

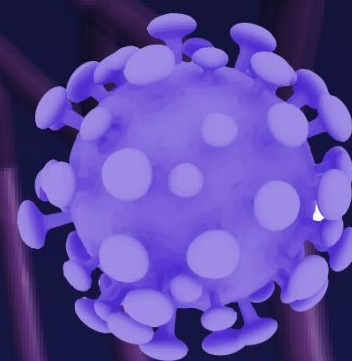


Virtual

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

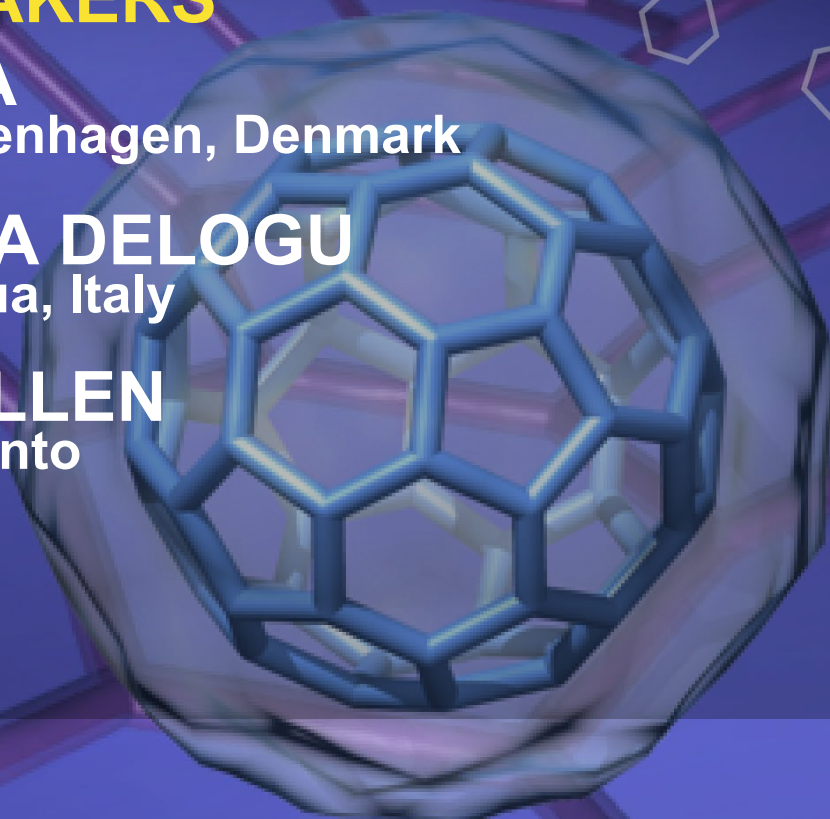
University of Copenhagen, Denmark

LUCIA GEMMA DELOGU

University of Padua, Italy

CHRISTINE ALLEN

University of Toronto



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RÉSEAU D'INNOVATION NANOMÉDECINES

For questions:
URS.HAFELI@UBC.CA

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VANCOUVER NANOMEDICINE DAY 2020 - THURSDAY, SEPTEMBER 17, 2020

<https://www.nanomedicines.ca/nmd-2020/>

8:00 AM	Urs Hafeli	Welcome to the 6th Vancouver Nanomedicine Day 2020	Pharmaceutical Sciences, UBC
Session 1			Chair: Urs Hafeli, UBC
8:05 AM	Emmanuel Ho	Introduction to Nanomedicines	School of Pharmacy, University of Waterloo
8:25 AM	Mads Daugaard	Targeting Glycosaminoglycans in Solid Tumors	Vancouver Prostate Centre, UBC
8:40 AM	INVITED TALK: Vito Foderà	Protein self-assembly: the good, the bad and the ugly	Department of Pharmacy, University of Copenhagen, Denmark
9:20 AM	SHORT BREAK		
Session 2			Chair: Marcel Bally, UBC + BC Cancer
9:30 AM	Karla Williams	Nanoscale Flow Cytometry Analysis of Extracellular Vesicles for Liquid Biopsy Development in Cancer	Pharmaceutical Sciences, UBC
9:45 AM	INVITED TALK: Christine Allen	Complexity and Reality: The Case of Thermosensitive Liposomes	Leslie Dan Faculty of Pharmacy, University of Toronto
10:25 AM	SHORT BREAK		
Session 3: Nanomedicines for Drug Delivery			Chair: Christian Kastrup, UBC
10:30 AM	Shyh-Dar Li	Development and Fabrication of Surfactant-based Liposomes for Drug Targeting	Pharmaceutical Sciences, UBC
10:45 AM	Marcel Bally	Metals in Liposomes	BC Cancer & UBC
11:05 AM	KEYNOTE TALK: Robert Langer	Microtechnologies and Nanotechnologies in Drug Delivery	Massachusetts Institute of Technology, Boston, USA
11:45 AM	Robert Langer	Extended Keynote Q&A	
11:55 AM	Diana Royce / Pieter Cullis	A Canadian Catalyst: NanoMedicines Innovation Network (NMIN)	NMIN, Canada
12:00 PM	LUNCH BREAK & POSTER SESSION		
Session 4: Covid-19 Related Nanomedicines			Chair: Federica Di Palma, Genome BC
12:40 PM	INVITED TALK: Lucia Gemma Delogu	Nanomaterials, Graphene and Immune Cells - From Biomedical Applications to Fighting COVID-19	University of Padua, Italy
1:20 PM	Ying Tam	A Novel Vaccine Approach Using Messenger RNA-Lipid Nanoparticles: Preclinical and Clinical Perspective	Acuitas Therapeutics, Vancouver, BC
1:35 PM	Ralph Pantophlet	Neutralizing Monoclonal Antibodies to SARS-CoV-2 and Prospective Applications	Health Sciences, Simon Fraser University
1:50 PM	SHORT BREAK		
Session 5: Rapid Talks (5 min each including discussion)			Chair: Kathy Saatchi, UBC
2:00 PM	Daniel Gonzalez-Carter	Targeting Nanoparticles to the Brain by Exploiting the Blood/Brain Barrier Impermeability to Selectively Label the Brain Endothelium	Innovation Center of NanoMedicine, Kawasaki, Japan
2:05 PM	Maria Poley	Chemotherapeutic Nanoparticles Accumulate in the Female Reproductive System During Ovulation Affecting Fertility and Anticancer Activity	Technion - Israel Institute of Technology, Haifa, Israel
2:10 PM	Pamela Schimmer / Michael Valic	Large Animal Species for Evaluating Long-circulating Nanomaterial Toxicokinetics: Comparisons Between Primates, Canines, and Rabbits	Princess Margaret Cancer Centre, Toronto, ON
2:15 PM	Ben Ouyang	The Dose Threshold for Nanoparticle Tumour Delivery	University of Toronto, Institute of Biomaterials and Biomedical Engineering
2:20 PM	Richard Holland	PH-Responsive Endosomal Release Agents to Enhance RNAi Conjugate Activity Across Multiple Cell Types and Receptors	Genevant Sciences, Vancouver, BC
2:25 PM	Jayesh Kulkarni	Spontaneous, Solvent-Free Entrapment of siRNA Within Lipid Nanoparticles	Center for Molecular Medicine and Therapeutics, UBC
2:30 PM	Marta Overchuk	Photodynamic Priming as a Means of Enhancing Nanomedicine Delivery and Overcoming Tumour Desmoplasia	Princess Margaret Cancer Centre, University Health Network, Toronto, ON
2:35 PM	SHORT BREAK		
Session 6: Debate			Chair: Emmanuel Ho, University of Waterloo
2:40 PM	Marcel Bally / Kishor Wasan	Debate: Are Nanomedicines Still the Next Big Thing?	BC Cancer & UBC / UBC & iCo Therapeutics
3:10 PM	Urs Hafeli	Poster Prizes	Pharmaceutical Sciences, UBC
3:15 PM	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 Columbia,
Vancouver, BC, Canada urs.hafeli@ubc.ca
Lundbeck Foundation Joint Professor, Department of Pharmacy, University of
Copenhagen, Denmark

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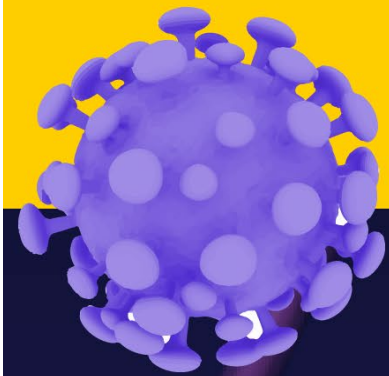


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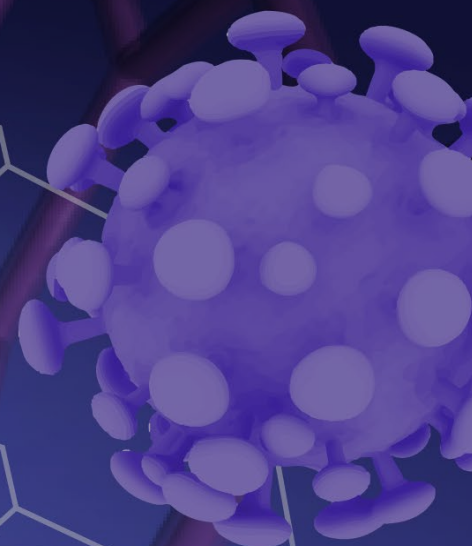
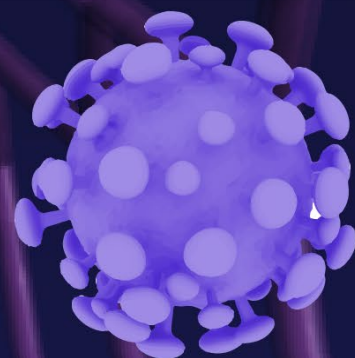
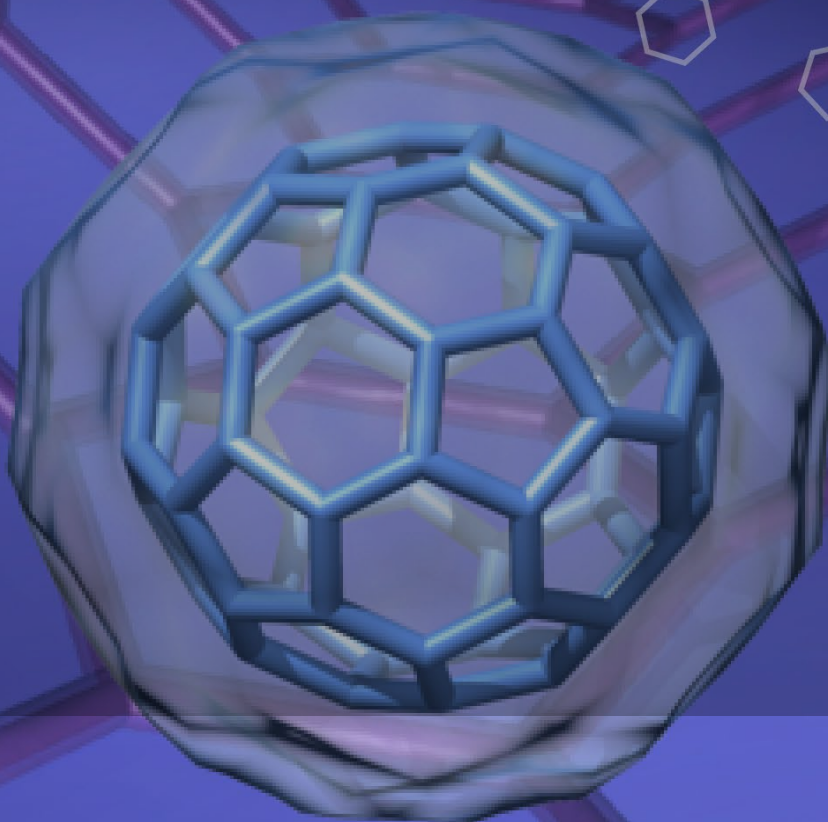
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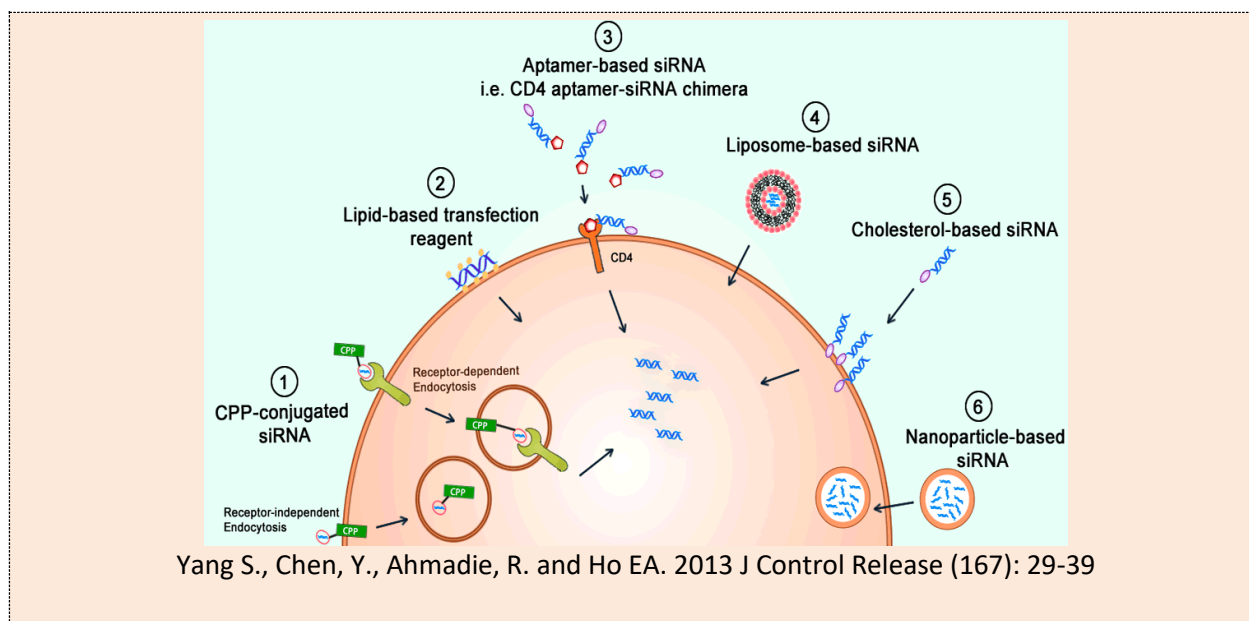
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Vancouver, BC



TALKS



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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

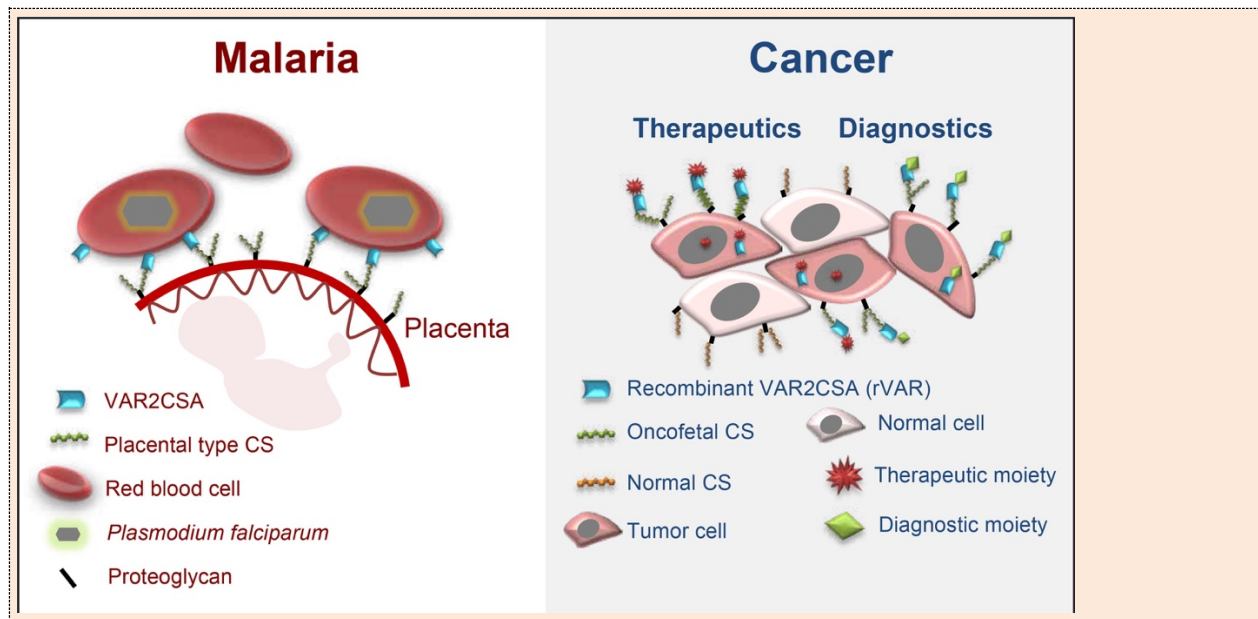
emmanuel.ho@uwaterloo.ca

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.

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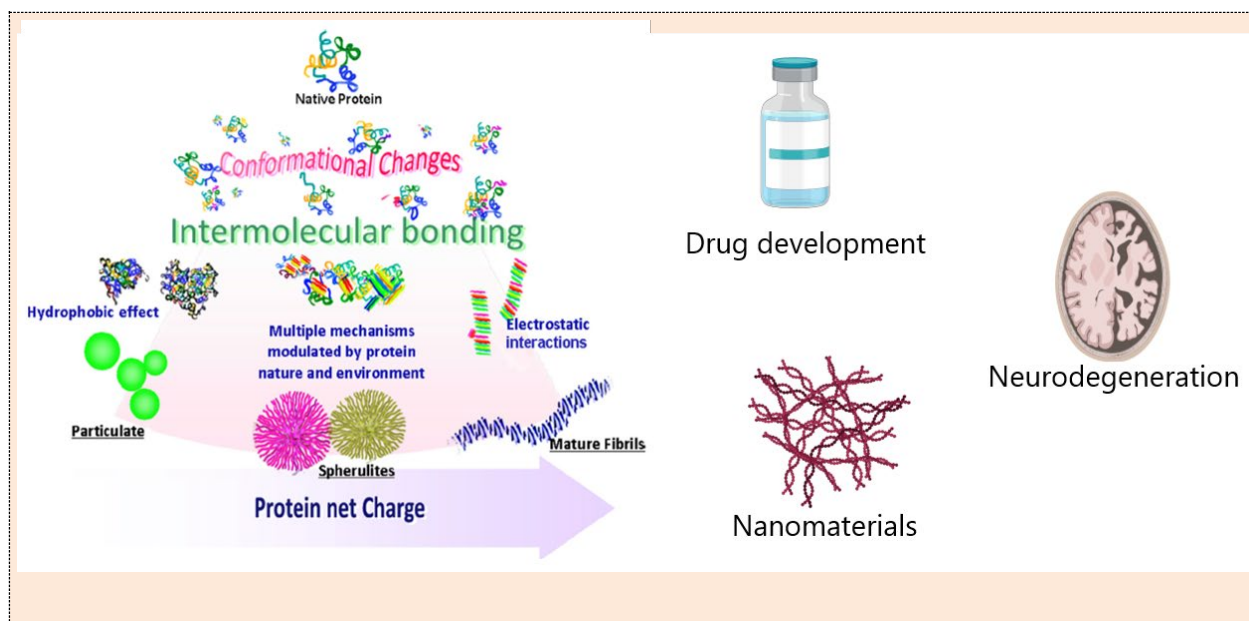


Targeting glycosaminoglycans in solid tumors

Mads Daugaard

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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].

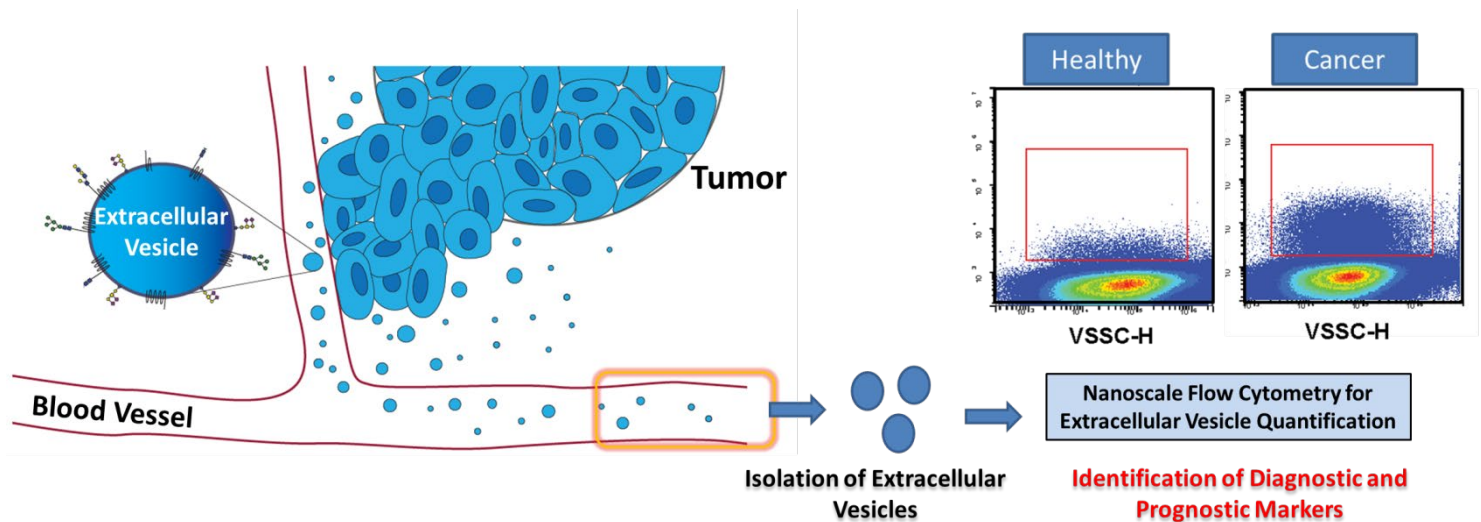
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[5] Kalouta et al. **2020, Mol. Pharm.** *in press*



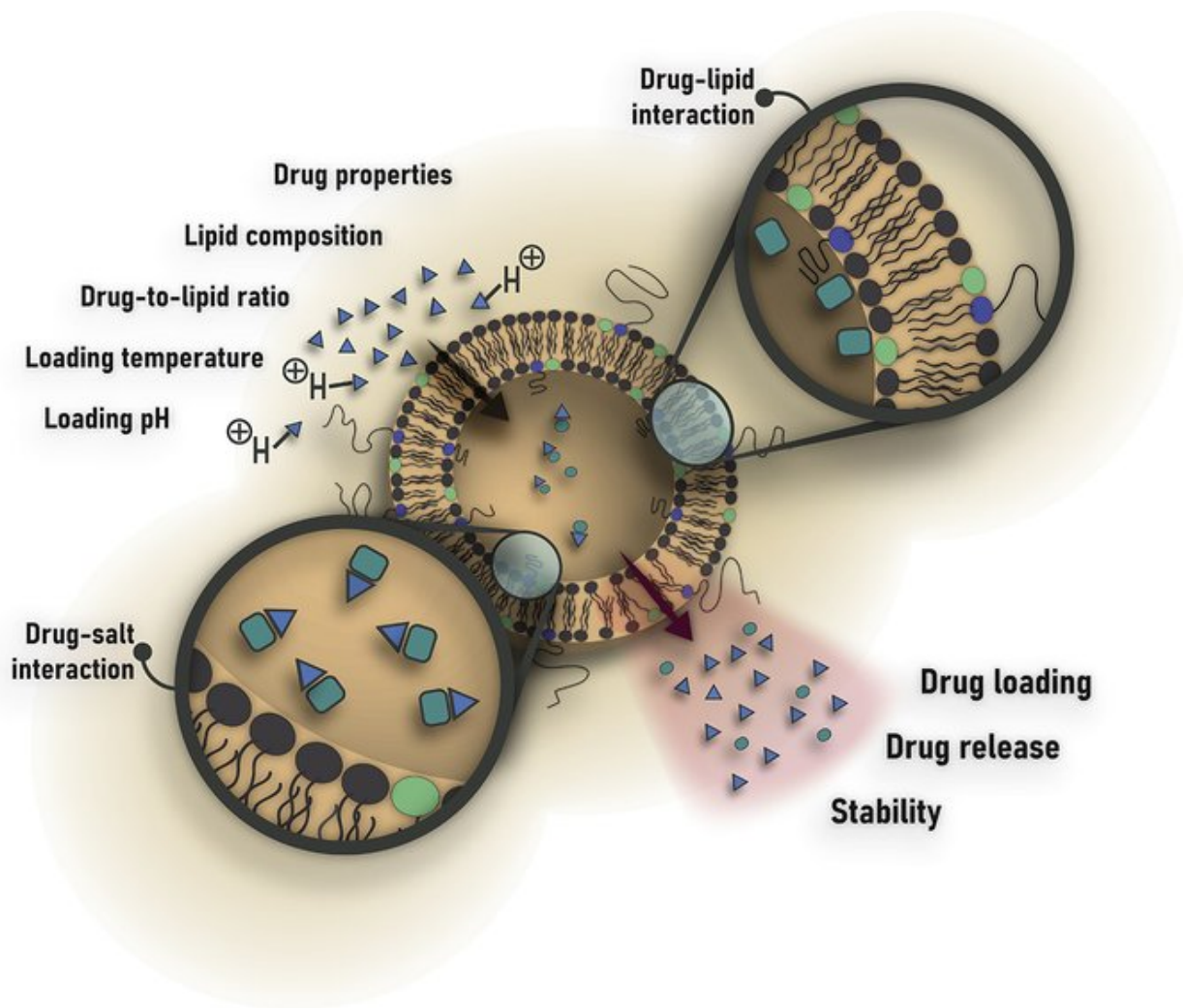
Nanoscale flow cytometry analysis of extracellular vesicles for liquid biopsy development in cancer

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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.

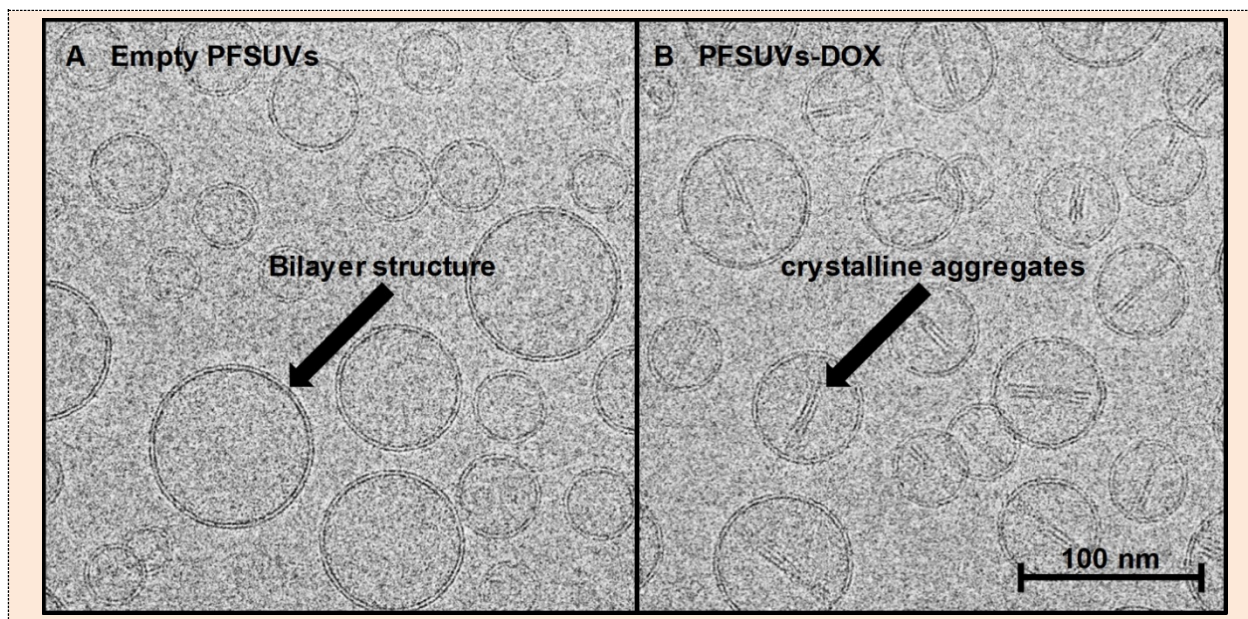
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Complexity and Reality: The Case of Thermosensitive Liposomes

Christine Allen

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Development and Fabrication of Surfactant-based Liposomes for Drug Targeting

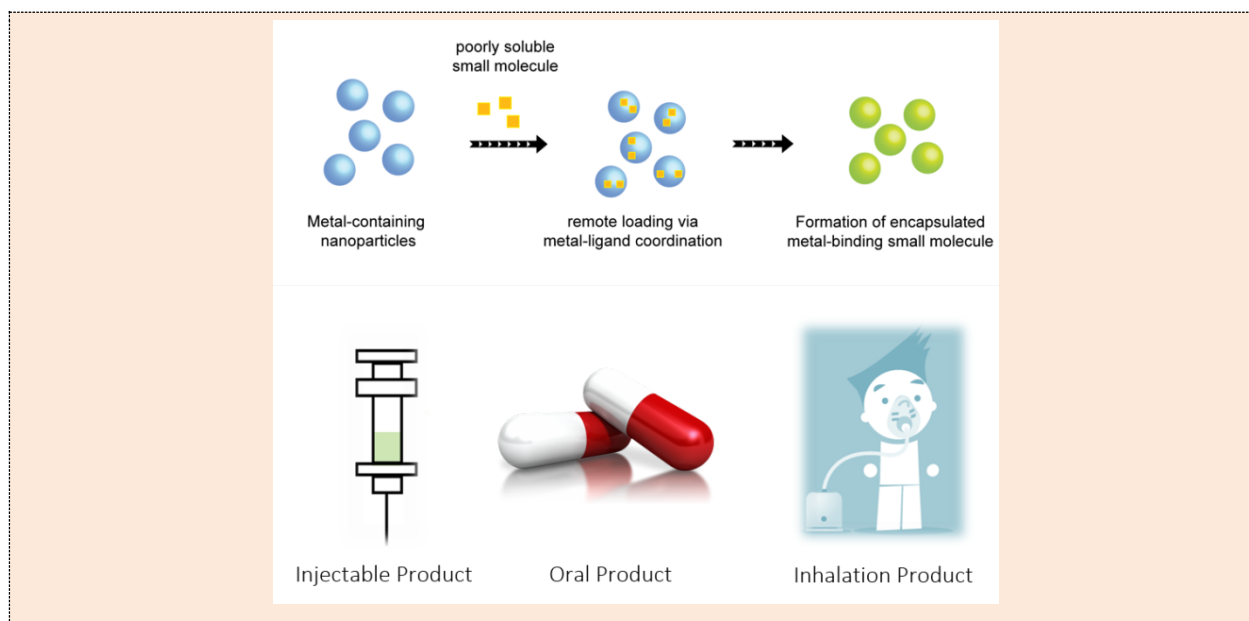
Shyh-Dar Li

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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.

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Metals in Liposomes

Marcel B Bally^{1,2,3,5,6}, Thomas Redelmeier², Mike Abrams²,
Kevin Sun^{2,4}, Kent Chen^{2,5}, and Ada Leung²

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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.

Microtechnologies and Nanotechnologies in Drug Delivery

Dr. Robert S. Langer, Sc.D.
Institute Professor
Massachusetts Institute of Technology

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*}

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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 evaluate 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.

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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

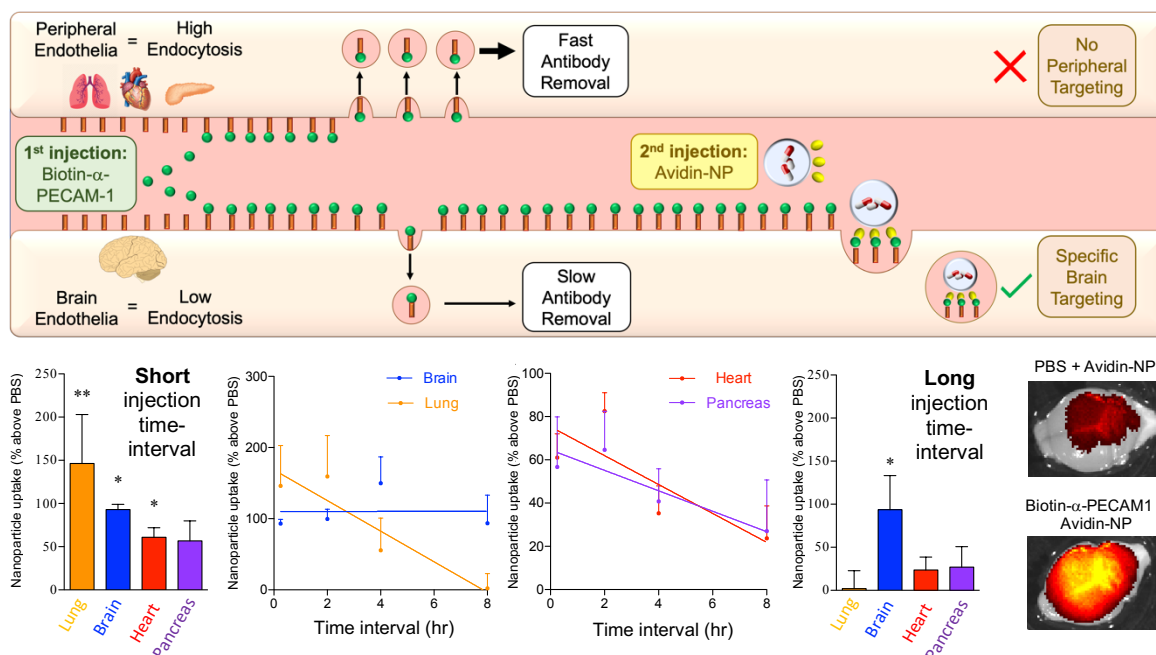
Ralph Pantophlet

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.

Scheme 1.



Targeting nanoparticles to the brain by exploiting the blood–brain barrier impermeability to selectively label the brain endothelium

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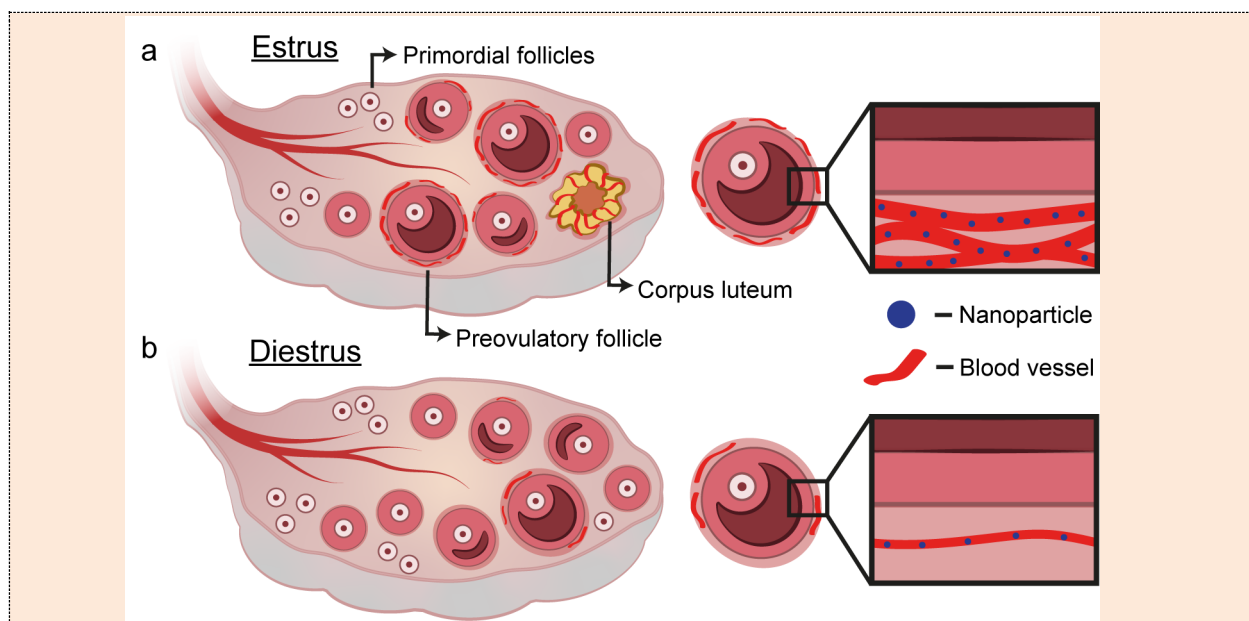
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Nanoparticle (NP) brain-delivery strategies targeting proteins overexpressed at the brain microvasculature (*e.g.* TfR1, Glut1) have substantial specificity limitations due to significant protein expression in peripheral organs ¹. We have developed 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.

References: ¹ Fillebeen, et al. (2019). *Blood*, 133 (4): 344-355; ² Gonzalez-Carter, et al. (2020) *PNAS* doi: 10.1073/pnas.2002016117 (online ahead of print); ³ Ben-Zvi, et al. (2014). *Nature*, 509 (7501): 507-511.



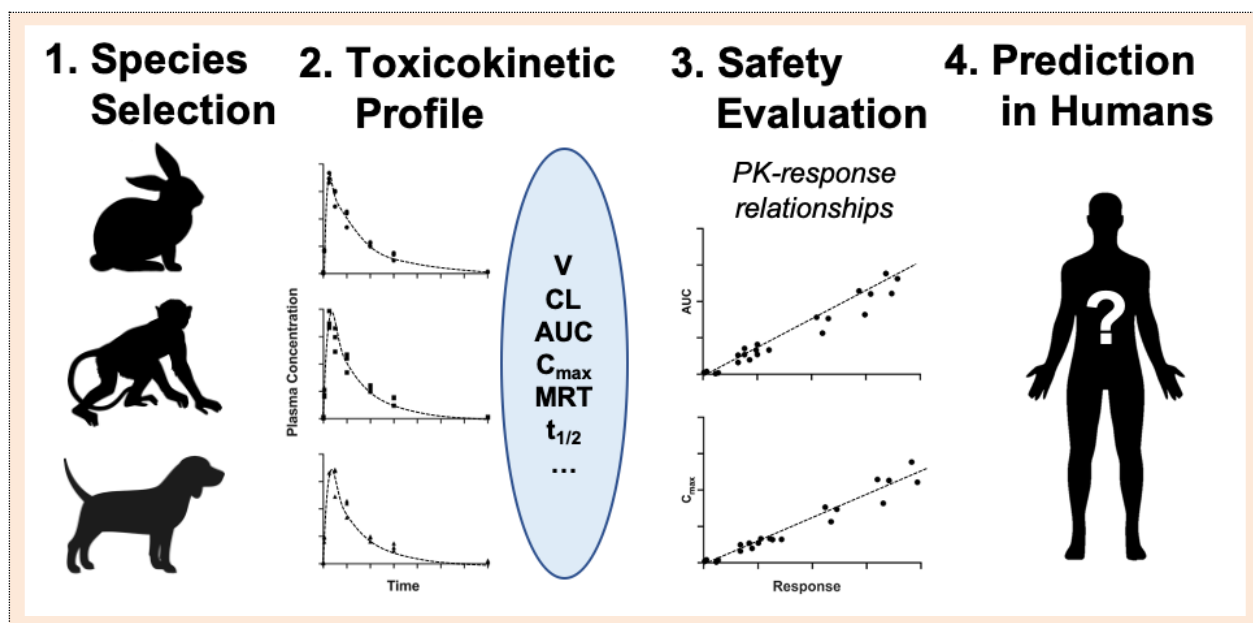
Chemotherapeutic Nanoparticles Accumulate in the Female Reproductive System during Ovulation Affecting Fertility and Anticancer Activity

Maria Poley¹, Yael Shammai¹, Maya Kaduri¹, Lilach Koren¹, Omer Adir^{1,2}, Jeny Shklover¹, Janna Shainsky¹, Irit Ben-Aharon^{3,4}, Assaf Zinger^{5,6,*} and Avi Schroeder^{1,*}

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, 320000, 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*}

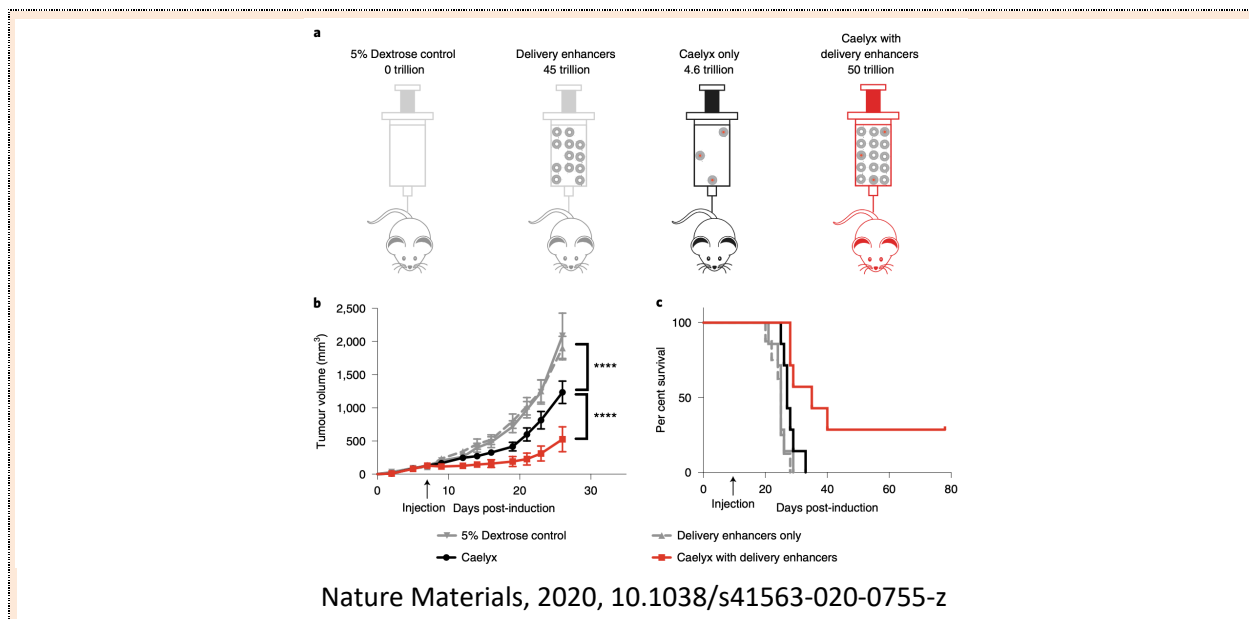
¹Princess Margaret Cancer Centre, University Health Network, Toronto, ON M5G 2C1, Canada;

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.

1. Caron WP, Morgan KP, Zamboni BA, Zamboni WC (2013). **A Review of Study Designs and Outcomes of Phase I Clinical Studies of Nanoparticle Agents Compared with Small-Molecule Anticancer Agents.** Clin Cancer Res 19(12), 3309–3315.



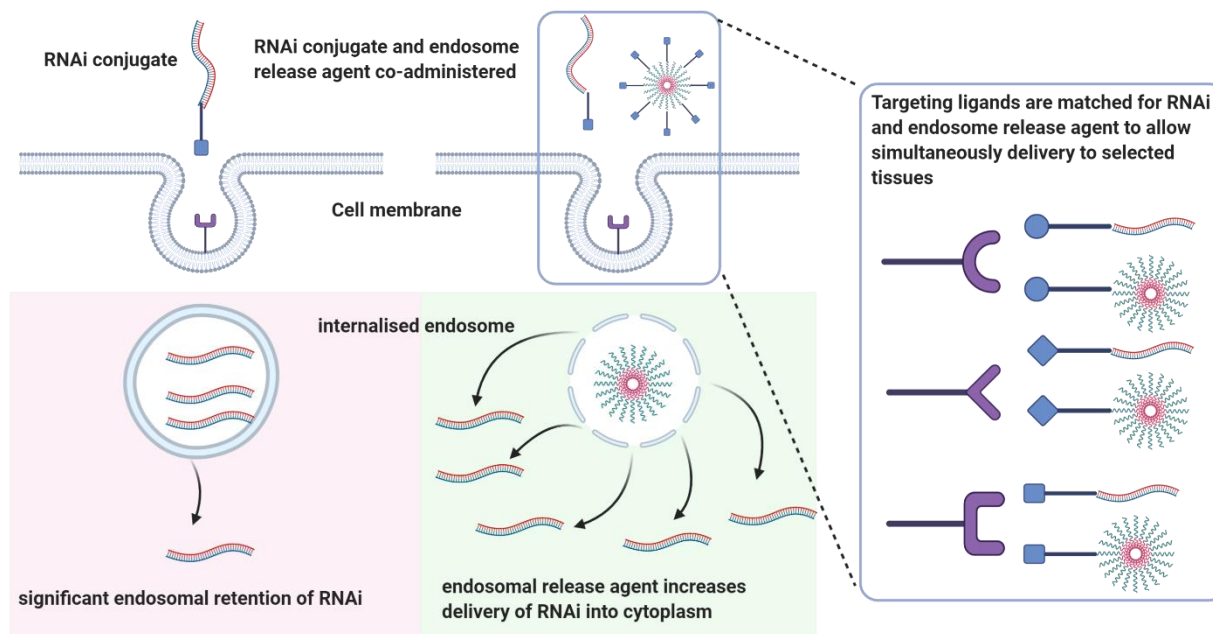
The dose threshold for nanoparticle tumour delivery

Ben Ouyang^{1,2,3}, Wilson Poon^{# 2,3}, Yi-Nan Zhang^{# 2,3}, Zachary P. Lin^{2,3}, Benjamin R. Kingston^{2,3}, Anthony J. Tavares^{2,3,4}, Yuwei Zhang^{3,5}, Juan Chen⁶, Michael S. Valic⁶, Abdullah M. Syed^{2,3}, Presley MacMillan^{3,5}, Julien Couture-Sen cal^{2,3,7}, Gang Zheng^{2,6,8}, Warren C.W. Chan^{* 2,3,9,10,11}

¹MD/PhD Program, University of Toronto, Toronto, ON M5S 1A8, Canada ²Institute of Biomaterials and Biomedical Engineering, University of Toronto, Rosebrugh Building, Room 407, 164 College Street, Toronto, Ontario M5S 3G9, Canada. ³Terrence Donnelly Centre for Cellular and Biomolecular Research, University of Toronto, 160 College Street, Room 230, Toronto, Ontario M5S 3E1, Canada. ⁴School of Life Sciences, Faculty of Humanities and Social Sciences, Sheridan College, Brampton, Ontario L6Y5H9, Canada. ⁵Department of Chemistry, University of Toronto, Toronto, Ontario, Canada. ⁶Princess Margaret Cancer Centre, University Health Network, 101 College Street, Toronto, ON M5G 1L7, Canada. ⁷Division of Engineering Science, University of Toronto, 35 St. George Street, Toronto, Ontario, M5S 1A4, Canada. ⁸Department of Medical Biophysics, University of Toronto, 101 College Street, Room 15-701 Toronto, Ontario M5G 1L7, Canada. ⁹Department of Chemical Engineering, University of Toronto, 200 College Street, Toronto, Ontario M5S 3E5, Canada. ¹⁰Department of Chemistry, University of Toronto, 80 St George Street, Toronto, Ontario M5S 3H6, Canada. ¹¹Department of Material Science and Engineering, University of Toronto, 184 College Street, Suite 140, Toronto, Ontario M5S 3E1, Canada.

[#]Equal contribution. ^{*}Corresponding Author: warren.chan@utoronto.ca.

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

Richard.holland@genevant.com Genevant Sciences Corporation, 155-887 Great Northern Way,
Vancouver, British Columbia, Canada, V5T 4T5

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 an 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.

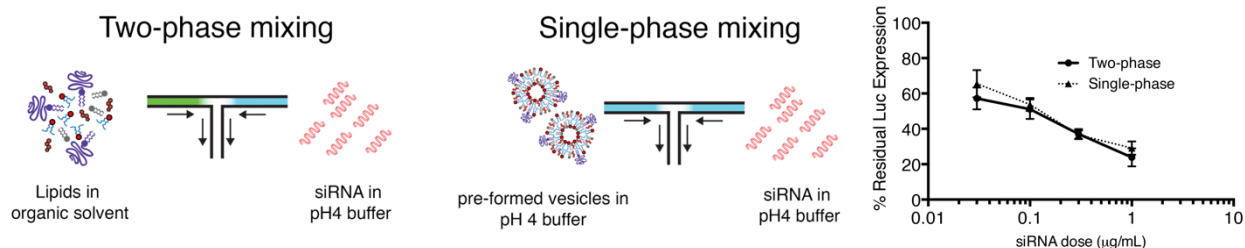
Spontaneous, solvent-free entrapment of siRNA within lipid nanoparticles

Jayesh A. Kulkarni^{1,2,3,4*}, Sarah B. Thomson², Josh Zaifman^{4,5,6}, Yuen Yi C. Tam^{4,5}, Pieter R. Cullis^{1,4*}, Terri L. Petkau^{2,3}, Blair R. Leavitt^{2,3}

¹NanoMedicines Innovation Network; ²Center for Molecular Medicine and Therapeutics; ³Incisive Genetics; ⁴Department of Biochemistry and Molecular Biology; ⁵Integrated Nanotherapeutics; ⁶Department of Chemistry, University of British Columbia. Email: j.kulkarni@alumni.ubc.ca

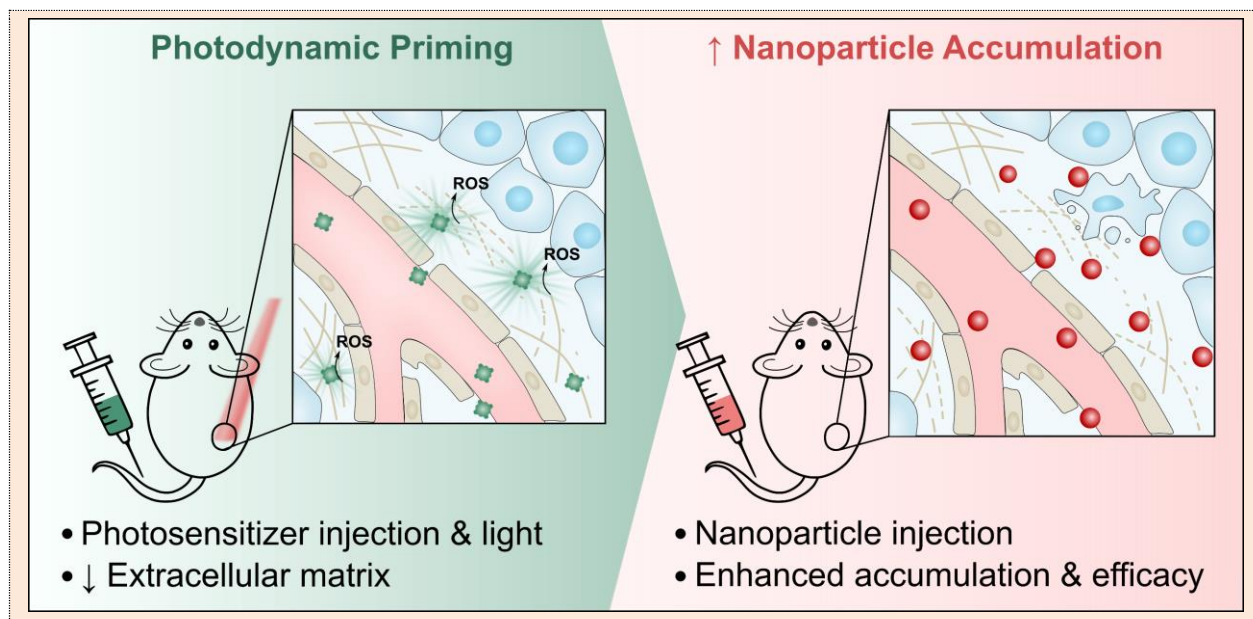
Lipid nanoparticle (LNP) formulations of nucleic acid have established clinical utility and are the enabling technology of the leading vaccines against COVID19, and of Onpattro, the first-ever FDA-approved RNAi therapeutic. These LNPs are composed of ionizable cationic lipids (such as KC2 or MC3), cholesterol, 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

- 1 Kulkarni, J. A. *et al.* On the Formation and Morphology of Lipid Nanoparticles Containing Ionizable Cationic Lipids and siRNA. *ACS nano* **12**, 4787-4795, doi:10.1021/acsnano.8b01516 (2018).
- 2 Kulkarni, J. A. *et al.* Fusion-dependent formation of lipid nanoparticles containing macromolecular payloads. *Nanoscale*, doi:10.1039/C9NR02004G (2019).



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

Marta Overchuk^{1,2}, Kara M. Harmatys¹, Shrey Sindhwani², Abdullah M. Syed², Maneesha A. Rajora^{1,2}, Danielle M. Charron^{1,2}, Juan Chen¹, Lili Ding¹, Martin G. Pomper⁴, Brian C. Wilson^{1,5}, Warren C.W. Chan², Gang Zheng^{1,2,5}

¹Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario M5G 1L7, Canada; gang.zheng@uhnresearch.ca ²Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario M5G 1L7, Canada; ³Krembil Research Institute University Health Network, Toronto, Ontario M5G 1L7, Canada; ⁴Department of Radiology, Johns Hopkins School of Medicine, Baltimore MD 21205, USA ⁵Department of Medical Biophysics, University of Toronto, Toronto, Ontario M5G 1L7, Canada

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.

1. Snyder JW, Greco WR, Bellnier DA, Vaughan L, Henderson BW (2003), **Photodynamic Therapy: a Means to Enhanced Drug Delivery to Tumors**. Cancer Research, 63 (23), 8126-31.



Debate: Are Nanomedicines Still the Next Big Thing?

Marcel B Bally^{1,2,3,4,5}, Kishor Wasan^{6,7,8}

Moderated by Emmanuel Ho^{9,10}

¹Experimental Therapeutics, BC Cancer's Vancouver Research Centre, Vancouver, BC, V5Z 1L3 mbally@bccrc.ca; ²Cuprous Pharmaceuticals Inc., Vancouver, BC; ³Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC; ⁴Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC; ⁵Nanomedicines Innovation Network, NCE, Canada

⁶Director of Research, iCo Therapeutics Inc. Vancouver, BC, V6Z 2T3; ⁷Adjunct Professor and Distinguished University Scholar, Department of Urologic Sciences, Faculty of Medicine, University of British Columbia; ⁸Chief Medical and Scientific Officer, Skymount Medical Group Inc., Calgary, Alberta T3C 0J8, kishor.wasan@ubc.ca

⁹School of Pharmacy, University of Waterloo, 10A Victoria St. S., Kitchener, Ontario, N2G 1C5, emmanuel.ho@uwaterloo.ca

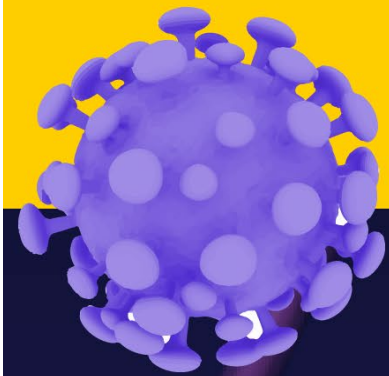


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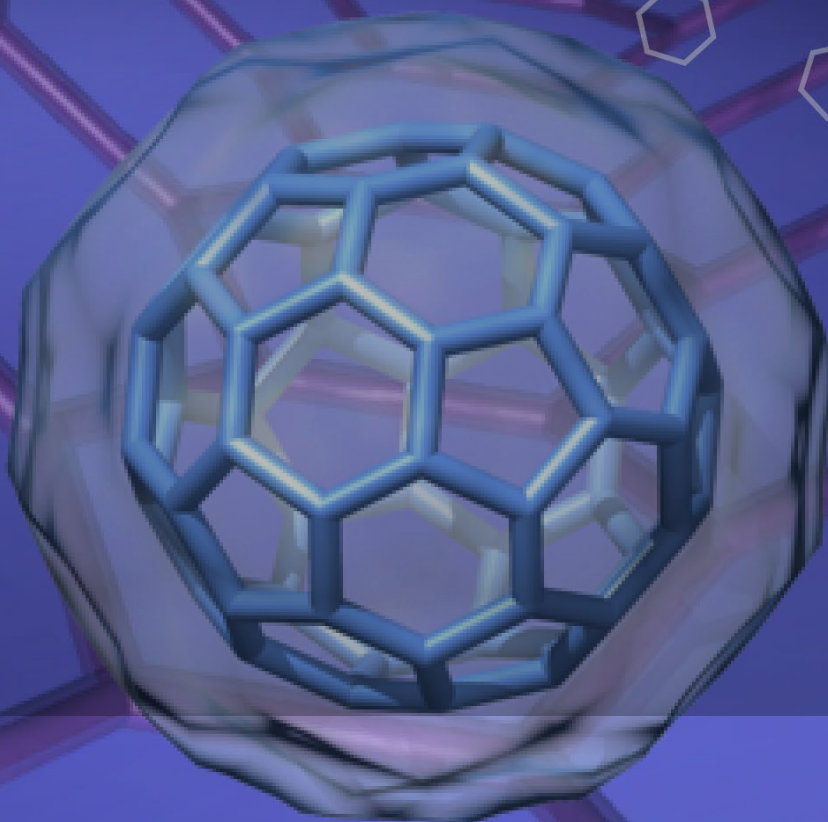
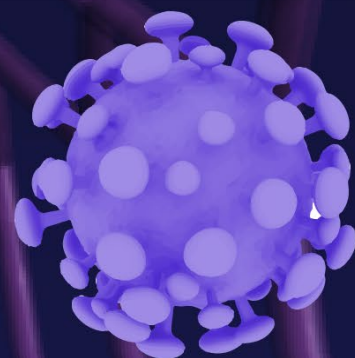
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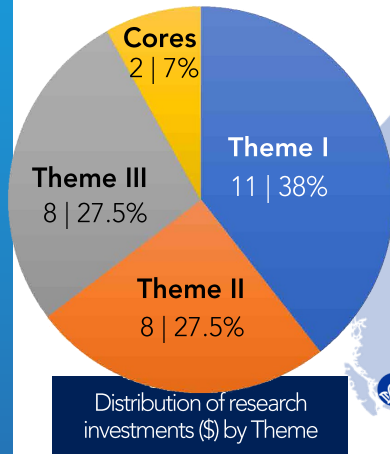
to establish and mobilize a **network** drawn from academia, industry, and other not-for-profit research enterprises to maintain and improve Canada's position as a **global leader in developing next generation nanomedicines**

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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



Distribution of research investments (\$) by Theme

The **29** projects in NMIN's current research investment span **7** member institutions across **5** provinces

- The University of British Columbia (BC)
- University of Alberta (AB)
- University of Saskatchewan (SK)
- University of Toronto, University Health Network & Queen's University (ON)
- Polytechnique Montréal (QC)

Total current NMIN
research investments
\$5,662,561

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

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

NMIN

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PARTNERS

Total partner organizations: 73

By country

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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%

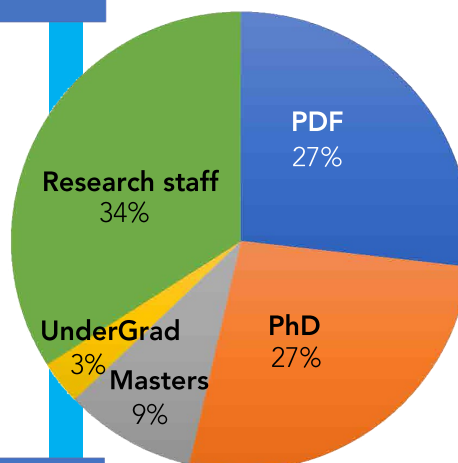
By sector

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

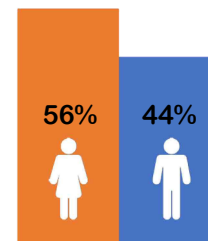
HQP (working on NMIN projects)

Total NMIN HQP: 97

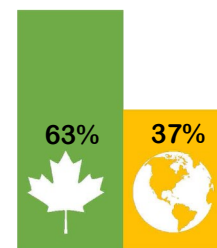
By level



By gender



By nationality



HQP = Highly Qualified Personnel

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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

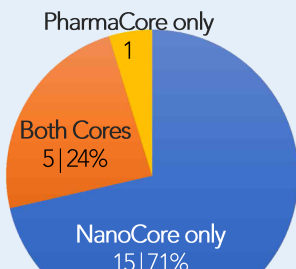
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PharmaCore Nancy Dos Santos | Admin Lead | ndossantos@bccrc.ca

NMIN projects working with Core Facilities

21 out of 29 projects | 78%



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- *In vivo* oral bioavailability / PK

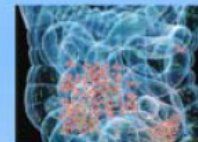


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