with macrophage accumulation near terminals and in the proximal nerve driven by the peptide hormone Angiotensin II (Ang II). Therefore, we predict that by utilizing a non-invasive treatment *via* local hydrogel injection, we can offer a sustained drug release. With these drug-loaded hydrogels, we can reduce nerve dysfunction and promote nerve healing in DPN patients.
Methods:
Drug-loaded hydrogels were created by encapsulating a macrophage modulating ACE inhibitor into a micelle, which was then embedded into a hydrogel matrix. Thermoresponsive behavior was assessed using rheology. To test product efficacy, drug-loaded hydrogels were tested against drug-free using Ang II ELISA. Additionally, drug-loaded hydrogels were injected into wild-type or type 2-diabetic mice ($Lepr^{db/db}$ males, 18 weeks of age).
Results:
Drug-free and drug-loaded hydrogels demonstrated excellent product stability and sterility. Rheology displayed low gel viscosity at room temperature and high viscosity at 37C. Drug-loaded hydrogels significantly inhibited ANG I to ANG II conversion in comparison to drug-free hydrogels. *In vivo* experiments in mice treated with drug-loaded hydrogels displayed normalized mechanical sensitivity in $Lepr^{db/db}$ mice, restoring baseline sensitivity compared with WT mice.
Conclusions:
Through careful formulation design, ACE-inhibiting drugs were successfully encapsulated in the micellar matrix of a hydrogel. These thermoresponsive hydrogels were designed to flow at room temperature for ease of injection and solidify at physiological temperature to allow for sustained drug-release at the site of local injection. Efficacy of these drug-loaded hydrogels were displayed through ELISA and *in vivo* trials. While sensitivity was restored to treated $Lepr^{db/db}$ mice showing management of sensory deficits for DPN patients, we hypothesize that these gels can also be used to facilitate neuro-regeneration as well.
Keywords: Diabetic neuropathy (DPN), thermoresponsive hydrogels, angiotensin converting enzyme (ACE) inhibitor.

Spray-Dried Inhaled Solid Dispersion of Amodiaquine for Respiratory Disorder

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Purpose:
Non-small-cell lung cancer (NSCLC), a diverse group of tumors, accounts for roughly 85% of lung cancer diagnoses. There is rising evidence that repurposed medications work extremely well against many cancers. In our earlier studies, we have shown feasibility of an antimalarial drug, amodiaquine (AQ), in treating NSCLC. In this study, we developed inhaled solid dispersion of AQ to enable local accumulation in the lungs, and enhanced formulation stability and efficacy against NSCLC. We utilized spray drying for producing solid dispersions which enables quick solvent evaporation and accelerates the conversion of an API-carrier solution into solid API-carrier particles.

Methods:
AQ solid dispersions were developed using a spray drier. Mannitol and Leucine were used as a carrier in different proportions to prepare solid dispersion. 30% of the drug load was used with 2% solid content. Drug and carriers were weighed in various ratios and dissolved in water. Spray drying was performed on these solutions using one nozzle Buchi Mini Spray Dryer B-290. The operating parameters were kept as follows: Aspirator-100%, Inlet temperature-100^0C, Feed rate-20%. The powder was collected and % yield was calculated for all the formulations. Afterwards, these powders were characterized with DSC, PXRD and drug content was calculated for the same.

Results:
The appearance of spray dried solid dispersion was yellow in color. A significant increase was observed in % yield of the spray-dried formulation with increase in leucine content of the formulation (49.9% yield for 0% leucine vs. 87.6% for 75% leucine). The drug content analysis for optimized *Formulation 4* (25% Mannitol + 75% Leucine) was found to be 0.241 mg AQ/mg of formulation. The DSC data demonstrated that formulation 4 has the capacity of changing the drug in amorphous form, hence stabilizing it. Further studies for optimized solid dispersions are in progress to determine particle shape, *in-vitro* lung deposition, and stability.

Conclusions:
Solid Dispersion of Amodiaquine was successfully prepared using spray dryer. Higher percentage of Leucine resulted in an amorphous formulation with high % formulation yield.

Developing an Inhaled Nano-Emulsion for Repurposing a Herbal Drug for Non-small Cell Lung Cancer

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Purpose:
Nano-emulsions (NEs) are oil-in-water (O/W) or water-in-oil (W/O) dispersion of two immiscible liquids stabilized using a surfactant. They have a mean droplet size of <500 nm which discourages destabilization processes like creaming, sedimentation, and coalescence. Celastrol (Cela), a principal ingredient of *Tripterygium wilfordii*, has been found to have anticancer, anti-inflammatory, antidiabetic and antimicrobial efficacy. However, its low aqueous solubility and poor bioavailability have deterred its clinical translation. Therefore, we aim to encapsulate Cela in a stable nano-emulsion with acceptable levels of surfactant which can be used for treatment of non-small cell lung cancer (NSCLC).

Methods:
A clear stable Cela-NE was prepared using Capmul MCM, Tween 80, Transcutol HP and deionized water as oil, surfactant, co-surfactant and aqueous phase, respectively. Briefly Cela was solubilized overnight in Capmul MCM (25%) followed by gentle vortexing with S_{mix} (25%) (Tween 80: Transcutol HP 4:1) to form the oil phase. The volume of aqueous phase (50%) was determined using water titration method. The resulting NEs were characterized for physiochemical parameters. MTT assay in NSCLC cells were performed to assess the cytotoxic potential of Cela-NE against its plain drug counterpart.

Results:
The encapsulation of Cela was evaluated to be 97.2±1.8%. The mean globule size was 201.4±3.7 nm with a PDI of 0.4±0.1. The zeta potential was -15.7±0.2 mV indicating stability. The *in-vitro* studies performed in A549 and H1299 cells demonstrated Cela-NE to have better cytotoxicity (IC_{50} 0.3±0.1 µM) as compared with its plain drug counterpart (IC_{50} 1.2 ± 0.2 µM).

Conclusions:
These preliminary results corroborate NE to be a promising delivery system, that can be employed for repurposing of Celastrol for NSCLC. Future experiments involving comprehensive *in-vitro* and *in-vivo* response would further help in understanding its potential as a drug delivery system.

Keywords:
Nanoemulsion, Repurposing, Lung cancer, Inhalation, Drug delivery

Enhanced Solubility and Anticancer Efficacy of Lorlatinib-Cyclodextrin Inclusion Complex

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Purpose:
Lorlatinib is a medication that is primarily used to treat a specific type of non-small cell lung cancer called ALK-positive non-small cell lung cancer. It has been demonstrated to be useful in reducing tumor growth and enhancing patient survival. However, due to its high lipophilicity, lorlatinib is practically insoluble in water (less than 0.1 mg/mL). In this study, a drug-cyclodextrin inclusion complex was created, so as to increase the medication's solubility in water, hence improving drug stability, and lowering susceptibility to degradation.

Method:
In our phase solubility investigation, we introduced 1 mg of medication to 1 mL of cyclodextrin (sulfobutylether-β-cyclodextrin; SBE—CD) aqueous solution at various concentrations (25–200 mM). For equilibration, suspensions were placed in a bath sonicator for 5 minutes and were put on rotation for 24 hours at room temperature. After 24 hours, the solution was filtered using a 0.22 μm polyvinylidene fluoride syringe filter to separate it. The inclusion complex of Lorlatinib with SBE-β-CD were measured using a UV spectrophotometer at 310 nm. For each formulation, the % complexation was computed. Using DSC and NMR, we identified the formation of inclusion complex.

Results:
It was observed that lorlatinib's solubility increased linearly when CD concentration increased. By creating soluble drug-CD complexes, a linear curve shows that the overall drug solubility rises as a function of CD concentration. The aqueous solubility of Lorlatinib increased with increasing CD concentrations, as demonstrated by 2,231.2 μM (2.23 mM) with SBE-β-CD (200 mM), as compared to 150 μM for plain drug (a ≈ 15-fold solubility enhancement). A DSC thermogram demonstrated an absence of the characteristic sharp endothermic peaks of Lorlatinib and SBE-β-CD, which may be suggestive of successful inclusion of Lorlatinib into the SBE-βCD cavity.

Conclusion:

Present work successfully investigated the complex formation of Lorlatinib with SBE-β-CD, aiming to improve its solubility. Further investigations into stability, and anticancer efficacy of lorlatinib-SBE-β-CD complex are currently being performed.

Development of a Flow-based *in*-vitro Multicellular Tumor Spheroid Model for Testing Anti-Cancer Therapeutics

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Purpose:
To develop a cost-efficient, *in*-vitro Multicellular tumor spheroid (MCTS) model that captures various attributes of an *in*-vivo tumor microenvironment (TME) such as 3-Dimensional architecture, cellular heterogeneity, presence of extracellular matrix, and most importantly fluid-flow.

Methods:
Spheroids consisting of two different cell types of lung carcinoma namely A549 (Non-drug resistant cells), and H69/AR (Drug-resistant cells) were cultured in a regular 96-well plate using an optimized liquid overlay technique. Microscopy was used to monitor the morphology and size of the spheroids. For the introduction of the flow component, the spheroids were transferred to a regular 6-well plate equipped with tubing that circulated the culture medium containing the treatment with the help of a peristaltic pump. A flow cytometry method was developed to monitor the efficacy and targeting ability of a well-documented mitochondriotropic liposomal formulation designed to demonstrate selective toxicity against drug-resistant cells. The efficacy was calculated as a fold change in the ratio of A549:H69/AR cells compared to the control.

Results:
Two different starting ratios of A549 and H69/AR (1500:1500 and 1500:2500 cells) were used to culture the MCTS. Spheroids of maximum sizes of 1mm in diameter were obtained reproducibly in each well of the 96-well plate over 15 days. Distinct proliferative and necrotic zones were visible in the spheroids when subjected to a microscope. At the end of Day 5, the spheroids containing the cell ratio of 1500:2500 cells were compact, easy to isolate, and comprised about 50% of each cell population with a size of ~450 µm. These spheroids were further used to test the efficacy of the liposomal preparation. The liposomes had a particle size of 129 $\pm$ 3nm and a zeta potential of 33 $\pm$ 4mv. When compared with a co-cultured monolayer, a significant decrease ($P < 0.05$) from 1.6 to 1.36 and 1.2-fold in efficacy was observed for the spheroids with and without the flow, respectively.

Conclusions:
This model allows the cost-effective development of MCTS and the testing of treatments in a circulating fluid-flow. It has the potential to replace standard *in*-vitro models currently used to screen anti-tumor therapeutics.

Keywords: Tumor microenvironment, Multicellular tumor spheroids, Fluid-flow.

Optimization of Nanosensor Response for the Detection of Anthracyclines Using Machine Learning

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Purpose:

Pharmacokinetic variables such as interindividual variation in metabolizing and eliminating drugs after first dosage makes dose selection of chemotherapeutic anthracyclines increasingly difficult. One potential solution to determining dosing levels of an anthracycline is the development of non-invasive sensors to monitor their pharmacology in vivo. Single-walled carbon nanotubes (SWCNT) have substantial potential for in vivo sensor development, as they exhibit near-infrared fluorescence in the tissue-transparent window and a robust response to their local environment. An emerging method for optimizing SWCNT sensor response is through machine learning.

Methods:

In this study, anthracyclines Daunorubicin, Doxorubicin, Epirubicin, Valrubicin, Mitoxantrone and Idarubicin, were used to interrogate 12 SWCNT preparations wrapped with short oligonucleotide sequences. In triplicate, each combination of oligonucleotide and anthracycline were evaluated for concentrations ranging from 0.04µM - 1000µM via near-infrared fluorescence analysis in a high-throughput format. A machine learning algorithm was implemented using MATLAB's machine learning toolbox which translated DNA sequences into numerical vectors, using cross validation, which were matched with various anthracyclines for chemometric screening.

Results:

Analysis of each anthracycline-SWCNT combination revealed specific patterns of fluorescence modulation. The developed machine learning algorithm allowed for optimized prediction of responses in fluorescence signal, including changes in wavelength and intensity, for a specific combination following laser excitation and high-throughput spectroscopy.

Conclusion:

We found that such an algorithm can be utilized not only for precision medicine but also for analyzing patterns in responses of fluorescent nanosensors to a class of chemotherapeutics. We anticipate future work in developing multi-purpose nanosensors that monitor the pharmacokinetics of active pharmaceutics and potentially for disease biomarkers that measure response to drug treatment.

Keywords:

Nanosensors, Machine Learning, Anthracycline, Pharmacokinetics, Chemotherapy

Comparative Effectiveness of Annonacin in Human Prostate Cancer (PC-3) Cells

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Purpose:
Prostate cancer is one of the leading causes of death in men due to its poor prognosis and high metastatic rates. Annonacin, a highly lipophilic annonaceous acetogenin, obtained from *Annona muricata* native to tropical regions is a mitochondrial complex 1 (NADH-dehydrogenase) inhibitor. Annonacin has been used in traditional folk medicine and has demonstrated significant antineoplastic activity against a variety of multidrug-resistant cancers, including breast, colon, and pancreatic cancer. However, despite its therapeutic benefits, annonacin has several side effects, the most serious of which is high-risk, life-threatening neurotoxicity. Therefore, the goal of this study was to assess if combination therapy with docetaxel might reduce the necessary drug concentration needed of annonacin for inducing cytotoxicity in prostate cancer (PC-3) cells and maintaining the effectiveness while minimizing the neurotoxic potential in neuroblastoma (SH-SY5Y) cells.

Methods:
The lactate dehydrogenase (LDH) assay kit was used to assess the cytotoxicity of PC-3 and SH-SY5Y cells in response to treatment. LDH, a plasma membrane damage marker, was measured in cells by measuring absorbance at 450 nm. Similarly, antiproliferative effect of annonacin and docetaxel was evaluated using a colorimetric BrdU cell proliferation kit where the absorbance value directly correlates to the amount of DNA synthesis and thus to the number of proliferating cells present.

Results:
There was a substantial concentration-dependent reduction in the cell viability of PC-3 and SH-SY5Y after treatment with annonacin and docetaxel ($p<0.05$). Cell proliferation was significantly ($p<0.05$) inhibited in both prostate cancer and neuroblastoma cells when treated with annonacin and docetaxel. The results suggest that both the drugs induce cytotoxicity via inhibiting cell proliferation.

Conclusions:
According to the above-mentioned results, docetaxel and annonacin both impede cell growth and induce cell death. The exact mechanism by which annonacin and docetaxel induce cell death and inhibit cell proliferation is not known.

Keywords:
(Prostate cancer, annonacin, docetaxel, cell proliferation, neurotoxicity)

Polymer-based precipitation: The molecular weight and concentration of polyethylene glycol (PEG) affects exosome recovery

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Purpose:
Exosomes, nano-sized extracellular vesicles, are promising candidates for drug delivery for an array of diseases. Although this benefit in nanomedicine is established in various research work, the recovery rate of exosomes hinders their use in a large setting. Accordingly, several isolation methods have been developed to improve exosome recovery, one of which is the polymer-based precipitation method using polyethylene glycol (PEG). Inspired by its use as an excipient, PEG, a biocompatible polyether, has been used to precipitate exosomes to achieve a reported >90% exosome recovery. Though PEG, with a molecular weight of 6000, is commonly used in this method, there is limited research that compares exosome recovery using different molecular weights and concentrations.

Methods:
In this study, a quantitative analysis of exosome recovery from four molecular weights of PEG (400, 3350, 6000, 8000) and subsequent concentrations (5%-30%), using exosome-specific (CD63) quantitative assays was conducted. In addition, particle size analysis and protein assays were used to identify protein concentration and exosome size. Exosomes isolated through ultracentrifugation served as the control group.

Results:
The results showed that exosome recovery increased as the molecular weight increased, with PEG 6000 and PEG 8000 producing the highest exosome recovery rate. In addition, the concentrations (5%, 10%, 15%, 20% and 30%) of PEG applied at the different molecular weights recorded increased exosome recovery, with PEG 6000 at 30% concentration showing the greatest exosome recovery ($p<0.05$). Importantly, the protein concentration of PEG 3350 was significantly lower than PEG 6000 ($p<0.05$), whereas PEG 400 and PEG 8000 showed higher protein concentrations than PEG 6000. Noteworthy, the molecular weight of PEG used affects the size of the isolated exosomes.

Conclusions:
The analysis of the optimum molecular weight and concentration would prove invaluable for maximum exosome recovery to assist in the bench to bedside use of exosomes in nanomedicine.

Keywords:
Polyethylene glycol, exosome, polymer-based precipitation

Modeling of Nanomilling of Drug Suspensions via Population Balances

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Purpose:
We aimed to develop a fundamental understanding as to how drug particles break, and nanoparticles are produced during wet media milling *via* a population balance model (PBM).

Methods:
A suspension of 10% fenofibrate (FNB, a model poorly water-soluble drug) was wet-milled in a lab-scale Microcer stirred media mill for 180 min along with two stabilizers: 7.5% hydroxypropylcellulose (HPC-L, an adsorbing neutral polymer) and 0.05% sodium dodecyl sulfate (SDS, an anionic surfactant). The milling chamber was filled with 55 vol.% of 400 µm yttrium-stabilized zirconia beads, and the rotor speed was set 3000 rpm. The particle size distribution (PSD) was measured via laser diffraction at regular time intervals. A PBM was formulated with several specific breakage rate S functions, which were discriminated based on goodness-of-fit to experimental data, and a one-term self-similar breakage distribution function B.

Results:
The wet media milling led to a stable fenofibrate nanosuspension with a median size of ~180 nm. The PSD shifted to finer particle size domain as milling progressed. Within the first 32 min, the PSD was bimodal due to aggregation of particles, and when sufficient time for stabilizer adsorption was given during prolonged milling, the PSD became unimodal. Among all S models tested, the combined power law–logistic function model with a shape factor of $sf = 14.06\ \mu m^{-1}$ and a cut-off size of $x^* = 341$ nm best explained the PSD evolution. Our results suggest that there was a drastic drop in the specific breakage rate for particles with sizes below 341 nm. This could be explained by the difficulty of capturing such fine particles by the 400 µm beads and their inherent high strength.

Conclusions:
A novel PBM was developed to describe the PSD evolution during the production of a drug suspension by wet media milling, which revealed a dramatic transition of particle breakage behavior in the submicron scale.

Keywords:
Wet media milling, population balance modeling, drug nanoparticles, breakage kinetics

Inhalation of spray-dried nisin ZP peptide for non-small cell lung cancer (NSCLC) treatment

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Purpose:
Lung cancer is the leading cause of cancer mortality, with most of the reported cases (>85%) associated with non-small cell lung cancer (NSCLC). Recently, antimicrobial peptides (AMPs) have gained interest as anticancer agents as they selectively target cancer cells and decrease the possibility of resistance. Nisin ZP, an antimicrobial peptide (AMP) produced by the bacterium *Lactococcus lactis*, has previously demonstrated anticancer activity in NSCLC (A549) cells. In this study, we formulated a nisin ZP dry powder (NZSD) using a spray dryer to facilitate inhaled delivery for the treatment of NSCLC.

Methods:
NZSD powders were prepared using different nisin ZP content (10, 20, and 30% w/w) with mannitol, L-leucine, and trehalose in a ratio of 75:15:10 using Büchi mini spray-dryer B-290. The spray-dried powder was characterized for yield, peptide content, residual moisture content (TGA), morphology (SEM imaging), solid-state characteristics (DSC and PXRD), and storage stability. Aerosolization performance of dry powders was evaluated using Plastiape RS01 dry powder inhaler device in Next Generation Impactor (NGI™).

Results:
NZSD powder revealed a good powder yield of >55% w/w with ≤3 % w/w moisture content and high nisin ZP drug loading for all the peptide ratios. The NZSD powder particles were irregularly shaped with corrugated morphology, and the semi-crystalline powder nature of NZSD was confirmed by presence of an endothermic peak in DSC thermograms and attenuated crystalline peaks in PXRD diffractograms. The anticancer activity of nisin ZP was maintained after fabricating it into NZSD powder and showed a similar inhibitory concentration to free nisin ZP in NSCLC cells (A549, H1299, and H1975). Stability studies indicated that NZSD powders were stable for three months at 4 and 25 ℃ with more than 90% drug content and semi-crystalline nature, as confirmed by DSC and PXRD. Aerosolization studies performed using NGI indicated an aerodynamic diameter (MMAD) within the desired range (1-5 µm) and a high fine particle fraction (FPF > 75%) for all peptide ratios, suggesting powder deposition in the lung's respiratory airways.

Conclusions:
In conclusion, a dry powder of nisin ZP was formulated using a spray dryer with enhanced storage stability and suitable for inhaled delivery.

Keywords:
Dry Powder; Nisin ZP; Inhaled Delivery; Antimicrobial Peptides (AMPs); Non-small Cell Lung Cancer (NSCLC)

Modification of Polymeric Mesoscale Nanoparticles for Enhanced mRNA Loading

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Purpose:
In prior work, we successfully formulated mRNA-loaded, kidney-targeted, polymeric nanoparticles, and studied their uptake kinetics and mRNA expression in vitro. The aim of these studies was to develop kidney-targeted gene therapies for kidney diseases and renal cancer. In ongoing work to maximize protein expression in vivo using rodent models, we aimed to increase the total loading of the mRNA cargo within the nanoparticle by optimization of formulation parameters.

Methods:
We sought to enhance mRNA loading by modifying our original system with various biomolecules and other excipients via charge or other interactions with our polymeric nanoparticle system. To do so, we performed mRNA nanoparticle loading optimization studies and assessed them against our original formulation via Quant-iT RiboGreen assays and in vitro fluorescent protein reporter translation using renal cell lines. Thereafter, we aimed to test the biocompatibility of our modified formulation through cell viability assays.

Results:
Prior studies found near-complete encapsulation efficiency with 5ug- 10ug of cargo, though we found reduced encapsulation efficiency at higher loading masses. We found these particles can deliver functional mRNA into renal proximal tubular epithelial cells, with expression of a fluorescent protein reporter within one hour of incubation.

Conclusions:
Modification of mesoscale nanoparticles to retain their size and surface parameters necessary for renal targeting is possible with mRNA encapsulation. Ongoing in vivo studies are aimed toward maximizing renal targeting capabilities of the nanoparticle system, as well as the renal expression of exogenous protein, with a focus on intervention in renal disease.

Keywords:
Polymeric nanoparticles, mRNA loading, kidney disease, gene delivery

Optimization of mesoscale nanoparticle formulation process through the design of experiments approach

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Purpose:
Polymeric nanoparticles with a diameter of 350 – 400 nm (mesoscale) have been shown to selectively accumulate in the kidneys, thus presenting a promising delivery system for kidney disease therapeutics. This kidney-targeting property is specifically attributed to the nanoparticle size in the mesoscale range. Therefore, it is crucial to be able to precisely control the nanoparticle characteristics via the formulation process. In this work, we aim to optimize the formulation conditions of the mesoscale nanoparticles to achieve desired characteristics using the design of experiments (DoE) approach.

Methods:
Mesoscale PLGA-PEG nanoparticles encapsulating edaravone as a model drug were prepared using the nanoprecipitation method. Different formulation parameters have been screened to establish the significance of their influence on the nanoparticle characteristics such as size, polydispersity index, zeta potential, drug loading, and yield. Fractional factorial 2^{8-4} resolution IV design was used for the screening step. Further experiments were aimed at building a model for the nanoparticle formulation process and finding optimum levels of the formulation parameters that allow for obtaining desired nanoparticle characteristics. This step employed response surface methodology.

Results:
Formulation parameters that have a significant effect on mesoscale nanoparticle characteristics (size, polydispersity index, zeta potential, drug loading, and yield) were identified. Then the mathematical model of the formulation process was established and represented in the form of a response surface plot. Based on this data, formulation parameter levels were optimized to achieve nanoparticle size in the range of 350 – 400 nm, as well as minimize polydispersity index, and maximize drug loading and yield.

Conclusions:
This study has systematically evaluated and mathematically described the impact of various formulation process variables on the resulting mesoscale nanoparticle characteristics. Such a thorough understanding of the formulation process is fundamental for consistently obtaining desired nanoparticle specifications and, hence, successful drug delivery to the disease site.

Keywords:
Nanoparticles, kidney-targeted delivery, formulation, design of experiments.

Accelerated Stability Modeling of Gelatin Capsule Disintegration Time

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Purpose:
Crosslinking of gelatin capsules on long-term storage can significantly slow drug dissolution *in vivo* and potentially limit a drug's bioavailability. Traditional methods of determining the shelf life of these capsules can take many months. This work sought to determine if exposure of capsules to a range of temperatures and relative humidities (RH) in a short time could be used to effectively model the disintegration behavior for long-term storage using a modified Arrhenius equation. The work also attempted to establish whether excipients impact this stability.

Methods:
Hard gelatin capsules, with and without starch-1500, were distributed to canning jars containing saturated salts to control the RH at the following conditions, all below the glass transition temperature (T_g) of gelatin: 50°C/42% RH, 60°C/26% RH, 65°C/49% RH, 70°C/28% RH, 80°C/11% RH, 80°C/41%, 85°C/25% RH, 90°C/10% RH. Disintegration testing (n = 10) was done visually (Sotax DT2 disintegration apparatus) after storage at various time points. The resulting failure points were modeled using ASAP*prime*® software.

Results:
Models were constructed from the storage times at each condition where disintegration failed. Data for both filled and empty capsules were well-fit to the modified Arrhenius equation. The parameter fits were similar for both systems.

Conclusions:
Slowdown in disintegration time of stressed gelatin capsules was able to be modeled in ASAP*prime*® supporting the use of accelerated stability modeling for determining the physical stability of gelatin capsule drug products. The use of this process can shorten the development time for new drug products. The fact that added starch (and other excipients screened as part of this project) had minimal effects on the gelatin crosslinking calls into question the general belief that such crosslinking is linked to excipient aldehyde impurities versus other mechanisms intrinsic to the gelatin itself.

Keyword*:*
ASAP*prime*®, Accelerated Stability, Capsule Stability, Stability Modeling

Overcoming Aging-Associated Poor Influenza Vaccine Responses with CpG 1018 Adjuvant

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Purpose:
Aging is associated with diminished immune system function, which renders old people vulnerable to influenza infection and less responsive to influenza vaccination. This study explored whether the CpG 1018 adjuvant was effective in enhancing influenza vaccine efficacy in aged mice equivalent to human beings in their late 50s to early 60s.

Methods:
This study used the influenza pandemic 2009 H1N1 (pdm09) vaccine as an example to explore whether CpG 1018 was effective in enhancing its humoral and cellular immune responses and protection in an aged mouse model.

Results:
We found that the CpG 1018 adjuvant could significantly enhance the pdm09 vaccine-induced serum antibody titer, while the pdm09 vaccine alone failed to elicit significant antibody titer. In contrast, the pdm09 vaccine alone elicited significant antibody titer in young adult mice. Antibody subtype analysis found that the pdm09 vaccine alone elicited Th2-biased antibody responses in young adult mice, while incorporation of the CpG 1018 adjuvant promoted the elicitation of potent Th1-biased antibody responses in aged mice. The pdm09 vaccine alone was further found to induce significant expansion of Th2 cells in young adult mice, while incorporation of the CpG 1018 adjuvant stimulated significant expansion of Th1 cells in aged mice. The CpG 1018 adjuvant also stimulated vaccine-specific cytotoxic T lymphocytes in aged mice. The pdm09 vaccine in the presence of CpG 1018 elicited significant protection against lethal viral challenges, while the pdm09 vaccine alone failed to confer significant protection in young adult or aged mice.

Conclusions:
Our study provided strong evidence to support the high effectiveness of the CpG 1018 adjuvant to boost influenza vaccination in aged mouse models.

Keywords:
CpG 1018; CpG; aged mice; influenza vaccine; immunosenescence

Improved Dissolution of Nintedanib Amorphous Solid Dispersion Prepared by Hot-melt Extrusion

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Purpose:
Nintedanib, a tyrosine kinase inhibitor, has been approved by FDA for treatment of idiopathic pulmonary fibrosis. However, it has an extremely poor water solubility, leading to challenges in absorption and bioavailability. In this work, nintedanib amorphous solid dispersion (ASD) was prepared by using a hot-melt extrusion (HME) to improve the solubility and bioavailability.

Methods:
Nintedanib and Kollidon® VA64 (PVP VA64) were blended at a weight ratio of 1:10. The blend was processed by a 16 mm twin screw HME with a screw speed of 40 rpm. The barrel temperature was controlled at the range from 80 °C to 220 °C. The prepared ASD was characterized by differential scanning calorimetry (DSC), X-ray powder diffraction (PXRD) and
polarized light microscope (PLM). Drug dissolution behavior of the ASD was investigated in phosphate buffer solution (PBS, pH 6.8) where pure nintedanib powder was used as a reference.

Results:
The ASD was smoothly prepared by using the HME. DSC thermogram showed that the melt peak of nintedanib powder was 254.6 °C while it disappeared in ASD. PXRD patterns displayed that characteristic diffraction peaks (2θ) of nintedanib powder at 10.36, 11.17, 11.74, 12.68, 14.89, 16.06, 17.00, 19.27, 19.64 and 22.75 were absent in the ASD. PLM images showed no nintedanib crystalline birefringence was observed in the ASD. Dissolution profiles demonstrated that compared with that of the pure nintedanib, the dissolution rate of nintedanib ASD was significantly increased 25.7 folds in a pH 6.8 PBS.

Conclusions:
DSC, PXRD and PLM studies confirmed that the crystal structure in nintedanib was disrupted in the polymer matrix, and was transformed into the amorphous form, because of which the dissolution was remarkably improved. This ASD will be a promising formulation to tailor low solubility and bioavailability commercial nintedanib on the market and achieve better oral absorption and bioavailability.

Keywords:
Nintedanib; Hot-melt extrusion; Amorphous solid dispersion; Dissolution

Coarse-grained Molecular Dynamics Modeling to Investigate the Aggregation of ssDNA Loaded Adeno-Associated Viral Capsids

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Purpose:

Adeno-associated virus (AAV) is a small virus that is roughly 26 nm in diameter. It has an icosahedral, nonenveloped shape and is considered a promising vector for encapsulating a single-stranded genome (ssDNA) for *in vivo* gene delivery. However, little is known about the primary driving force or the mechanism of AAV capsid aggregation during the upstream and downstream manufacturing and storage processes. Additional uncertainty surrounds the role of loaded ssDNA in the aggregation process. As a result, a coarse-grained molecular dynamics (CG-MD) simulations approach was adopted to probe the underlying mechanism of the interaction between capsids. The CG-MD model was further validated with previous experimental data.

Methods:

The CG-MD simulations and their analyses were implemented using the GROMACS package with the MARTINI force fields. The AAV Serotype 8 (AAV8) was chosen as the model viral capsid (PDB: 6v12) with 2.2kb single-strand DNA. The steepest descent algorithm was used in energy minimization followed by a 10 ns equilibration step. The simulation production runs were performed in an isothermal-isobaric ensemble using the Nosé−Hoover thermostat and the Parrinello−Rahman barostat at a pressure of 1 bar for each 20-fs time step.

Results:

The capsid aggregation was approved to be involved in complex protein aggregations and the multiple residue interactions, including hydrophobic, polar, and charged residues. Two mechanisms of aggregation were identified: fivefold face-to-face contact and edge-to-edge contact. At higher temperatures, the capsid structure was determined to be unstable due to a decrease in intramolecular hydrogen bonds, an increase in conformational deviations of protein subunits, and increased fluctuations of residues. Additionally, the size of the loaded ssDNA was found to expand significantly under higher temperature conditions.

Conclusions:

The stability and electrostatic charges of the capsids and the free ssDNA molecule were successfully evaluated using this developed computational model. Our simulations provide general dynamical information about the structure of the ssDNA and capsids on a microsecond timescale, revealing behavior that is unobtainable from experimental studies. The CG-MD simulations are demonstrated to be a powerful tool in the simulation of macromolecular complexes and are capable of guiding the interpretation, explanation, and direction of experiments.

Keywords: Adeno-associated viruses, molecular dynamics, capsid aggregation, protein interaction, ssDNA.

Formulation of Lovastatin loaded Bilosomes for Enhanced Oral Bioavailability

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Purpose:
Lovastatin (LV) is an HMG-CoA reductase inhibitor, used to treat hypercholesteremia. LV is water insoluble and undergoes extensive first-pass metabolism, contributing to poor oral bioavailability (<5%). Nanoparticle formulations have been used to overcome these problems by reducing the particle size and enhancing surface characteristics. In our study, bilosomes were formulated to enhance the oral bioavailability of LV. Bilosomes are composed of bile salt molecules integrated between the phospholipid bilayer membrane. Bile salts addition imparts higher stability to the vesicle by reducing vesicle disintegration upon exposure to acidic enzymes.

Methods:
Bilosomes were prepared using 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and sodium deoxycholate (SDC). Briefly, LV and DPPC were dissolved in chloroform which was evaporated to a thin film using the rotary evaporator. The resulting film was rehydrated using phosphate buffer containing SDC. The formulation was then extruded by probe extrusion to reduce the particle size and subjected to 3 freeze-thaw cycles to promote drug encapsulation. Different bilosomal systems were prepared using variable formulation parameters such as number of extrusion cycles, volume of the hydrating solution, and amount of DPPC. Particle size (PS), zeta-potential (ZP) and encapsulation efficiency (EE%) of formulation systems were measured and optimized.

Results:
Formulated systems showed PS range from 159.7 nm to 5,732 nm, ZP values from -9.24 mV to -27 mV and EE% of (8.40% - 73.59%). The optimum formulation was selected with PS of 219.7 nm, ZP of -20.3 mV and the EE% was 41.6% for further characterization.

Conclusion:
The results showed that the extrusion was successful in reducing the PS of vesicles without compromising the EE%. On the other hand, EE% was enhanced by applying 3 consecutive freeze/thaw cycles. Moving forward, a pharmacokinetic study is planned to compare the bioavailability of the optimized LV-loaded bilosomes with normal drug solution upon oral administration.

Keywords:
Lovastatin, Bioavailability, Bilosomes, Sodium Deoxycholate

Upregulation Of Adipsin Drives Proliferation In ESR1 Mutant Breast Cancer

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Purpose:
Although many endocrine therapies have demonstrated clinical benefits for breast cancer with ESR1 mutations, the development of resistance remains a significant challenge. Much evidence displayed that the complement system is a critical factor in tumor development. A recent study showed that adipsin plays an important role in breast cancer growth.

Methods:
We utilized a human cytokine array to identify secreted factors in ESR1 mutant cells. Real-time qRT-PCR and ELISA assay were performed to validate factors. High through put cell viability assay was performed to assess a function of Adipsin.

Results:
In this study, we characterized the role of complement pathway mediated adipsin in ESR1 mutant cell lines (Y537S and D538G). We identified the upregulation of adipsin using a human cytokine array and discovered the upregulation of C3, and C3aR, which highly induced C3a protein in ESR1 mutant cells. The interaction between C3a and C3aR enhanced ESR1 mutant cell growth while C3aR inhibition abolished the cell growth and increased apoptosis rate. The combination treatment of C3aR inhibitor and fulvestrant or CDK4/6 inhibitors showed a synergistic inhibitory effect in ESR1 mutant cells.

Conclusions:
Overall, we provided evidence to support the role of the complement pathway in ESR1 mutant cell proliferation and propose that C3aR is a potential target to circumvent ESR1 mutant breast cancer growth and metastasis.

Keywords:
Breast cancer, ESR1 mutation, Adipsin, and Endocrine resistance

An In Vitro Human Mammary Epithelial Cell Permeability Assay to Assess Drug Secretion into Breast Milk

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Purpose:
Determining the amount of a drug transferred into breast milk is critical for benefit-risk analysis of breastfeeding when a lactating mother takes medications. In this study, we developed a human mammary epithelial cell (MEC)-based permeability assay to assess drug permeability across the mammary epithelium.

Methods:
Different supplement combinations in cell culture medium were evaluated to promote tight junction formation of mammary epithelial MCF10F cells cultured on transwell. The trans-epithelial electrical resistance (TEER) was measured to determine if tight junctions were formed. Qualitative determination of paracellular permeability and monolayer integrity was also assessed using fluorescein isothiocyanate (FITC)-inulin and Lucifer yellow markers. Immunofluorescence was used to image the tight junction protein Zonula Occludens 1 (ZO-1) and transmission electron microscopy (TEM) was used to show cell morphology. Quantitative Real-Time PCR was used to quantitate P-gp mRNA expression in MCF10F cells and Caco-2 cells. Six P-gp transporter substrates, clarithromycin, doxorubicin, digoxin, loratadine, pefloxacin, and venlafaxine were used to estimate the permeability.

Results:
Human MEC cell MCF10F formed tight junctions with our customized culture medium and formation of integral cell barrier were confirmed by assessing TEER, flux of fluorescent tracers and imaging with confocal microscope and TEM. Compared to Caco-2 permeability data, MCF10F cell permeability data improved M/P ratio predictions for four P-gp substrates (clarithromycin, doxorubicin, digoxin and pefloxacin), particularly when pH correction factors were included.

Conclusions:
The predicted milk to plasma (M/P) ratios were reasonably good. This assay may have a potential to be developed as a useful in vitro technique for determining the transfer of small-molecule therapeutic drugs into breast milk directly using our new IVIVE approach or produce permeability parameters for building lactation physiological based pharmacokinetic modeling (PBPK) models.

Keywords:
M/P ratio; permeability, PBPK modeling, mammary epithelial cells

Role of Nuclear MMP-2 in Osteosarcoma Migration

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Purpose:

Cancer metastasis accounts for most of the osteosarcoma death. However, effective treatments of metastatic cancer are still lacking. Therefore, identifying novel therapeutic targets in metastasis is critical to improve therapeutic outcomes in cancer patients. Matrix metalloproteinase-2 (MMP-2) is a central protease and prognostic marker in osteosarcoma metastasis. Extracellular MMP-2 has been a drug target for preventing cancer metastasis, but no inhibitors have shown clinical efficacy to date. Notably, these inhibitors were designed and tested based only on the extracellular role of MMP-2 in metastasis. There is, however, increasing evidence of MMP-2 localization and function intracellularly inside the nucleus of cancer cells. Recent evidence indicates that targeting MMP-2 inside cells is more effective in preventing metastasis. Further, our preliminary data show that MMP-2 resides inside nuclei of metastatic osteosarcoma U2OS cells. The purpose of this study is to correlate levels of MMP-2 inside nuclei with cell migration and metastatic potentials of osteosarcoma cell lines

Methods:

Osteosarcoma cell lines; U2OS, HOS and Hs888.T are used. Nuclear extracts are isolated from cell lines using Qiagen Cell Compartment fractionation kit. Nuclear levels of MMP-2 are assessed using both immunoblotting and gelatin zymography. Metastatic potentials and cell migration are assessed using Transwell Cell Migration assays and will be correlated with nuclear levels of MMP-2.

Results:

MMP-2 was detected in nuclear fractions of all cell lines. U2OS and HOS cell lines have higher level of nuclear MMP-2 than that of Hs888.T cells. Interestingly, both U2OS and HOS cell lines have higher migration ability than that of Hs888.T cells.

Conclusions:

We identified positive correlation between MMP-2 levels/activities inside the nucleus and the metastatic potentials in Osteosarcoma cell lines. Our findings indicate a novel role of MMP-2 inside the nucleus in regulation cancer cell migration.

Keywords:

MMP-2, nucleus, Osteosarcoma, metastasis

Assessing the Impact of Microstructural Properties on *In Vitro* Drug Release from Minocycline Hydrochloride Microspheres

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Purpose:
In the development of complex generic products such as microspheres, qualitative (Q1) and quantitative (Q2) sameness is not always sufficient, which means that the microstructure (Q3) sameness must also be considered. The Q3 properties can affect drug release and consequently, the efficacy and safety. The objective of this work was to investigate the relationship between microstructure and the release characteristics of microspheres using advanced imaging technology.

Methods:
Using minocycline hydrochloride as a model drug, four compositionally equivalent microsphere formulations were prepared *via* a coacervation method. *In vitro* release testing of the microspheres was conducted using a sample-and-separate method. The internal microstructures from different microsphere formulations were investigated using focused ion beam scanning electron microscopy (FIB-SEM). Through repeated FIB milling and subsequent SEM imaging, the quantification of 3D microstructure properties including volume fraction, size distribution, and spatial distribution of all visible phases (polymer, drug, and pore) were achieved.

Results:
The four in-house formulations with different processing conditions showed different *in vitro* drug release characteristics. The FIB-SEM results indicated that all the internal drug particles and pores were clearly identified. The *in vitro* release rate was confirmed to be related to the porosity and material spatial distribution. The formulation with the lowest porosity showed the lowest release rate. Additionally, the polymer content in the outer layer was correlated to the release constant from the first-order model fitting of four in-house formulations. A monotonic relationship between polymer content in the outer layer and release rate was observed with a linear fit.

Conclusions:
Microstructural properties (e.g., volume fraction and spatial distribution of polymer, drug, and pores) of four in-house microsphere formulations were determined using FIB-SEM. Internal phase fractions and phase spatial distributions were all identified that related to the release performance. The established correlation between microstructural properties and release characteristics will allow for a more robust understanding of the impact of the microstructure properties underlying the release mechanisms of microspheres and facilitate the establishment of Q3 equivalence.

Keywords: Microspheres; Q3 sameness; Minocycline Hydrochloride; *In vitro* release; focused ion beam scanning electron microscopy (FIB-SEM).

Acknowledgment: Funding for this project was made possible, by the U.S. Food and Drug Administration through Contract # 75F40119C10157.

Preparation of albendazole amorphous solid dispersion by Supercritical Fluid technology

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Purpose:
Albendazole (ABZ) is an anthelmintic drug used to treat neurocysticercosis, an infection of the nervous system caused by pork tapeworms. ABZ has very poor aqueous solubility and bioavailability and thus solubility enhancement is imperative to achieve therapeutic concentration. The purpose of this research is to prepare the amorphous solid dispersion using supercritical fluid technology (SCF) to enhance the solubility and dissolution rate of albendazole.

Methods:
An array of hydrophilic polymers with diverse chemical backbone including Kollidon VA64, Soluplus, Eudragit EPO, HPMC-AS, PVA and PVP K30 were screened. The miscibility studies were also conducted by DSC depression method. The most suitable polymer was selected to prepare solid dispersion with ABZ at different drug:polymer ratio, temperatures, pressures, and reaction time. The optimized ABZ solid dispersion was characterized using DSC, XRD and SEM. Dissolution study was carried out using USP dissolution apparatus I at pH 1.2 and 6.8.

Results:
Eudragit EPO and PVA were miscible with ABZ according to melting point depression method but did not result in soluble extrudates when prepared using SCF. HPMC-AS did not form a coherent solid matrix with ABZ. Kollidon VA64 was selected as the polymeric carrier for ABZ for further study due to the porous structure of the final product, which resulted in better drug solubility and release. 80°C, 1500 psi and 2h reaction time was the optimized condition for SCF to prepare ABZ solid dispersion. The ABZ/VA64 solid dispersion showed around 85% drug release vs. 2% for pure ABZ at pH 1.2 and > 7% drug release vs. negligible release of pure ABZ at pH 6.8.

Conclusions:
The solid dispersion made by SCF technology can successfully improve the dissolution rate of ABZ at both acidic and basic environments. SCF can serve as solvent free, quick and reliable method as surrogate material sparing technique for the preparation of ASD.

Keywords:
Albendazole, Solid dispersion, Supercritical fluid, Dissolution improvement.

Albumin and Polysorbate 80 Coated Nanosuspension: Mebendazole Delivery for Glioblastoma treatment

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Purpose:
Mebendazole (MBZ), an antiparasitic agent showed anticancer activity by preventing tubulin polymerization. Several studies demonstrated mebendazole as a potential anticancer agent for brain cancer treatment. But poor solubility, multiple polymorphs and insufficient blood–brain barrier (BBB) permeability restrict translational efficiency. Polysorbate 80 has been reported to enhance brain uptake of nanoparticles while albumin facilitates stabilization and long circulation. The aim of our study was to formulate and characterize albumin and polysorbate 80 coated MBZ nanoparticles (NPs) in different glioma cell lines.

Methods:
MBZ NPs were prepared using different concentrations of MBZ, Bovine Serum Albumin (BSA) and Polysorbate 80. The nano-milling was carried out using 0.3 mm Zirconium beads in NETZSCH DeltaVita®. The particle size, Poly dispersibility index (PDI) and zeta potential were analyzed by Malvern zeta sizer. *In vitro* cytotoxicity study of MBZ and MBZ NPs was evaluated on U-87 and LN-229 using MTT assay. Tumor growth and cell apoptosis were evaluated in multicellular 3D spheroids of U-87 glioma cell line. Ongoing studies are clonogenic assay, western blot assay, *in vitro* hemolysis study, and *in vitro* migration assay.

Results:
Batches with single stabilizers show rapid phase separation while combination of albumin and polysorbate resulted in stable batch. Processing temperature and drug concentration played a significant role in the %yield. The optimized MBZ NPs depicted particle size of 177.2 ± 0.2nm with PDI of 0.2 and zeta potential of -0.76 ± 0.86 mV. Crystallinity of mebendazole was confirmed by differential scanning calorimetry. The IC 50 of MBZ and MBZ NPs were found to be 4.7±0.09 µM and 0.48 ± 0.05 µM in U-87 and 0.66 ± 0.15 µM and 0.48 ± 0.02 µM in LN-229, respectively. MBZ NPs led to substantial reduction in area of 3D spheroids of U-87 over 6 days with marked increase in apoptotic surface. 3D spheroids study clearly depicted that very high concentration of MBZ required for the activity which is achievable using such nanoformulation.

Conclusions:
Albumin-polysorbate coated nanosuspension could be useful parenteral delivery of mebendazole. *In vivo* studies are sought to investigate the brain uptake and anticancer efficacy in brain tumor xenograft model.

Keywords: Mebendazole, Polysorbate 80, Nanoparticles, Glioblastoma

Controlled release nanocrystalline edaravone: A novel therapeutics approach for the prevention of preterm Birth

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Purpose:
Preterm birth is when a baby is born 37 weeks before gestation. It is the leading cause of infant mortality and long-term disability and prematurity in children. One of the main reasons for this includes infection associated with inflammation. Unfortunately, there is no FDA approved therapy for prevention of preterm birth.
Edaravone is an FDA approved molecule with potent antioxidant and anti-inflammatory properties. It has been reported to reduce lipopolysaccharide (LPS) induced inflammation thus we are proposing to investigate it for preterm birth. Controlled release nanocrystal is an emerging and translational technology for molecules requiring high drug loading. In this study, a stable nanocrystalline formulation of edaravone stabilized with parenteral grade stabilizers was developed and currently under investigation for prevention of preterm birth.

Methods:
Edaravone nanocrystal formulation was prepared by top-down wet media nano milling method. Various batches were prepared with suitable stabilizers alone and in combination e.g., tween-80, lecithin, poloxamer-407 and bovine serum albumin and optimized for concentration. Edaravone with different drug concentration (5% and 10% w/v) was suspended in different stabilizer solutions followed by milling. Nanosuspension was characterized for particle size, poly dispersity index (PDI), zeta potential, %yield, injectability and stability. Currently we are evaluating - *in-vitro* drug release, efficacy and safety studies in RAW264.7 cells and *in vivo* studies in CD51 mice.

Results:
The optimized formulation stabilized by egg lecithin and poloxamer 407 combination demonstrated; particle size of 133.5 ±3.2nm, zeta potential of -27.5±4.6 mV and % yield of 34.0±2.0%. Drug loading was as high as 45%w/w. Batches with BSA and tween 80 showed very poor injectability due to large particles while lecithin/poloxamer were injectable via $25G_{1/2}$ needle. Batches were stable for two weeks at room temperature. pH played a significant role in %yield and particle size (>400 nm at pH 4) due to ionization of edaravone which affected surface stabilization.

Conclusion:
Combination lecithin and poloxamer at neutral pH are required for the preparation of nanocrystalline edaravone. *In vivo* efficacy will be necessary to provide proof of concept for sustained release antioxidant-anti-inflammatory agent for prevention of LPS induced preterm. birth.

Keywords:
Nanocrystal, edaravone, sub-cutaneous injection, sustained release, preterm birth.

Development of Swellable Vaginal Ring Using 3D Printing for Treatment of Vaginal Infections

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Purpose:
Women's health is succumbed to a plethora of hormonal changes associated with female reproductive system. Due to decreased patient compliance of the locally delivered semisolid formulations, the development of vaginal inserts for sustained release is crucial. 3D printing technology has evolved since last few decades, there are recent reports on delivering drugs vaginally in form of inserts. The objective of current research was to develop and optimize a novel polymeric matrix of polymers PEO(Poly-ethylene-oxide) and PETOx (Poly(2-ethyl-2-oxazoline) for 3D printing.

Methods:
The model drug(miconazole) was molecularly dispersed within the polymers using hot melt extrusion (HME), which provided filaments for 3D printing. The work of penetration and swellability index of rings were performed using texture analyzer. The mucoadhesion study was performed on a mucin-PVA based hydrogel mimicking the vaginal mucosa. The *in vitro* dissolution studies were performed in simulated vaginal fluid (SVF) with 1% SLS.The *in vitro* biocompatibility studies for the excipients used in the MZ vaginal rings were performed using HeLa cells.

Results:
The HME of polymers was performed at 170 ^{O}C. The batches were extruded with varying ratios of PEO: PETOx 25:75,50:50,75:25 and 25:75 respectively. The filaments with only PEO were not printable. We observed that for sustained released and maximum swelling index, more than 25% of PEO was essential in the matrix. Consequently, with swelling 50:50 and 25:75 was explored further for in vitro dissolution studies. The swelling patterns of rings were unique, wherein both from inner and outer sides provided the erosion fronts. The insight into the swelling patterns aids in understanding the drug release patterns wherein the swelling increased maximum until 4h, with drug release <50%. Once, the gelling and erosion were maximum, the drug release >80% at 8h which was diffusion and erosion controlled for 50:50 proportion. We observed 1183±34.23% swelling at 4h which was dependent on concentration of PEO. The maximum radius increase was at 4h, which further decreases, and erosion takes place completely within 8h.

Conclusions:
Depending on the *in vitro* biocompatibility studies, the swellability studies and mucoadhesion testing, PEO: PETOx provided a novel swellable polymeric matrix for developing customizable vaginal inserts.

Keywords: 3D Printing, PETOx (Poly(2-ethyl-2-oxazoline), 3D Printed Vaginal Rings

Design, Synthesis, and Characterization of MYC-targeting Oligonucleotide with Improved Pharmaceutical Properties

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Purpose:
The use of oligonucleotides (ODNs) to block gene expression has become a promising therapeutic approach for many diseases, including cancer and various inherited genetic disorders. Despite their therapeutic possibilities, ODNs present three significant limitations: 1) poor permeability; 2) rapid metabolisation by serum and lysosomal nucleases; and 3) lack of cell specificity. Our team has previously reported using a 28-mer DNA interference (DNAi) sequence that targets a G-quadruplex (G4) in the promoter region of the oncogene MYC, forming a "clamp" that holds the G4 formation and inhibits transcription. Herein we present our work on optimizing the utility of the DNAi sequence through: 1) the addition of cell-penetrating peptides (CPPs) to boost the membrane permeability 2) changing the ODN backbone to a polymorpholino ODN (PMO) to enhance the stability and 3) The incorporation of an antibody to increase specificity.

Methods:
A series of synthetic methods were developed to couple a non-cleavable (MCC) and a cleavable linker (mcValCitPABC) to a MYC G4-targeted ssDNA and a PMO. We then demonstrate the attachment of various CPPs and antibodies to the oligonucleotide. All compounds were examined for cellular penetrance and cytotoxic activity in diffuse large B cell (SUDHL-2) and mantle cell (GRANTA-519) lymphoma cells.

Results:
We successfully conjugated the PMO to four CPPs and four antibodies using cleavable and non-cleavable linkers. Our research has demonstrated an increase in permeability and efficacy in vitro when the PMO clamp is conjugated to a CPP, particularly to the peptide VSRRRRGGRRRRRR (R10). In a similar manner, we demonstrate that a PMO-antibody conjugate exhibits increased permeability and tumor-specificity as compared to the "naked" PMO.

Conclusions:
The incorporation of a CPP or antibodies help overcome the limitations of ODNs and may benefit PMO-containing therapeutics. Conjugating to these structures exhibits an increase permeability, efficacy, and specificity and could benefit many lives in the future.

Keywords:
Oligonucleotide (ODN), polymorpholino ODN (PMO), Antibody Conjugate, Cell Penetrating Peptides, Targeted Delivery

Expression, purification, crystallization, and structural analysis of cytochrome P450 2C9*2 variant

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Purpose:
Cytochrome P450 (CYP) enzymes are heme-containing enzymes involved in the metabolism of xenobiotics. The CYP2C9 enzyme is highly polymorphic and the *2 allele, which represents an amino acid substitution from arginine to cysteine at position 144 (Arg144Cys), is found in up to 20% of different populations. It is one of the two most well-characterized CYP2C9 variants. Individuals homozygous for CYP2C9*2 are known to have reduced ability to metabolize drug substrates including s-warfarin, tolbutamide, phenytoin, etc. The goal of the study is to express, purify, crystallize, and determine the three-dimensional structure of CYP2C9*2 in the absence or presence of various drug substrates that include s-warfarin.

Methods:
The CYP2C9*2 variant was expressed in *E.coli Rosetta2* cell line to produce high yield of recombinant protein. It was further purified to high quality using affinity and ion-exchange chromatography methods and crystallized in the presence of anti-coagulant s-warfarin. The crystals were shipped to Stanford Synchrotron Radiation Light source for remote data collection and processing, followed by structure determination using X-ray crystallography.

Results:
The structure of CYP2C9*2-s-warfarin complex suggested the presence of electron density corresponding to s-warfarin near the access channel region further away from the heme iron. Moreover, as seen previously with the CYP2C9*2-losartan complex, the Arg144Cys amino acid in the *2 variant disrupts the hydrogen-bonding interactions with the neighboring residues near the D-helix. The effect of such amino acid change is transduced to several secondary structural elements near the access channel region that may impact the binding of the drug. Crystallization of CYP2C9*2-s-warfarin complex to achieve higher resolution is in progress that will further help understand the binding of s-warfarin in the access channel.

Conclusions:
To conclude, the results yield insights into the role of genetic polymorphisms and its effect on the binding of drug with the CYP2C9*2 genetic variant.

Keywords:
CYP2C9, cytochrome, *2

Epigenetic targeting of PRMT5 inhibits pediatric neuroblastoma growth

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Purpose:
Neuroblastoma (NB) is the most common extracranial solid pediatric tumor, and the current treatments are highly toxic and lack effectiveness. Despite the availability of advanced multi-modal therapies, high-risk NB has an extremely low survival rate and presents a major clinical challenge due to the frequent relapse of both metastatic and refractory tumors. Current limitations of NB treatment warrant the development of less toxic and more effective novel therapeutic strategies. The epigenetic enzyme protein arginine methyltransferase 5 (PRMT5) has been implicated in a variety of cancers including NB. In the present study we aim to 1) determine the role of PRMT5 in NB, 2) pre-clinically evaluate a specific small molecule PRMT5 inhibitor in NB.

Methods:
NB patient datasets were analyzed using the R2 Genomic analysis and visualization dataset. Cell-Titer AQueous One Solution was used to perform cell proliferation assays. Clonogenic and 3D spheroidal tumor assays were performed using standard methods. All assays were performed with three replicates and repeated thrice.

Results:
In the present study, we analyzed different NB patient datasets and found that an increase in PRMT5 expression was strongly correlated with decreased overall patient survival in multiple NB patient datasets. We also found a strong correlation between PRMT5 expression and NB stage progression. This data indicates the role of PRMT5 in NB growth and disease progression. Furthermore, inhibition of PRMT5 using a specific small molecule inhibitor significantly inhibits cell proliferation in different NB cell lines in contrast to control treatments. The inhibition of NB cell proliferation showed greater potency in MYCN amplified cell lines compared to MYCN non-amplified cell lines, indicating a direct interaction of PRMT5 with MYCN. PRMT5 inhibition showed potential in inhibiting NB growth by blocking NB proliferation and spheroidal tumor growth.

Conclusions:
Our data suggest that PRMT5 inhibition is a novel therapeutic approach for NB. We will further analyze the effects of PRMT5 inhibition on NB growth using in vivo xenograft mouse model. Further, we will combine these epigenetic targeting strategies with current chemotherapies to develop an effective therapeutic approach for children battling deadly NB.

Keywords:
Neuroblastoma, Cancer Pharmacology, PRMT5, Pediatric cancer, Epigenetics

A Nature Inspired Octopus-Shaped 3D Printed Floating Drug Delivery System

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Purpose:
3D printing offers customization, complex geometries, precise drug release control and rapid prototyping for gastroretentive drug delivery systems (GRDDS). Current research explores a nature-inspired design, "Octopus-shaped drug delivery system" by combining the benefits of material properties and customizability of the 3D printing.

Methods:
Drug-loaded filaments of levodopa as a model drug were prepared using hot melt extrusion (HME) with an 11mm twin screw extruder. 3 types of material viz. a) Swellable polymers- Poly ethyl oxide (PEO), Hydroxy propyl methyl cellulose (HPMC) b) Polymers for sustained release- Ethyl cellulose (EC), Hydroxy propyl methyl cellulose acetate succinate (HPMC-AS) c) Printability enhancing polymers- Hydroxy propyl cellulose (HPC), Poly(2-ethyl-2-oxazoline) (PETOX) were used. The printability was evaluated by three-point bend test (3PBT) using TA.XTplus Texture Analyzer. Design was created using Tinkercad software. Re-floating ability of octopus was tested by immersing it in media for 5 seconds per hour. The *in vitro* dissolution testing was performed in 0.1 N HCl.

Results:

The process of (HME) was conducted within temperature range of 120-180^{o}C. 10% w/w drug loading was utilized in conjunction with various polymer combinations, comprising of 3 polymers, one from each group (a, b, c). Filaments that had less than 30% of HPMC and/or HPC, PETOX failed 3PBT due to lack of material strength. Filaments consisting of more than 30% of EC or 40% of HPMCAS passed the 3PBT but were not printable due to poor adhesion between layers during printing which led to flimsiness of octopus. Infill densities of head of the octopus (0%, 20%, 50% and 95%) influenced the center of gravity of the octopus. The octopus was designed to have a center of gravity below the head part, slightly above half of the leg's length, to keep the octopus in a vertical position while floating for every infill density. The dimensions were 8mm x 8mm x 15m, which fit within a size 000 capsule. Maximum floating was observed with octopus consisting of 20% Polyethylene oxide (PEO). *In vitro* release was optimized to sustain release for 24 h.

Conclusions:
Material characterization of different polymers with addition of unique octopus design provided a novel gastroretentive drug delivery system.

Keywords:
Fused Deposition Modeling (FDM), 3D printing, gastroretentive drug delivery system (GRDDS), Hot melt extrusion (HME).

Development of Rapidly Soluble Mebendazole Nanosuspension for Colorectal Cancer

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Purpose:
Mebendazole (MBZ) has been proven for the treatment of various cancers. Unfortunately, poor water solubility and bioavailability limit its application as a potential molecule. Therefore, MBZ must be reformulated using the benefits of nanotechnology that can deliver drugs specifically at the desired site to avoid first-pass metabolism, improve drug effectiveness, and enhance drug bioavailability. The objectives of the study are: (a) To formulate and characterize MBZ Nanosuspension (MBZ-NS). (b) To investigate MBZ-NS anticancer activity in various colorectal cancer cell lines.

Methods:
MBZ-NS was formulated by nano-milling using a combination of Hydroxy Propyl Methyl Cellulose E5 (HPMC E5) and Sodium Lauryl Sulfate (SLS) as stabilizers. The optimized MBZ-NS was characterized using dynamic light scattering particle size analyzer for particle size, polydispersity index (PDI), zeta potential (ZP), and drug release was investigated. *In vitro* cytotoxicity of MBZ, MBZ physical mixture (MBZ-PM), and MBZ-NS was assessed on HT29 and HT116 using an MTT assay. Also, *In Vitro* Live/Dead Cell Assay was performed to see the effect of MBZ and MBZ-NS on cell viability within 3D multicellular tumor spheroids of HT 116.

Results:
The optimized MBZ-NS resulted in particle size of 362.6 ± 12.3 nm, PDI of 0.167 ± 0.01, and ZP of -14.6 ± 1.208 mV. Furthermore, MBZ-NS exhibited 20 folds higher dissolution than MBZ in colonic pH. DSC data revealed the crystallinity of the MBZ-NS. IC_{50} of MBZ-NS was found to be significantly lower than the MBZ-PM in HT29 and HT116 as shown in Table 1. Additionally, 1.5 folds and 1.8 folds reduction in the area of 3D tumor spheroids after treatment with MBZ-NS was observed compared to control and MBZ-PM. From the *In Vitro* Live/Dead Cell Assay higher amount of red fluorescence in treatment groups confirmed large number of dead cells compared to the control.

Conclusion:
In conclusion, the optimized MBZ-NS increased dissolution rate and anticancer efficacy in colorectal cancer cell lines.

Keywords:
Mebendazole, Nanosuspension, Dual centrifugation, *In vitro* cytotoxicity, and 3D spheroid model.

Application of 3D Printing Technology for development of dose adjustable Geriatric and Pediatric formulation of celecoxib

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Purpose:
Production of safe and effective formulation for the geriatric and pediatric population is a complicated task due to swallowability and palatability. The 3D minitablets or sprinkles are the preferred administration for these population due to smaller size and flexible dose adjustment. Celecoxib, a nonsteroidal anti-inflammatory (NSAID) drug, is used in treatment of mild to moderate pain and relive symptoms of arthritis, but it is a poorly water-soluble compound with an estimated solubility of <1.15 µg/mL. The purpose of this current study is to develop 3D printed sprinkles using a hot melt extrusion and enhance solubility and oral bioavailability of celecoxib.

Methods:
Three different formulations of 10% w/w celecoxib with or without surfactant (TPGS or Sophorolipids) with Aquazol were prepared by hot-melt extrusion (HME). The three-point bend test was performed using TA.XTplus Texture Analyzer. Differential scanning calorimetry (DSC) and X-Ray diffraction of the powders of drug, polymer, and extruded filament were carried for solid state characterization (SSC). Three different shapes of sprinkles were designed; star, heart and donut shape using Tinkercad software. Sprinkles printed with 95% infill using fused deposition modeling (FDM) 3D printer. The sprinkles were evaluated for in vitro dissolution.

Results:
HME was carried out at the temperature range of 80-160 °C. The % torque observed during the extrusion of drug-polymer with surfactant was lower (20-30%) compared to without surfactant (60-70%). A sharp crystalline melting endotherm peak for neat celecoxib was observed at 162.3 °C and crystalline halos corresponding to celecoxib were also observed. Absence of a characteristic endothermic event and halo peaks for celecoxib in the filament confirmed the amorphization of celecoxib by SSC. Saturation solubility studies of the filaments suggested that there was an increase in celecoxib solubility. The dimensions of the 3D printed sprinkles were 4mm × 4mm × 1.5mm. Printing speed for star shape sprinkles was slower than the other two shapes due to sharp angles at edges. The dissolution of the 3D printed sprinkles showed an 80-90 % drug release within 45 minutes.

Conclusions:
We have successfully printed 3D sprinkles by using hot-melt extrusion coupled with FDM-3D printing technology with enhancement of celecoxib solubility.

Keywords:
Personalized medicine, Fused deposition modeling 3D printing, 3D sprinkles

Inhibition of Menin-MLL1 Interaction Inhibits Cancer Stem Cells to Inhibit Neuroblastoma Growth

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Purpose:
Epigenetic regulators such as MLL1 play an important role in cancer progression, metastasis, and relapse. MLL1, forms a COMPASS complex with Menin and other binding partners to function as an epigenetic enzyme, H3K4 methyltransferase. Menin-MLL1 interaction regulates the expression of MLL target genes. Neuroblastoma (NB) is an extracranial solid pediatric cancer, and the overall long-term survival rate is still less than 50%, with high relapse and metastatic conditions. In this current study, we hypothesized that disrupting the protein-protein interaction of menin-MLL1 by a small molecule inhibitor will inhibit neuroblastoma cancer stem cells (NB CSCs; CD114+ cells) to inhibit overall NB growth in *in vivo* and *in vitro* NB models.

Methods:
Publicly available NB patient datasets were analyzed using R2 Genomic analysis and visualization platform. In vitro cell proliferation studies were performed using 2D and 3D cell culture models. Apoptosis and cell cycle assays were performed using the Attune Flow Cytometer. Gene expression analysis was performed using QuantStudio™ 3 Real-Time PCR.

Results:
We analyzed different NB patient datasets and found that high expression of menin is inversely correlated with the overall patient survival rates. Inhibition of menin-MLL1 interaction significantly inhibited NB cell proliferation in a dose-dependent manner in contrast to control fibroblast cell lines. Furthermore, we found that inhibition of menin-MLL1 interaction significantly inhibits NB CSC population compared to control treatments by specifically inducing apoptosis and arresting cell cycle in NB CSCs, in contrast to non-CSCs in *in vitro* cell culture models. Additionally, inhibition of menin-MLL1 interaction in NB mouse models significantly inhibited the overall NB tumor burden and tumor growth by directly inhibiting tumor NB CSCs. Further, we observed a dose-dependent reduction of the expression of multiple oncogenic cell signaling pathways, cancer stemness-related genes, and various MLL1 fusion partner genes in both *in vivo* and *in vitro* NB models. Additionally, and as expected, our western blot analysis showed a significant reduction of H3K4me3 levels.

Conclusions:
Overall, our data highlights the role of the epigenetic mechanisms regulating the NB CSCs and NB growth. Our study also highlights the inhibition of Menin-MLL1 interaction could be a novel therapeutic approach for NB.

Keywords:
(Menin; H3K4 methyltransferase; Neuroblastoma; Pediatric cancer: Cancer Pharmacology)

MAPK Signaling Cascade of Myocardial Infarction: A Deciphered Pharmacological Mechanism of Spathulenol

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Purpose:
Prediction of targets of selected small molecules from traditional plants using an integrated bioinformatics approach for myocardial infarction.

Methods:
Targets are predicted using different web servers and software from plants of interest. The methanolic extract of *Aganosoma. dichotoma* was screened and the presence of small molecules was confirmed by GC-MS analysis. Targets of small molecule were predicted using Swiss target prediction and Swiss ADME was used for prediction of Pharmacokinetic analysis. Toxicity prediction was done using ProTox-II sever for optimal results. In order identify the genes datasets of Myocardial Infarction, NCBI datasets are used. Furthermore, Venn diagram was constructed to identify overlapping genes between gene datasets and targets of small molecules. Cytoscape was used to construct protein - protein interaction network and to identify hub genes. Molecular docking was done using PyRx software for top ten hub genes and binding affinity value is saved to identify signaling pathways.

Results:
In this study, spathulenol is a tricyclic sesquiterpenoid, which was identified as a small molecule (220.35gms/mole). Pharmacokinetic and toxicity prediction of tricyclic sesquiterpenoid showed high GI absorption, accepting all rules of Lipinki and LD50≥ 3900mg/kg. Differentially expressed genes were identified from the datasets and overlapping genes were assessed for gene enrichment analysis pathways with $p < 0.05$. A PPI network was constructed, and hub genes were identified. Molecular docking studies were conducted to top 10 hub genes and based on their binding affinity value two genes were selected and signaling pathway to MI was identified through KEGG and major pathway are mitogen-activated protein kinase (MAPK).

Conclusions:
Prediction of targets of the small molecule spathulenol gave promising results and may act against myocardial infarction caused by ischemia, stress and free radical generation, but needs to be validated through further *in vivo* studies.

Keywords:
Myocardial infarction, differentially expressed gene, molecular docking.

A Disintegrant Extracted from Banana Peel Waste

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Purpose:
Nanocrystalline cellulose (NCC) is a non-fibrous and partially depolymerized form of cellulose. NCC has appealing properties such as biocompatibility, good thermal stability and high aspect ratio. The nanocellulose field has undergone a major revamp in the last few years with reference to its preparation, functionalization and interesting applications in biomedical, material and other allied sciences. In the current study we are focusing on the application of NCC as excipient in oral drug delivery. The objective of this paper is to study the disintegrating potential of Nano crystalline cellulose (NCC) extracted from Banana peel powder (BPP) for Diclofenac Potassium immediate release tablets.

Methods:
NCC was prepared from BPP by using acid hydrolysis technique. Diclofenac potassium was used as a model for studying the properties of NCC as a disintegrant. Tablets were prepared by direct compression method.

Results:
Tablets prepared using NCC were compared with the commercial tablets. Results showed that tablets prepared using NCC as disintegrant have the fastest disintegration rate compared to other tablets. Dissolution efficiency (DE) and mean dissolution time (MDT) were calculated. It was found that NCC tablets showed DE = 66% and MDT = 12 whereas commercial reference showed DE%= 58 and MDT= 18.2.

Conclusions:
It was found that NCC tablets have more DE% and less MDT compared to other tablets. Size reduction has been always a valid reason for enhancement of performance of tablets. The results helped to understand the role of NCC as an excipient prepared from agricultural waste. It can be concluded that NCC can be used as an emerging excipient for immediate drug delivery of API. There is a scope of further modification for achieving various other properties.

Keywords:
Banana peel powder (BPP), Nanocrystalline cellulose (NCC), Dissolution efficiency (DE), Mean dissolution time (MDT).

Roundtable: Long-Acting Delivery

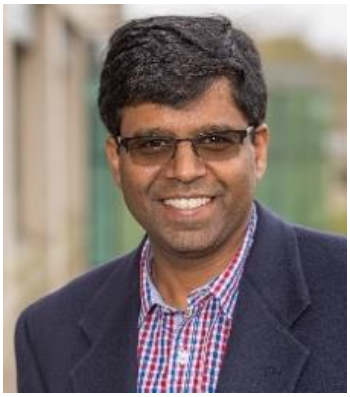
Manish Gupta, PhD
GSK Senior Fellow; R&D, Drug Product Development - Steriles
Collegeville, PA

Design and Performance Opportunities for Long-Acting Injectables

Abstract

Long Acting Injectables (LAIs) are an excellent platform to enable patient centric medicine. This presentation will focus on the design and performance opportunities for LAIs using an integrated cross-functional approach across stability, manufacturability, and biopharmaceutics. A holistic biopharmaceutics approach across in-vitro/ in silico/ in-vivo aspects is key via cross-disciplinary engagement & effective cross-functional partnership. Such approaches can help us address gaps in our current understanding of LAI performance. Examples will be shared on how integrated workstreams are useful to build knowledge and help deliver our upcoming LAI portfolio for patients.

Speaker Biography



Manish is a GSK Senior Fellow and a member of R&D's Fellows Leadership Team. He is passionate about connecting biology and drug product design to create the best medicine for the patient. He is particularly proud of the design and industrialization of a long-acting injectable platform at GSK/ ViiV and the understanding thereof to enable future LAI products.

Manish has championed science and risk-based product development for multiple oral and parenteral commercial drug products and has successfully led interactions across regulatory agencies. Manish has 20 plus years of industrial experience and is currently leading Drug Product Development Steriles team (~100 scientists) across small molecules and biologics products.

Roundtable: Long-Acting Delivery

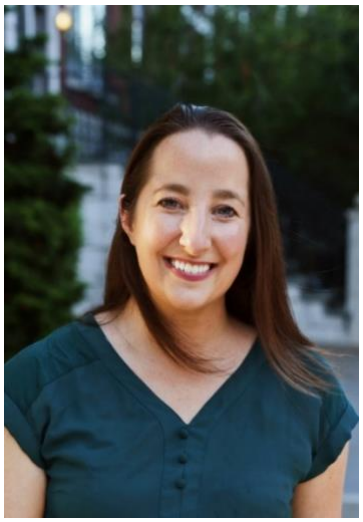
Ashley Johnson, PhD
Associate Principal Scientist, Merck & Co., Inc.
Kenilworth, New Jersey

Formulation and Biopharmaceutics Considerations in the Development of Long-acting Injectable Suspensions

Abstract

Development of long-acting injectable products has the potential to transform human health through by enabling patient adherence to improve outcomes. The formulation of long-acting injectable products is technically complex and necessitates consideration of a large set of interdependent variables. This talk will explore several different case studies in formulation of long-acting products, including Merck's approach to dosing two different phase 1 studies, opportunities to accelerate chemical entry, appropriate interpretation of preclinical models, and the interplay between API physical form and formulation performance

Speaker Biography



Ashley Johnson in an Associate Principal Scientist at Merck & Co., Inc. based in Kenilworth, New Jersey. She joined Merck in 2016 after obtaining a PhD in biomedical engineering at the University of North Carolina at Chapel Hill. In her role within the Sterile and Specialty Products organization at Merck, she leads formulation design and clinical manufacturing of long-acting injectable suspensions.

Roundtable: Long-Acting Delivery

Cameron Lee, PhD
Novartis Institutes of Biomedical Research
Cambridge, MA

Long Acting Technologies for Biologics to Treat Ocular Diseases

Abstract
Long acting injectables have been developed traditionally using a variety of different approaches such as oily solution, aqueous suspensions, gels, nanosuspensions and microspheres. However, what molecular properties, physical chemical, and PK properties of a drug, are suitable for which technology to enable success is not established. The presentation will provide a background on depot and show a model based on PK and physical chemical properties of drug to select the appropriate technology. Ideally with the model, one can select the most likely LAI or depot technology that will provide sustained PK profile in vivo for a candidate with examples.

Speaker Biography

Cameron is Associate Director in the Global Discovery Chemistry Department at the Novartis Institutes of Biomedical Research in Cambridge, MA, where he leads teams in the development of novel drug delivery technologies and new modalities. He received his PhD in chemistry at the University of California, Berkeley.

Roundtable: Long-Acting Delivery

Jaymin C. Shah, PhD
Research Fellow and Head of Topical and Advanced Drug Delivery Group, Pharmaceutical Sciences Small Molecules
Pfizer, Inc, Groton, CT

Back to Basics: Model for Long-Acting Parenteral Delivery Systems

Abstract

Long acting injectables have been developed traditionally using a variety of different approaches such as oily solution, aqueous suspensions, gels, nanosuspensions and microspheres. However, what molecular properties, physical chemical, and PK properties of a drug, are suitable for which technology to enable success is not established. The presentation will provide a background on depot and show a model based on PK and physical chemical properties of drug to select the appropriate technology. Ideally with the model, one can select the most likely LAI or depot technology that will provide sustained PK profile in vivo for a candidate with examples.

Speaker Biography

Jaymin Shah is a Research Fellow in Pharmaceutical Sciences and heads a topical and advanced drug delivery group in Pfizer R & D. He also holds an adjunct faculty appointment at the University of Houston. He obtained his Ph.D. in Pharmaceutics from University of Houston. From 1988-1999 he served as Associate Professor (Tenured) of Pharmaceutical Sciences at Medical University of South Carolina, where he led a lab developing sustained release parenteral delivery systems and modeling of skin transport and mentored 7 Ph.D. and 2 MS graduates. Jaymin joined Pfizer in 1999 where he has led formulation groups and project teams supporting development of various candidates as parenteral/ophthalmic dosage forms, peptide and oligonucleotides development and research initiatives in parenteral and ophthalmic delivery including LAI, depots, sterile suspensions, implants, and nanoparticles. Jaymin has been recognized with achievement awards for leadership and innovation in Pfizer. Jaymin has published 63 papers, 10 patents/patent applications, 75 abstracts and made more than 114 presentations at various scientific forums such as Arden House Conference, AAPS symposia, CRS, FDA and academic centers. His current research interests include topical drug delivery, parenteral sustained release (depot), nanoparticles, ophthalmic delivery, and topical formulation development.

Roundtable: Targeted Delivery Roundtable

Debra Auguste, PhD
Northeastern University
Boston, MA

Insights into Targeted Drug Delivery

Abstract

Lipid nanoparticles are safe and effective drug delivery vehicles that can encapsulate, deliver, and improve the pharmacokinetic profiles of a wide variety of drugs to combat disease. Yet, most nanocarriers do not deliver their payload at the intended target site due to four main barriers to drug delivery: uptake by the mononuclear phagocytic system, the inability to traverse the tumor vasculature and tissue, and lack of selective cell internalization. My lab has shown that nanocarrier surface chemistry and mechanics affect in vivo tumor accumulation, which presents an exciting opportunity to transform cancer drug delivery. We focus on molecular assembly, which drives targeted delivery and therapeutic outcomes. Through the synthesis and optimization of tunable nanocarrier platforms, higher tumor accumulation is achieved. We will present in silico, in vitro, and in vivo data to support our discovery pipeline of well-characterized nanoparticles that enhance in vivo tumor delivery.

Speaker Biography

Debra Auguste, PhD is a Professor of Chemical Engineering at Northeastern University. She received her S.B. in Chemical Engineering from MIT in 1999 and her Ph.D. in Chemical Engineering from Princeton University in 2005. She was trained as a Post-Doctoral Associate at MIT. Her interests include drug and gene delivery, targeted drug delivery, stimuli sensitive materials. Dr. Auguste is the principal investigator on grants from the National Institute of Health, Office of Naval Research, Defense Advanced Research Projects Agency, and National Science Foundation. She is a recipient of various awards including: the Presidential Early Career in Science and Engineering, the NIH Director's New Innovator Award, NSF CAREER Award, and the DARPA Young Faculty Award. Dr. Auguste was elected as a Fellow of the Biomedical Engineering Society and the American Institute of Medical and Biological Engineering.

Roundtable: Targeted Delivery Roundtable

Liping Zhou, PhD
Advanced Drug Delivery, Pharmaceutical Sciences, BioPharmaceuticals R&D
AstraZeneca, Boston, US

The industrial design, translation, and development strategies for long-acting peptide delivery

Abstract

Peptides are widely recognized as therapeutic agents in the treatment of a wide range of diseases. However, their use has been limited by their short half-life, due to significant metabolism by exo- and endo-peptidases as well as their inherent poor physical and chemical stability. Research with the aim of improving their half-life in the body, and thus improving patient compliance (by decreasing the frequency of injections) has gained significant attention. Emphasis is placed on identifying challenges in drug product manufacturing and desirable critical quality attributes that are essential for activity and safety, providing insights into chemistry and design aspects impacting peptide release, and summarizing important considerations for CMC developability assessments of sustained release peptide drugs. Substantial advances have been made in the field of sustained delivery of peptides despite their complexity. The key is early-stage product design and development to mitigate risk in developing sustained release peptide drug products.

Speaker Biography

Dr. Liping Zhou is currently a senior director at AstraZeneca Boston R&D center. She is heading the Advanced Drug Delivery – Boston team, developing preclinical and clinical formulations supporting AstraZeneca internal synthetic modality pipeline projects. Dr. Zhou has 20 years of post-PhD technical and managerial experience in research and development functions in the biotechnology/pharmaceutical industry. She has diversified expertise especially in pre-formulation, formulation development and drug delivery technologies focusing on small molecules, peptides, and nucleic acids. She has been actively involved in preclinical and clinical programs, life-cycle management and due diligence projects in multiple therapeutical areas as well as efficiently and strategically managing external collaborations in the US, Europe and Asia. Dr. Zhou's previous employment includes but not limited to Novartis, Ipsen, and Ra Pharmaceuticals (now UCB). She co-authored more than 20 scientific publications in the leading biomedical journals and book chapters.

Dr. Zhou received her Ph.D. degree in Chemistry from University of Connecticut and her bachelor's degree from Peking University.

Roundtable: Targeted Delivery Roundtable

Himanshu Bhattacharjee, PhD
Director, Emerging Drug Delivery Platforms
GlaxoSmithKline

Targeted Drug Delivery: Design of Delivery

Abstract

Drug Delivery involves the delivery of the right active molecule to the right cell, tissue, organ system or to the whole body. The design of a successful drug delivery system is based on an understanding of the biology of the target and how it interacts with the delivery system. Additionally, building on fundamental understanding of molecule design and therapeutic target in combination to alternate routes of administration can provide critical information during early stages of medicine development to develop robust drug products. The benefits of improved drug delivery design include enhanced efficacy, improved therapeutic index, improved outcomes, reduced side effect, decreased drug requirements and the ability to deliver new therapies to specific targets within the body that are not possible by standard drug delivery approaches. This discussion topic will highlight elements of rational biology-based drug delivery concepts and cases studies to illustrate the advantages of such an approach.

Speaker Biography

Himanshu Bhattacharjee, PhD is the Director of Emerging Drug Delivery Platforms at GlaxoSmithKline and leads early-stage drug delivery activities. He has 12+ years of experience focusing on early and late-stage development of multiple drug product modalities. He is passionate in driving rational, patient centric drug product design, leveraging biology and disease pathophysiology, and exploring alternate routes of administration to design safe and efficacious medicines. His late-stage development experience of managing CMC activities for small molecules, peptides and oligonucleotide drug products provides a unique perspective on translation of drug delivery concepts from bench to clinic. Prior to working with GSK, he has worked at Pfizer and Merck in formulation development and drug device combination products.

Roundtable: Process Scale Up – Current Considerations and Emerging Trends

Bing-Shiou Yang, PhD
Boehringer-Ingelheim Pharmaceuticals, Inc
Ridgefield, CT

Drug Substance Property Controls in Scale Up

Abstract

This presentation provides an overview of the drug development workflow and emphasizes the importance of controlling the physical properties of drug substances (DS) in order to ensure optimal processing and performance of drug products (DP). Specifically, the focus will be on solid-state properties, such as solid form and particle size, and how their development and scale-up through isolation processes, such as crystallization and drying, can impact DS properties. The presentation will include case studies that illustrate these concepts. The first case study will demonstrate how a crystallization process can be developed to produce small crystals via solid form conversion, thereby improving dissolution rate. The second case study will explore the identification of root causes and mitigation strategies for a manufacturing process in which the residual solvent level exceeded specifications.

Speaker Biography

Bing-Shiou Yang is a Ph.D. Chemical Engineer with 20+ years of pharmaceutical development experiences in the areas of API isolation development, solid-state and engineering technologies and project management. He is currently the Director and Head of Solid-State Science & API Engineering in Material & Analytical Sciences (MAS) at Boehringer Ingelheim in Ridgefield, CT. In BI, he leads a multidisciplinary group that broadly facilitate BI's small molecule portfolio through scientific leadership and innovation in areas of crystallization, separation technology, continuous processing, process engineering and process analytical technology (PAT). He also leads multidisciplinary project teams to streamline the Drug substance and Drug product CMC development interfaces based on solid form, API isolation process and material science profiling. Bing-Shiou represents BI in multiple working groups in International Consortium for Innovation and Quality (IQ) and Enabling Technology Consortium (ETC) and serves as a Board of Director for ETC.

Prior to BI, Bing-Shiou worked at Process Research and Development at Bristol-Myers Squibb (BMS) where he served as a crystallization and particle engineering specialist and had made significant contribution to portfolio compounds including ELIQUIS® (Apixaban). Bing-Shiou received his B.S. and M.E. degrees from National Taiwan University and Ph.D. in Chemical Engineering from Princeton University. Bing Shiou has co-authored over 70 publications, patents, book chapter and presentations.

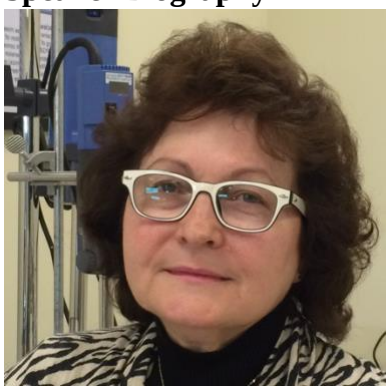
Roundtable: Process Scale Up – Current Considerations and Emerging Trends

Carmen Popescu, PhD
Global Pharma/Biopharma Technical Developer
Pharmaceutical Applications
Roquette America, Inc., Geneva, IL

Tablet Development Support (TaDeS) in Direct Compression Process

Abstract
MCS (Manufacturing Classification System) is providing guidance on how to match the properties of a given API (molecular, particulate, surface, etc.) with a particular pharmaceutical process in order to enable the finished drug product manufacturing. There are few tools available to visualize risk assessment based on relevant API properties and target attributes of drug product. In this presentation we will focus on Tablet Development Support (TaDeS) a radar (spider) diagram to predict powder mix processability in direct compression process. Powder mix (API and excipients) properties represented by eleven physical parameters are divided in five categories reflecting quality (powder mix homogeneity and stability) and powder processability (die filling, flowability and compactibility).Depending on the mass ratio of components the behavior of the powder mixture ,in direct compression, can be calculated (predicted) resulting in a startup formulation allowing the decrease of experiments number by increasing their quality and speed.

Speaker Biography



Dr. Carmen Popescu got her B.S. degree in Physics and Ph.D. in Biophysics at University of Bucharest, Romania. She is a Global Pharma/ Biopharma Technical Developer at Roquette America Inc., located in Geneva, Illinois. She came to USA in 1999, as an Associate Professor with University of Illinois at Chicago, College of Pharmacy (Pharmaceutics Department) where she is still an Adjunct Associate Professor. Then, Dr. Popescu moved to Pharmaceutical Industry working at Morton Grove Pharmaceutical, Baxter and DeCode Genetics. In her career, she focused on the development of classic dosage forms (liquid, semi-solid and solid dosage forms formulation) as well as drug delivery systems (microparticles, nanoparticles, liposomes, noisome) for small and large molecules. Dr. Popescu has published over 120 research papers, book chapters and presentations. You can find her publications on: https://www.researchgate.net/profile/Carmen_Popescu3
She is also Adjunct Associate Professor with Roosevelt University, University of Tennessee and University of Maryland at Baltimore. She is teaching in "Tablets & Capsules Hands-on Short Course" at Univ. of Maryland and "Hands-on Tablet Technology Course "at Univ. of Mississippi. Her activities include reviewer for the International Journal of Pharmaceutics, Journal of Pharmaceutical Sciences, and European Journal of Pharmaceutics and Biopharmaceutics as well as member of the editorial board of Journal of Pharma & Pharmaceutical Sciences. She is an active member of AAPS (Excipients Focus group; AAPS Chicagoland Discussion Group; NERDG Northeast Regional Discussion Group)

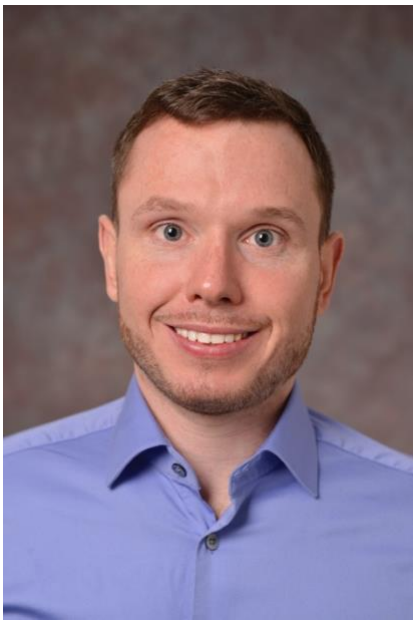
Roundtable: Process Scale Up – Current Considerations and Emerging Trends

Adam Gormley, PhD
Assistant Professor, Biomedical Engineering
Rutgers University
New Brunswick, New Jersey

AI and Automation to Accelerate the Scale of Drug Discovery and Development

Abstract
For decades, formulation scientists have designed around complexity by rationally designing new additive combinations either one experiment at a time or via high throughput screening. However, recent advances in laboratory automation, high throughput analytics, and artificial intelligence / machine learning (AI/ML) now provide a unique opportunity to fully automate the design process. In this talk, we put forth our efforts to develop a self-driving lab that can rapidly iterate through design spaces and identify unique excipients that perfectly synergize with formulation complexity.

Speaker Biography



Adam Gormley is an Assistant Professor of Biomedical Engineering at Rutgers University and an expert in nanobiomaterials. Prior to Rutgers, Adam was a Marie Skłodowska-Curie Research Fellow at the Karolinska Institutet (2016) and a Whitaker International Scholar at Imperial College London (2012-2015) in the laboratory of Professor Molly Stevens. He obtained his PhD in Bioengineering from the University of Utah in the laboratory of Professor Hamid Ghandehari (2012), and a BS in Mechanical Engineering from Lehigh University (2006). In January 2017, Adam started the Gormley Lab which seeks to develop bioactive nanobiomaterials using robotics and artificial intelligence. Dr. Gormley is currently the PI of an NIH R35 MIRA Award, an NSF CBET Award, and an NSF Designing Materials to Revolutionize and Engineer our Future (DMREF) Award. He was recently named a Rising Star by Advanced Healthcare Materials, is the recipient of the A. Walter Tyson Assistant Professorship, and the Young Innovator Award by Cellular and Molecular Bioengineering.

Roundtable: Regenerative Medicine

Vijay Gorantla, MD. PhD
Wake Forest Institute for Regenerative Medicine
Winston-Salem, NC

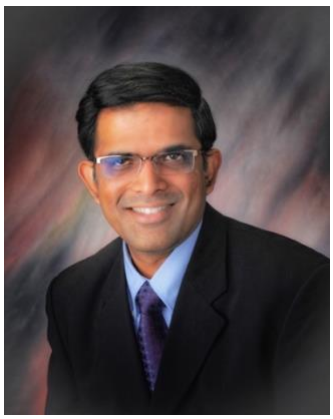
Drug Delivery, Biosensors, and Imaging – The Trifecta of Regenerative Surgery

Abstract

Regenerative surgery uses regenerative medicine techniques, to repair or replace damaged or diseased tissues and organs. In contrast to oral, injectable, or topical delivery, smart drug delivery can play a crucial role in outcomes after regenerative surgery by targeting drugs (small molecules), biologics, or growth factors directly to the site of tissue injury or repair to enhance the regenerative process while limiting systemic toxicity. For example, drugs can be delivered to grafts, or to suppress the immune response to reduce the risk of rejection in transplantation procedures. Implantable drug delivery platforms can be used to provide sustained and controlled release of drugs over time, improving the efficacy of the treatment.

Biosensors are devices that use electronic, enzymatic, antibody or other recognition elements to detect and quantify analytes in biologic samples. Biosensors can be used in drug delivery to monitor the efficacy of a treatment by measuring the concentration of drugs in real-time and detect toxicity. This information can be used to adjust the drug delivery to optimize treatment outcomes. Cellular and molecular imaging can help complement drug delivery and biosensing in personalized treatment of diseases by enabling the non-invasive diagnosis, timely prevention, and monitoring response to treatment. By integrating these technologies, the ideal goal is to create closed-or open-feedback-loop systems for regenerative surgery, in which biosensors, drug delivery, and imaging work together to renew, restore or rejuvenate while improving outcomes and reducing risk of complications.

Speaker Biography



My academic interests relate to basic and clinical research in restorative surgery, tissue engineering and regenerative medicine to address the critical needs of service men and women with traumatic injuries. As a DOD funded investigator, over the last decade, I have mostly engaged in convergent technologies that involve disruptive or transformative strategies in the restoration or rehabilitation of disabilities secondary to complex limb loss, TBI or vision loss. These include but are not limited to reconstructive transplantation (limb, face and other structures) after civilian or combat trauma, immunomodulation (cell therapies, immunobiologics), neuroregeneration (neurobiologics) and , triggerable graft targeted local immunomodulatory/suppressive therapeutics using nanotechnology or other biocompatible delivery platforms, gene therapy, ischemia mitigation/ex vivo preservation techniques, immunocloaking; and imaging strategies (non-invasive molecular/multimodality [ultrasound, MRI, nanotheranostics] in regenerative surgery.

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Roundtable: Regenerative Medicine

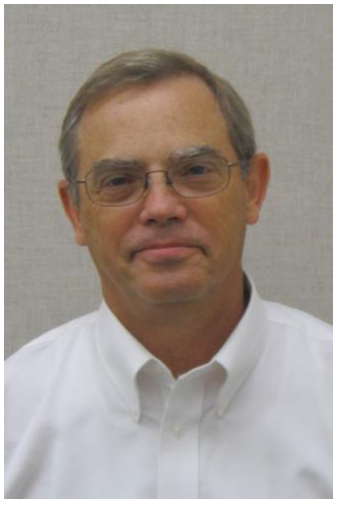
Phil Campbell, PhD
Research Professor, Biomedical Engineering
Carnegie Mellon University
Pittsburgh, PA

Engineering the Therapeutic Potential of Extracellular Vesicles

Abstract

Extracellular vesicles (EVs) are naturally occurring nanoparticles representing bilayer lipid membrane-bound nanovesicles containing proteins, lipids and nucleic acids. They are constituents of the cell secretome and are produced by all known living cellular organisms across Kingdoms. There is ever-increasing evidence that EVs are major drivers of intercellular communication, and it is this aspect is attractive to the therapeutic delivery arena where efficient and targeted delivery of biomolecules is desired but otherwise challenging. Multiple studies have demonstrated the therapeutic potential of EVs, especially those secreted by mesenchymal stem cells (MSCs), which also have the potential to be effective replacements for the delivery of living MSCs. However, challenges for EVs as therapeutic agents remain, including but not limited to their stability, rapid plasma clearance, cell targeting specificity, and limited tools for their functionalization. In recent years my lab has studied the role of EVs as "universal communicators," focusing on developing non-genetic platform-based strategies to engineer the surface and lumen cargo of EVs toward engineering the cell signaling microenvironment. Here, I will present representative examples of this work, including drug delivery and immunomodulation, emphasizing engineering EVs for their potential regenerative medicine translation.

Speaker Biography



Dr Campbell has been a Research Professor at CMU for well over 20 years. He has appointments in Biomedical Engineering, the Engineering Research Accelerator, Materials Science and Engineering, and Biology. He is active in both teaching and research. Prior to joining CMU he spent 10 years in the Department of Orthopaedics at Allegheny General Hospital, Pittsburgh where he directed basic Orthopaedic research toward cancer and regenerative medicine applications. Overall, he has over 30 years of experience in multidisciplinary research collaborating with basic life scientists, engineers and clinicians across the areas of drug delivery, biomaterials, tissue/biomaterial interface, biosensors and regenerative medicine. His primary training is in physiology, focusing on endocrinology, where he pursued growth factor regulation of tissue development toward engineering the stem cell microenvironment with special emphasis on musculoskeletal and craniofacial tissues, to spatially control angiogenesis, tissue regeneration and the immune system. Recently, his laboratory has been focused on extracellular vesicles (EVs) and aspects of spatial control of delivery, as well as engineering surface and luminal contents of EVs for therapeutic delivery, and pursuing EVs as cell-to-cell communication modalities.

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Roundtable: Regenerative Medicine

Andrew Shephard, B.Sc. Ph.D.
Assistant Professor, Department of Symptom Research, Division of Internal Medicine
MD Anderson Cancer Center, University of Texas
Houston, TX

Using Nanoemulsions and Hydrogel Formulations to Target Neuro-Immune Interactions in Chronic Pain

Abstract: Neuropathy and chronic pain arise from numerous disease states, are becoming more prevalent and lack effective treatments. In search of new therapeutic options, there is an increasing appreciation that neuro-immune interactions present a new potential suite of therapeutic targets. In recent years my lab has studied the role of macrophages, part of the innate immune system, as crucial participants in the immune response in the acute and chronic phases of pain. Here, I will present recent findings from two of our ongoing collaborative projects, one using a mouse model of diabetic neuropathy and the other using a novel mouse model of neuromuscular polytrauma. In these models, macrophage-targeted nanoemulsions laden with celecoxib or thermo-responsive hydrogels laden with the ACE inhibitor captopril were evaluated for their ability to treat neuropathy and pain. Our findings support the repurposing of existing drugs via novel formulation strategies as a means of controlling aberrant immune system function, thereby restoring normal sensorimotor function and treating chronic pain.

Speaker Biography

Dr. Shepherd is an Assistant Professor in the Division of Internal Medicine at the University of Texas MD Anderson Cancer Center in Houston. Prior to joining MD Anderson, he spent 4 years in the Department of Anesthesiology at Washington University in St. Louis where he carried out research to describe the neuro-immune mechanisms by which analgesics relieve neuropathic pain. Overall, he has over 15 years of experience in multidisciplinary research collaborating with pharmacologists, bioengineers and clinicians across the areas of drug delivery, neuropharmacology and neurodegeneration. His primary training is in neuropharmacology, focusing on interactions between the innate immune system and the somatosensory nervous system. Recently, his laboratory has collaborated with the lab of Dr. Jelena Janjic at Duquesne University in Pittsburgh to develop theranostic and sustained drug delivery approaches to modify macrophage activity to control pain and promote regeneration.

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