VANCOUVER NANOMEDICINE DAY

September 17, 2020
University of British Columbia
Vancouver, BC

KEYNOTE SPEAKER
ROBERT LANGER
Massachusetts Institute of Technology, Boston, USA

INVITED SPEAKERS
VITO FODERÀ
University of Copenhagen, Denmark

LUCIA GEMMA DELOGU
University of Padua, Italy

CHRISTINE ALLEN
University of Toronto

For questions:
URS.HAFELI@UBC.CA

https://nanomedicines.ca/nmd20/
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END OF VANCOUVER NANOMEDICINE DAY 2020
Dear Participants,

It is my great pleasure to welcome you to the 6th Vancouver Nanomedicine Day 2020. This time online and virtual. It is an honor to have so many of you check in with us and learn more about the truly amazing field of nanomedicine.

During Nanomedicine Day, you have the opportunity to listen to 18 talks and browse through 93 posters that highlight the discoveries and innovations in nanomedicines. Nanomedicines contribute to global progress in acute, chronic and orphan disease treatment and management. Nanomedicines have allowed us to deliver drugs directly to disease sites, to dramatically improve their efficacy and reduce their toxicity, and to enable gene therapies employing RNA and DNA with the potential to treat most human diseases, including COVID-19. Diagnostics and imaging agents based on nanotechnology will help us to detect disease earlier and to more accurately monitor the effectiveness of therapy.

We are very thankful to our sponsors in life science and startup biotechnology companies, that help with getting a great line-up of speakers, including the keynote by Robert Langer, three poster prizes, and a fun debate at the end of the day.

Please take the occasion of this meeting as a starting point for future collaborations with your Canadian research friends, both in- and outside the co-sponsoring Nanomedicines Innovation Network – NMIN, but also with the many international participants present. The statistics are not final yet, but as of two days before the meeting, we had 850 registered participants from 38 countries. What a lineup!

Thank you all for spending time with us and I hope to see you next year again.

For the organizing committee,

Urs Hafeli

Professor, Faculty of Pharmaceutical Sciences, University of British Colombia, Vancouver, BC, Canada urs.hafeli@ubc.ca

Lundbeck Foundation Joint Professor, Department of Pharmacy, University of Copenhagen, Denmark
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Virtual Vancouver Nanomedicine Day
September 17, 2020
University of British Columbia
Vancouver, BC

TALKS

https://nanomedicines.ca/nmd20/
Introduction to Nanomedicines

Emmanuel A. Ho

School of Pharmacy, University of Waterloo, Kitchener, Ontario Canada
Department of Chemical Engineering, Faculty of Engineering
Waterloo Institute for Nanotechnology
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Nanomedicine is broadly defined as the “application of nanotechnology for the diagnosis, prevention and treatment of disease and to gain increased understanding of the complex underlying pathophysiology of disease. The ultimate goal is to improve quality of life”\(^1\). For the past several decades, the field of nanomedicine has evolved significantly and rapidly. It is truly an interdisciplinary field that incorporates multiple branches of science including, but not limited to chemistry, pharmaceutical sciences, engineering, physics, biology, etc. Continued development of new nanomaterials has enabled its applications in a broad range of disease states, all with the hopes of improving global health care.

Dr. Ho’s research program is focused on the development and characterization of innovative drug delivery platforms and biomaterials for the treatment and prevention of sexually transmitted infections, chronic wounds and ocular diseases. This includes targeted nanomedicines, implantable devices for sustained drug delivery, and biodegradable platforms such as gels and films.

REFERENCES
Targeting glycosaminoglycans in solid tumors

Mads Daugaard

Vancouver Prostate Centre | Department of Urologic Sciences | University of British Columbia
E-mail: mads.daugaard@ubc.ca

Solid tumors reform expression and composition of glycosaminoglycans to promote tumor progression. Distinct cancer-specific GAGs are candidate targets for therapy, but GAG targeting is challenging due to lack of specific binding technologies. Malignant and placental tissue compartments display a common oncofetal chondroitin sulfate GAG subtype that can be targeted by recombinant malarial VAR2CSA (rVAR2) proteins (Graphical abstract). In most cancers, oncofetal chondroitin sulfate is redundantly conjugated to a limited repertoire of proteoglycans differentially expressed on the cell surface and in the microenvironment. Accordingly, rVAR2 proteins can be employed in diagnostic and therapeutic applications to detect and target various types of human tumors. Our work exemplifies how evolutionarily refined parasite host-anchor molecules can be conveniently exploited to target specific cancer-associated GAG chains.
Protein self-assembly: the good, the bad and the ugly

Vito Foderà

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Proteins are intrinsically prone to self-assembly and they may form, both in vivo and in vitro, a wide range of supramolecular structures. Understanding protein aggregation is crucial in neurosciences, pharmaceutical sciences and nanotechnology. Indeed, deposits of protein aggregates are associated with the onset of pathologies such as Alzheimer’s and Parkinson’s diseases. Equally important is the impact that protein aggregates may have on the quality of a protein drug product. Finally yet importantly, protein aggregates have unique structural properties, making them appealing materials for applications in drug delivery and nanomedicine.

Either one looks at protein aggregation in the context of diseases, drug development or biomaterials, unravelling the mechanisms ruling the self-assembly reaction is of vital importance.

In our team, we have reported the possibility for a large number of proteins to form a variety of protein aggregates, ranging from microparticles and core-shell structures to elongated fibrils (see graphical abstract) [1]. I will present our approach based on advanced fluorescence microscopy, small angle X-ray scattering and spectroscopy and aimed at identifying the key interactions responsible for such variability in structures and morphologies [1-3]. I will also present our platform for the design and production of highly tuneable electrospun protein nanomaterials for the release of antibiotics [4] and as advanced matrices for nicotine replacement treatments [5].

Nanoscale flow cytometry analysis of extracellular vesicles for liquid biopsy development in cancer

Karan Khanna¹, Nikki Salmond¹, Karla Williams ¹*

¹Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC V6T 1Z3, Canada; karla.williams@ubc.ca

Extracellular vesicles (EVs) are lipid membrane enclosed nano-sized structures released into the extracellular environment by all cell types. EV constituents include proteins, lipids and nucleic acids that reflect the cell from which they originated. The proteome of cancer cells is distinct as compared to healthy cells of the same tissue type, and this distinct proteome should be reflected by the EVs they release. This makes EVs desirable candidates for blood-based biopsy diagnosis of cancer. EVs can be time consuming to isolate therefore, a technology that can analyze EVs in complex biological samples in a high throughput manner is in demand. We have worked towards the optimization of nanoscale flow cytometry for use in the analysis of EVs in whole, unpurified, plasma samples.¹ Using this technology we have identified circulating STEAP1 (six-transmembrane epithelial antigen of the prostate 1)-positive EVs in the plasma of prostate cancer patients and evaluated its diagnostic and prognostic significance.² We find that STEAP1-positive EVs are elevated in prostate cancer and levels are significantly associated with a prostate cancer diagnosis. However, no association was found between STEAP1 EV levels and disease recurrence or overall survival. Our results identify and quantitate STEAP1-positive EVs in plasma and provide rationale for a diagnostic strategy in prostate cancer through the analysis of STEAP1-positive EVs.

Complexity and Reality: The Case of Thermosensitive Liposomes

Christine Allen

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Toronto ON M5S 3M2; cjallen@utoronto.ca
Development and Fabrication of Surfactant-based Liposomes for Drug Targeting

Shyh-Dar Li

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Surfactants can be incorporated into liposomes to grant specific functions for drug targeting. An ultra-fast thermosensitive liposomal (uTSL) formulation composed of DPPC and Brij78 (96:4, mol) was developed for targeted delivery of an anticancer drug, doxorubicin (DOX) [1]. This Heat-activated cytoToxic (HaT) uTSL formulation was stable at 37°C, but burst-released >80% DOX at 42°C in 20 s. The HaT formulation displayed increased DOX release rates at the mild hyperthermic temperatures (39-42°C), ~2-fold increased drug delivery to the locally heated tumor, and significantly enhanced antitumor activity compared to the standard Lysolipid Temperature-sensitive Liposomal (LTSL) formulation. One dose therapy with HaT-DOX effectively shrank the tumor in a murine breast cancer model.

A phospholipid-free small unilamellar vesicular (PFSUV) formulation composed of cholesterol and Tween80 (5:1, mol) was fabricated using microfluidics [2]. PFSUVs displayed a monodispersed particle size of 60 nm and maintained a transmembrane gradient for active loading of weak base drugs (Figure), which could be stably retained in PFSUVs when incubated with serum. After i.v. administration, PFSUVs effectively accumulated in the liver in 5 min. Within the liver, 70% and 30% of the hepatocytes and sinusoidal cells were positive with PFSUVs, respectively, indicating the high hepatocyte-selectivity. Preliminary data suggest that PFSUVs target hepatocytes via the LDL receptor pathway. PFSUVs is being investigated as a drug delivery platform for treating various liver diseases.

Remote loading technology, where a drug or drug candidate is added to the outside of pre-formed liposomes and is subsequently sequestered into the liposomes, was first described over 35 years ago. The method typically involves the use of a transmembrane pH gradient (inside acid or inside basic) and the addition of a drug candidate that has an ionizable function. If the pH outside the liposome is one where the majority of the candidate drug is in a neutral form, then it can permeate across the liposomal lipid bilayer. Once inside the liposome, the drug candidate encounters a different pH and becomes charged. Since the charged form of the drug candidate is far less permeable across the lipid bilayer it becomes essentially “trapped” inside. The rate of drug loading and the rate of drug release is dependent on a variety of factors including liposomal lipid composition, the stability of the transmembrane ion gradient, and temperature. The rate of drug release in biological assays (e.g. serum containing tissue cultures or following injection into animals) is also influenced by the presence of surface bound proteins (protein corona) and the presence of an external “sink” that can remove any of the candidate drug following dissociation from the liposome. Other approaches have been considered for remote loading drugs, one of which my team has a specific interest in and involves the use of divalent metal ions. One of the challenges with using divalent metals concerned the fact that as the pH increases to >6 metals can bind to hydroxide forming an insoluble precipitate. Thus metal ion gradients are typically formed using low pH solutions. Thus if a selected compound has a metal binding function and an ionizable group it has been difficult to differentiate between whether a compound is remote loaded in response to a pH gradient or a metal ion gradient. One way to address this is to use a metal that is pre-complexed to a compound such as gluconate. Copper gluconate is stable at pH 7 and is able to remote load selected drugs in response to just metal binding. Another way to address this is to select compounds that only have metal binding functions, thus the existence of a pH gradient would have no impact on remote loading potential. This thought lead to the creation of Metaplex technology: a technology where drug candidates can be encapsulated in preformed liposomes in response to a metal gradient (metal inside). This technology is being developed for a variety of applications and some of these will be discussed in the presentation.
There are numerous new technologies being developed that may impact the future of medicine. For example, new drug delivery technologies including microparticles, nanoparticles and nanotechnology promise to create new treatments for cancer, heart disease and other illnesses. Nanotechnology may also be useful in delivering DNA and siRNA as well. Approaches involving polymers, microchips, and lipids will be examined.
Nanomaterials, Graphene and Immune Cells - From Biomedical Applications to Fighting COVID-19

Laura Fusco 1, Arianna Gazzi 1,2, Marco Orecchioni 3, Lucia Gemma Delogu 1*

1Department Department of Biomedical Sciences, University of Padua, Padua, Italy; luciagemma.delogu@yahoo.it; luciagemma.delogu@unipd.it 2Department of Chemical and Pharmaceutical sciences, university of Trieste, Trieste, Italy; 3Department of Chemical and Pharmaceutical sciences University of Sassari, Sassari, Italy

The potential immune modulation induced by nanomaterials, such as graphene-based materials (GBMs) is a key aspect for their biomedical applications. We previously demonstrated that the different nanomaterial physicochemical properties dramatically modulate their impact on human immune cells [1,2]. We pioneered the use of innovative single-cell mass cytometry approaches in the context of carbon-based nanomaterials, to evaluated the impact of a large set of GBMs (graphene oxides, GOs) with different lateral size and functionalization. We demonstrate that the amino-functionalization of GO enhanced the immune compatibility of the material and was able to induce a specific M1-like activation on monocytes, skewing a cytotoxic-like response with the secretion of interleukin-4 and Granzyme-B from B cells. Moreover, combining graphene with inorganic quantum dots containing indium, we enabled its detection using single-cell mass cytometry on a large variety of primary immune cells. Our results demonstrated that monocytes and, unexpectedly, B cells, showed a superior ability to internalize GO compared to the other immune cell subpopulations. Also, we exploited the immune modulation of a specific GO in combination with the osteoinductive capacity of calcium phosphate to design a new nanomaterial (magoCAP) able to induce bone regeneration in vitro and in vivo [3,4]. Moreover, we reported how the abundance of engineered materials, identifiable by their useful specific physicochemical properties, can offer new approaches to cope with the COVID-19 pandemic [5]. Our results demonstrate that specific design of nanomaterials offers new strategies for the development of new biomedical applications exploiting their immune modulation as well as to fight the COVID-19 pandemic and infectious diseases in general, including future pandemics.

A Novel Vaccine Approach Using Messenger RNA-Lipid Nanoparticles: Preclinical and Clinical Perspective

Ying Tam¹

¹Acuitas Therapeutics, Vancouver, BC V6T 1Z3 Canada

Acuitas is developing lipid nanoparticle systems (LNP) that allow the efficient delivery and expression of mRNA for a variety of therapeutic applications including protein replacement, passive immunization and gene editing. The most advanced therapeutic application is the use of mRNA-LNP as a prophylactic vaccine against infectious disease. In addition to our internal core research program we support multiple industry and academic collaborations. Results from select academic and partnered collaborations describing preclinical and clinical studies of intradermally (id) and intramuscularly (im) administered mRNA-LNP vaccines to provide protection against infectious diseases will be presented. Further, this update will focus on the clinical translation of our mRNA-LNP as a prophylactic vaccine against SARS-CoV2. Information on the potency and safety profile of a id- and im- administered SARS-CoV2 mRNA-LNP vaccine will be presented.
Neutralizing Monoclonal Antibodies to SARS-CoV-2
and Prospective Applications

Ralph Pantophlet

Faculty of Health Sciences, Simon Fraser University, Vancouver, BC V5A1S6, Canada; rpantophlet@sfu.ca

More than 27 million people around the world have now been infected with SARS-CoV-2 (https://coronavirus.jhu.edu/map.html). There is general belief that only an effective vaccine will be able to prevent further spread of the virus and significantly curb the pandemic. However, until an effective COVID-19 vaccine is deployed globally, it will be necessary to have therapeutic agents that can at least help to reduce the severity of disease in individuals who become infected and require hospitalization.

In this presentation, I will review current understanding of the antibody response to SARS-CoV-2, which is relevant to vaccine development and immunotherapy with monoclonal antibodies. The talk will focus in particular on so-called neutralizing antibodies (nAbs), which can blunt infection when present at sufficiently high concentration at the time of transmission or limit viremia if administered therapeutically. NAbs against SARS-CoV-2 target the trimeric spike (S) glycoprotein that crowns the surface of virus particles and that is required for viral entry into host cells. Recent studies will be used to highlight important insight into the epitopes targeted by highly potent nAbs. Efforts from my own lab on probing the vulnerability of SARS-CoV-2 glycosylation to nAbs will also be presented.
Targeting nanoparticles to the brain by exploiting the blood–brain barrier impermeability to selectively label the brain endothelium

Daniel Gonzalez-Carter1*, Xueying Liu1, Theofilus Tockary1, Anjaneyulu Dirisala1, Kazuko Toh1, Yasutaka Anraku1,2, Kazunori Kataoka1,3

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Nanoparticle (NP) brain-delivery strategies targeting proteins overexpressed at the brain microvasculature (e.g. TfR1, Glut1) have substantial specificity limitations due to significant protein expression in peripheral organs 1. We have developed a new strategy 2 to target NPs to the brain by instead selectively labelling the brain microvasculature. We exploit the lower endocytic rate of brain endothelial cells (BEC)3 to promote retention of free ligands (i.e. labels) selectively on the surface of BEC. NPs capable of recognizing the endothelial label are subsequently targeted to the brain without peripheral targeting (scheme 1). We demonstrate the in vivo feasibility of this strategy by injecting biotinylated α-PECAM1 antibodies (to label endothelial cell surfaces) followed by injection of avidin-functionalized nanoparticles (Avidin-NP) at increasing time-intervals. While short time-intervals result in avidin-NP targeting to the lung, brain, heart and pancreas, long time-intervals result in avidin-NP targeting only to the brain.

The present work therefore provides the basis for a new targeting strategy which exploits the physiology of BEC to generate the required NP targeting specificity.

Chemotherapeutic Nanoparticles Accumulate in the Female Reproductive System during Ovulation Affecting Fertility and Anticancer Activity

Maria Poley1, Yael Shamai1, Maya Kaduri1, Lilach Koren1, Omer Adir1,2, Jeny Shklover1, Janna Shainsky1, Irit Ben-Aharon3,4, Assaf Zinger5,6,* and Avi Schroeder1,*

1Laboratory for Targeted Drug Delivery and Personalized Medicine Technologies, Department of Chemical Engineering, Technion – Israel Institute of Technology, Haifa 32000, Israel. 2The Norman Seiden Multidisciplinary Program for Nanoscience and Nanotechnology, Technion – Israel Institute of Technology, Haifa 32000, Israel. 3Oncology, Rambam Health Care Center, 3109601 Haifa, Israel. 4Technion Integrated Cancer Center, Faculty of Medicine, Technion, 32000, Haifa, Israel. 5Center for Musculoskeletal Regeneration, Houston Methodist Academic Institute, TX, USA. 6Orthopedics and Sports Medicine, Houston Methodist Hospital, TX, USA

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Throughout the female menstrual cycle, physiological changes occur that affect the biodistribution of nanoparticles within the reproductive system. This can have positive or negative effects. We demonstrate a 2-fold increase in nanoparticle accumulation in the ovaries during female mouse ovulation (Fig. 1a) compared to the non-ovulatory stage (Fig. 1b) following intravenous administration. Accumulation in the reproductive system is favored by nanoparticles smaller than 100 nm. Chemotherapeutic nanoparticles administered during ovulation increased ovarian toxicity and decreased short-term and long-term fertility when compared to the free drug. Breast cancer treated with nanomedicines during ovulation results in higher drug accumulation in the reproductive system rather than at the site of the tumor, reducing treatment efficacy. Conversely, ovarian cancer treatment was improved by enhanced nanoparticle accumulation in the ovaries during ovulation. Our findings suggest that the menstrual cycle should be considered when designing and implementing nanotherapeutics for females.
Large Animal Species for Evaluating Long-circulating Nanomaterial Toxicokinetics: Comparisons between Primates, Canines, and Rabbits

Michael S Valic 1, Carl J Fisher 1, Alexander Gregor 1, Pamela Schimmer 1, Michael Halim 1, Harley Chan 1, Nicholas Bernards 1, Donovan Eu 1, Hong-Zhuan Chen 2, Celina Li 1, Xiao-Ling Gao 2, Kazuhiro Yasufuku 1, Jonathan C Irish 1, Brian C Wilson 1, Gang Zheng 1*

1Princess Margaret Cancer Centre, University Health Network, Toronto, ON M5G 2C1, Canada; gang.zheng@uhnresearch.ca 2Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China.

The most critical assessment in the preclinical translation of novel nanomaterials is their safety evaluation in large, nonrodent animal species. Conventional routes of testing favour the selection of canine models in single and/or repeated-dose toxicity studies, with nonhuman primates (e.g., macaques) chosen only if canines are deemed scientifically unsuitable. Case in point, questions have been raised regarding the appropriateness of canine models (e.g., beagles) for toxicity and toxicokinetic testing of nanomaterial-based drug delivery systems [1]. Given the risks associated with these pivotal and costly studies for the translational success of nanomaterials, clearer empirically driven guidance on the challenges and considerations for selecting nonrodent animal species for toxicokinetic assessments with long-circulating nanomaterials are highly desired.

Our team performed dose-ranging studies and toxicokinetic assessments with a long-circulating porphyrin-lipid based nanomaterial (Porphysome) in rabbits, beagles, and cynomolgus monkeys. Striking similarities were discovered in the dose-equivalent disposition and pharmacokinetic profiles of Porphysomes in rabbits and monkeys, whereas the profiles in beagles were remarkably different. Specifically, we found greater pharmacokinetic and pharmacologic variability in beagles not observed in the smaller rabbits and monkeys at equivalent doses. Our findings recommend a preclinical translation strategy that employs rabbit and nonhuman primate models in favour of beagles for dose-ranging studies and toxicokinetic assessments of long-circulating nanomaterials.

Nanoparticle delivery to solid tumours over the past ten years has stagnated at a median of 0.7% of the injected dose. Varying nanoparticle designs and strategies have yielded only minor improvements. Here we discovered a dose threshold for improving nanoparticle tumour delivery: 1 trillion nanoparticles in mice. Doses above this threshold overwhelmed Kupffer cell uptake rates, nonlinearly decreased liver clearance, prolonged circulation and increased nanoparticle tumour delivery. This enabled up to 12% tumour delivery efficiency and delivery to 93% of cells in tumours, and also improved the therapeutic efficacy of Caelyx/Doxil. This threshold was robust across different nanoparticle types, tumour models and studies across ten years of the literature. Our results have implications for human translation and highlight a simple, but powerful, principle for designing nanoparticle cancer treatments.
PH-responsive endosomal release agents to enhance RNAi conjugate activity across multiple cell types and receptors

Richard Holland, Mark Wood, Kieu Lam, Lorne Palmer, Xin. Ye, James Heyes

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The great promise of ligand targeted RNA interference (RNAi) therapeutics was further realized in 2019 with the regulatory approval of Givosiran (Givlaari®), a GalNAc-targeted siRNA for treatment of acute hepatic porphyria AHP. Adaptation of this therapeutic modality for cell types beyond hepatocytes has been slow, and, for reasons that are not fully understood, GalNAc mediated delivery appears to be a unique case. Even though conjugates can be targeted to other cell types readily with appropriate ligand selection, little if any of the internalized conjugate escapes the endosome before cellular degradation occurs. This significantly curtails biological activity, in most cases completely.

Genevant has a proprietary, pH-responsive endosomal release agent which can be simultaneously delivered with an RNAi conjugate to cells and tissues of choice by matching the targeting ligand in both entities. Subcutaneous co-administration in nonhuman primate studies has been shown to speed onset of activity and substantially improve both potency and duration of effect of GalNAc conjugates. Moreover, we have a expanding portfolio of extra-hepatocyte ligands with demonstrated biological activity across different cell types positioned to benefit from this unique approach. The modular design of this platform could further enable the realization of RNAi conjugates as therapeutic agents far beyond hepatic diseases.
Spontaneous, solvent-free entrapment of siRNA within lipid nanoparticles

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Lipid nanoparticle (LNP) formulations of nucleic acid have established clinical utility and are the enabling technology of the leading vaccines against COVID19, and of Onpattro, the first-ever FDA-approved RNAi therapeutic. These LNPs are composed of ionizable cationic lipids (such as KC2 or MC3), cholesterol, phosphatidylcholine, and poly-ethylene glycol (PEG) lipids and are produced using rapid-mixing techniques where an ethanolic-lipid phase is combined with an acidic aqueous phase containing siRNA. The resulting LNP suspension is prepared for administration by buffer-exchange to neutral pH. The rapid-mixing procedure is a bottom-up manufacturing approach that achieves particle formation and nucleic acid entrapment in a single step. The current paradigm on the mechanism of particle formation suggests that destabilizing agents (such as ethanol or detergents) are essential to achieving efficient entrapment of siRNA, and that specialised mixers are required to improve particle homogeneity.

Recent work using cryo-transmission electron microscopy (cryo-TEM) has shown that rapid-mixing procedures for LNP synthesis generate liposomal structures at pH 4 when produced without nucleic acid. However, when produced with siRNA, a combination of electron-dense and liposomal structures are observed.1,2 These observations suggested that the presence of siRNA induces the formation of electron-dense structures, but how that occurs was unclear. Specifically, the question remained of whether the empty vesicles at pH 4 are capable of entrapping siRNA and the role of ethanol in that process. Here we show, using cryo-TEM and dynamic light scattering, that ethanol is not required for efficient siRNA entrapment, particle formation likely occurs prior to entrapment, and specialized mixers are not required. Based on data presented here and elsewhere, it is proposed that nucleic acid entrapment at pH 4 occurs through rupture and reformation of positively charged vesicles upon interaction with negatively charged nucleic acid. Finally, we leverage this phenomenon, to demonstrate that unloaded vesicles (at pH 4) can be used as functional genomic screening tools.

References
Photodynamic Priming as a Means of Enhancing Nanomedicine Delivery and Overcoming Tumour Desmoplasia

Marta Overchuk¹,², Kara M. Harmatys¹, Shrey Sindhwani², Abdullah M. Syed², Maneesha A. Rajora¹,², Danielle M. Charron¹,², Juan Chen¹, Lili Ding¹, Martin G. Pomper⁴, Brian C. Wilson¹,⁵, Warren C.W. Chan², Gang Zheng¹,²,⁵

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Excessive extracellular matrix (ECM) deposition is one of the major barriers to nanoparticle extravasation and subsequent penetration in tumours. Tumour photodynamic priming (PDP), which activates photosensitizers with light to locally generate cytotoxic reactive oxygen species (ROS), was proposed as a means to enhance nanomedicine delivery by inciting vascular permeabilization or cancer cell death [1]. However, its effects in the context of tumour ECM remain elusive. Here, we investigate the use of a porphyrin-based photosensitizer and subtherapeutic light irradiation to enhance nanoparticle tumour accumulation and therapeutic efficacy against PSMA+ PC3 PIP subcutaneous mouse prostate cancer xenografts.

PDP-enabled Caelyx® tumour accumulation enhancement resulted in an improved therapeutic efficacy in the absence of off target toxicity, wherein 5 mg/kg was equally effective in delaying tumour growth as 15 mg/kg of Caelyx®. Furthermore, we are the first to demonstrate that subtherapeutic PDP resulted in a ~2-fold decrease in tumour collagen deposition and a significant reduction of ECM density in the subendothelial zone. Overall, this study demonstrated the potential of PDP to enhance tumour nanomedicine accumulation and alleviate tumour desmoplasia, highlighting the utility of PDP as a non-invasive priming strategy that can improve nanomedicine therapeutic outcomes in desmoplastic tumours.

Debate: Are Nanomedicines Still the Next Big Thing?

Marcel B Bally¹,²,³,⁴,⁵, Kishor Wasan⁶,⁷,⁸

Moderated by Emmanuel Ho⁹,¹⁰

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to establish and mobilize a network drawn from academia, industry, and other not-for-profit research enterprises to maintain and improve Canada’s position as a global leader in developing next generation nanomedicines.

MISSION:
To develop novel therapeutics to cure high-burden human diseases and new diagnostics to detect disease more precisely; to commercialize these products to bring health and economic benefits to Canadians; and to train the skilled workforce required by the growing nanomedicines industry.

FUNDING:
NMIN was awarded $18,532,000 in funding over 6 years (2019-2025) by the Government of Canada through the Networks of Centres of Excellence (NCE) Program.

RESEARCH INVESTMENTS & NETWORK MEMBERS

**Total NMIN investigators:** 49  
**Total NMIN-funded PIs:** 23

**Distribution of research investments ($) by Theme:**
- **Theme I:** 11 | 38%
- **Theme II:** 8 | 27.5%
- **Theme III:** 8 | 27.5%
- **Cores:** 2 | 7%

**Total current NMIN research investments:** $5,662,561

**RESEARCH THEMES:**

**Targeted Drug Delivery (Theme I)**
Leaders: Dr. Marcel Bally, University of British Columbia  
Dr. Shyh-Dar Li, University of British Columbia

**Enabling Gene Therapies (Theme II)**
Leaders: Dr. Pieter Cullis, University of British Columbia  
Dr. Christian Kastrup, University of British Columbia

**Diagnostics (Theme III)**
Leaders: Dr. Shana Kelley, University of Toronto  
Dr. Gilbert Walker, University of Toronto

**CORE FACILITIES:**

**NANOCORE**  
Nanomedicines Formulation and Characterization Core Facility  
Leader: Dr. Pieter Cullis  
University of British Columbia

Co-leader: Dr. Christian Kastrup  
University of British Columbia

**PHARMACORE**  
Pharmacology/Toxicology and Scale-up Core Facility  
Leader: Dr. Marcel Bally  
University of British Columbia

Co-leader: Dr. Shyh-Dar Li  
University of British Columbia
Catalyzing the Nanomedicine Revolution
LRD 2021

Keep informed about upcoming events:
https://nanomedicines.ca/events/

About NMIN's Core Facilities

**NANOCORE**
Nanomedicines Formulation and Characterization Core Facility

**MISSION:** To develop high-quality, state-of-the-art lipid nanoparticles encapsulating small molecule or nucleic acid drugs that enable proof-of-concept (POC) animal studies.
- To standardize the physicochemical characterization in order to identify critical parameters.

**Formulation:** High-quality, state-of-the-art nanoparticle formulations encapsulating small molecule, peptide or nucleic acid drugs that enable proof-of-concept (POC) animal studies.

**Physicochemical characterization:** Comprehensive portfolio of characterization assays including sizing & structure analyses that guarantee reliable interpretation of in vitro & in vivo studies & further optimization.
- No nanoparticle formulation will enter animal studies in NMIN without being rigorously characterized.

**PHARMACORE**
Pharmacology/Toxicology and Scale-up Core Facility

**MISSION:** To help research partners develop promising nanomedicines and provide capabilities to advance new treatments from the bench to the clinic.

**Capabilities:** Pre-clinical in vitro, pre-clinical pharmacology, GLP-guiding safety, manufacturing

Contacts
- NanoCore: Dominik Witzgmann | Admin Lead | dominik.witzgmann@ubc.ca
- PharmaCore: Nancy Dos Santos | Admin Lead | ndossantos@bcrcc.ca

NMIN projects working with Core Facilities
21 out of 29 projects | 78%
- PharmaCore only: 1
- Both Cores: 5 | 24%
- NanoCore only: 15 | 71%

PARTNERS
Total partner organizations: 73

By country
- Canada 57 | 78%
- USA 10 | 13.5%
- Germany 2 | 2.5%
- Denmark 1 | 1.5%
- Ireland 1 | 1.5%
- Switzerland 1 | 1.5%
- United Kingdom 1 | 1.5%

By sector
- Federal Agencies 2 | 3%
- Other 6 | 8%
- Hospitals etc. 6 | 8%
- Non-Profits 8 | 11%
- University 16 | 22%
- Industry 35 | 48%

HQP (working on NMIN projects)
Total NMIN HQP: 97

By level
- Research staff: 34%
- UnderGrad: 3%
- Masters: 9%
- PhD: 27%
- PDF: 27%

By gender
- 56% Female
- 44% Male

By nationality
- 63% Canadian
- 37% International

HQP = Highly Qualified Personnel
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