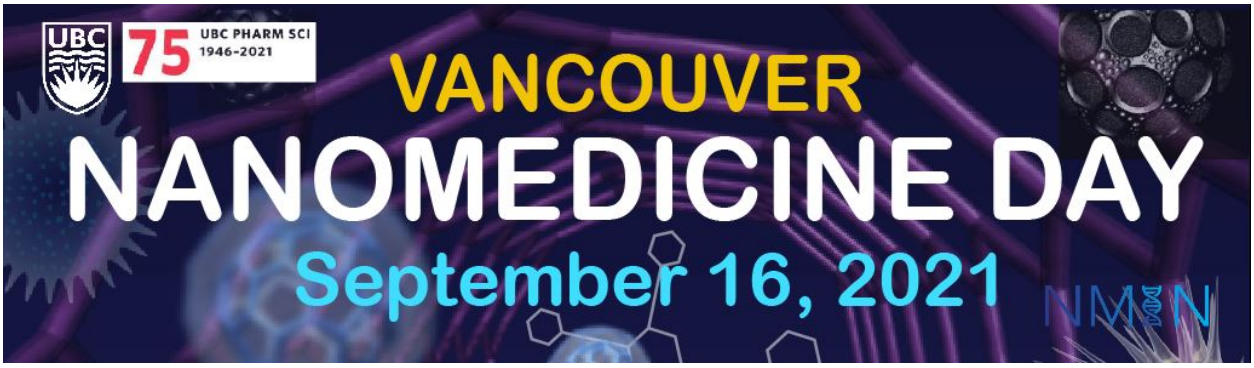
VANCOUVER NANOMEDICINE DAY 2021 - THURSDAY, SEPTEMBER 16, 2021

https://www.nanomedicines.ca/nmd-2021/

	Session 1: Introduction to Nanomedicines		
8:00 AM	**Urs Hafeli**	**Welcome to the 7th Vancouver Nanomedicine Day 2021**	Pharmaceutical Sciences, UBC
8:10 AM	**Invited Talk: David Brayden**	**Nanomedicines for oral delivery of peptides - what have we learned?**	University College Dublin, Ireland
8:50 AM	**SHORT BREAK**		
	Session 2: Radioactive Nanomedicines		**Chair: Lennart Bohrmann, UBC**
9:00 AM	**Bryce Nelson**	**In vivo and phantom imaging of cyclotron produced 133La as a theranostic radionuclide for 225Ac and 135La**	University of Alberta
9:20 AM	**Ekaterina Dadachova**	**Comparison of various radioactive payloads for a human monoclonal antibody to glycoprotein 41 for elimination of HIV-infected cells**	University of Saskatchewan
9:40 AM	**Miffy Cheng**	**Customizable multifunctional metal nanotexaphyrin as a radiotheranostics agent for cancer imaging and therapy**	University of Toronto
10:00 AM	**SHORT BREAK**		
	Session 3: Nanomedicines for Drug Delivery		**Chair: Shyh-Dar Li, UBC**
10:10 AM	**Diana Royce**	**A Canadian Catalyst: NanoMedicines Innovation Network (NMIN)**	NMIN, Canada
10:15 AM	**Ruby Sullan**	**Smart nanomaterials: a multi-pronged strategy towards targeting bacteria**	University of Toronto Scarborough
10:35 AM	**Todd Hoare**	**Sprayable nanoparticle network hydrogels for promoting intranasal drug delivery to the brain**	McMaster University
10:55 AM	**Lavasanifar Afsaneh**	**Nano-delivery of novel inhibitors of DNA repair for targeted chemo- and radio-sensitization of solid tumors**	University of Alberta
11:15 AM	**Suzie Pun**	**Discovery and application of novel SARS-CoV-2 –binding aptamers**	University of Washington, Seattle, WA, USA
11:35 AM	**Invited Talk: Anna Rosell**	**Magnetized nanocarriers targeting brain delivery after stroke**	Vall d'Hebron Institute of Research, Barcelona, Spain
12:15 PM	**LUNCH BREAK**		
	Session 4: mRNA Nanomedicines		**Chair: Colin Ross, UBC**
12:40 PM	**KEYNOTE TALK: Drew Weissman**	**Nucleoside-modified LNP mRNA therapeutics**	University of Pennsylvania, PA, USA
1:20 PM	**Deborah Chin**	**MicroRNA-145 delivery by targeted peptide micelles for atherosclerosis therapy**	University of Southern California, CA, USA
1:40 PM	**Blair Leavitt**	**Development and optimization of LNP-based gene therapy approaches in the brain**	Centre for Molecular Medicine and Therapeutics, UBC
2:00 PM	**Urs Hafeli**	**End of the 7th Vancouver Nanomedicine Day 2021**	Pharmaceutical Sciences, UBC



Dear Participants,

It is my great pleasure to welcome you to the 7th **Vancouver Nanomedicine Day 2021**. Like last year 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.

This year, we have 12 talks 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 detect disease earlier and help to monitor treatment success more accurately.

Due to our sponsors in life science and startup biotechnology companies, we will again be able to provide this one-day conference for free. Please check out their advertisements and job offers in this abstract booklet.

Three days before the meeting, already 720 participants from 40 countries have registered. It's wonderful! We are looking forward to spending this day with you. And please use the Q&A button freely during the meeting!

For the organizing committee,

Urs Hafeli

Professor
Faculty of Pharmaceutical Sciences
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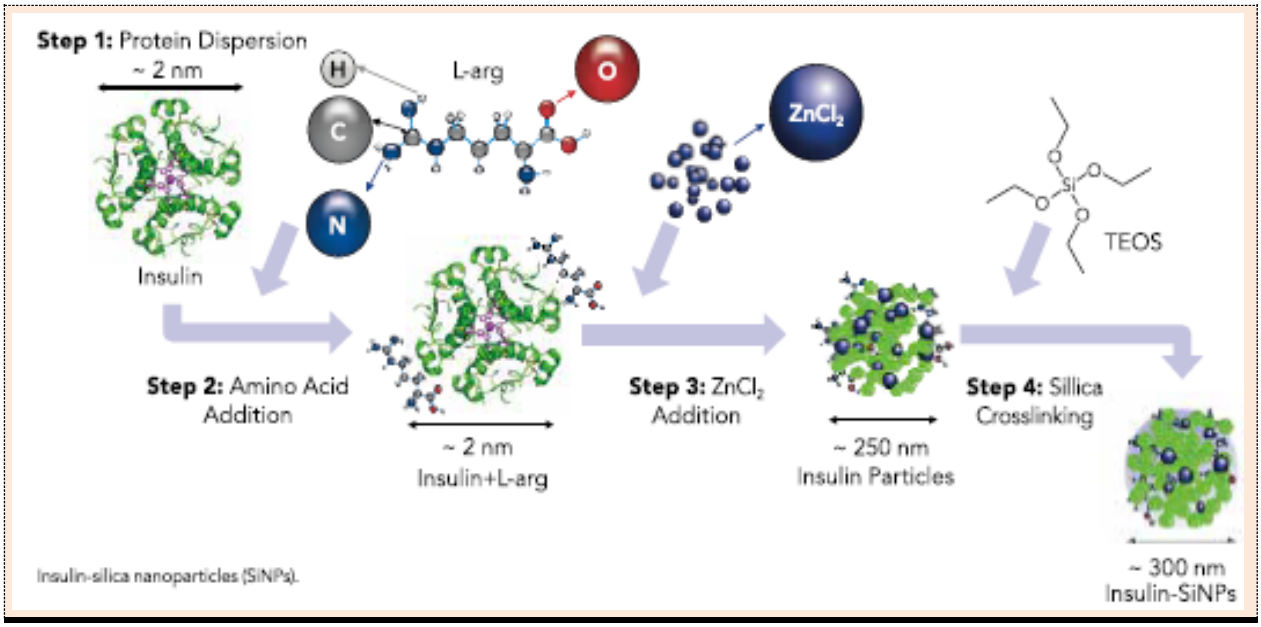
Abstracts



Nanomedicines for oral delivery of peptide - what have we learnt ?

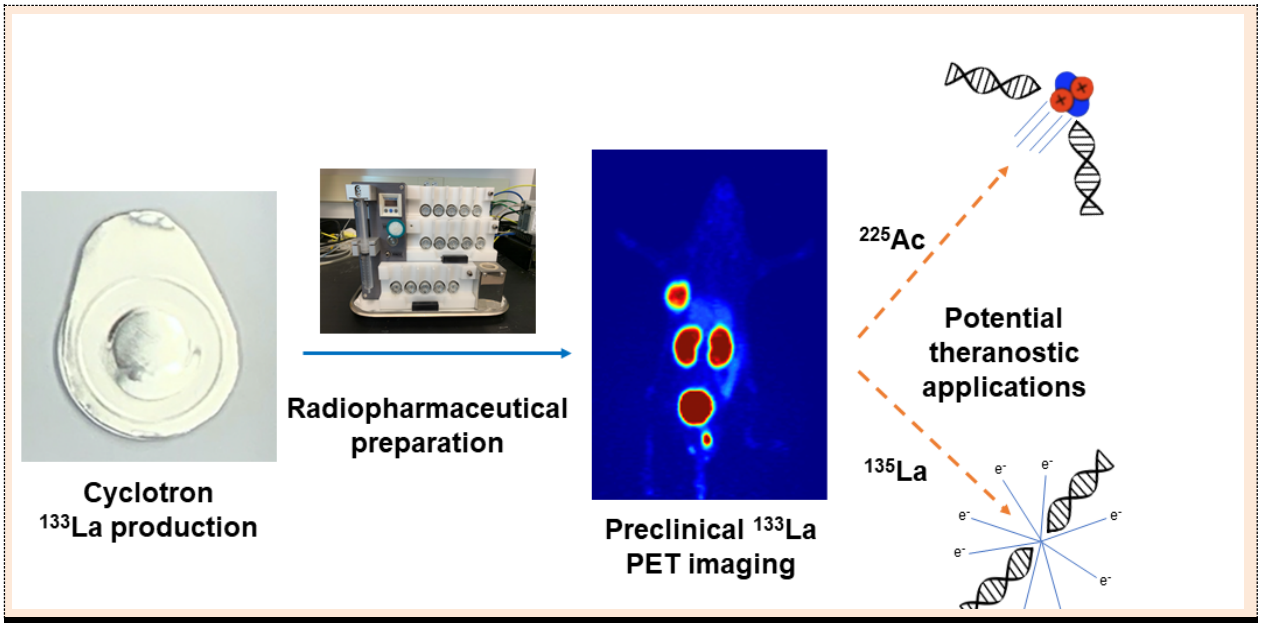
David J. Brayden

UCD School of Veterinary Medicine and UCD Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland. Email: David.brayden@ucd.ie

Oral peptide delivery remains of the great pharmaceutical challenges. To date, five peptides can be delivered orally to the systemic circulation, including two formulated with permeation enhancers in the past three years, semaglutide and octreotide [1]. The other more unusual ones arose from cyclisation and hydrophobicity, along with amino acid replacement. The return on investment has been poor overall and the oral formulations of semaglutide and octreotide yield oral bioavailabilities of < 1%, which is only suitable for niche potent molecules that just about justify the expensive synthetic costs. Nanotechnologies are part of the equation, but so far, they have overpromised and under-delivered due to overly complex unscalable designs, poor loading, lack of control of release in the intestine, and weak evidence of epithelial particle uptake *in vivo*. Here, we demonstrate that improved preclinical data in our lab can be achieved by co-entrapping permeation enhancers in nanoparticulates [e.g. 2] and **Figure 1** (showing an insulin-loaded core shell silica nanoparticle with two enhancer excipients). We also discuss how nanotechnology behavior is now better understood in terms of competing interactions with mucus and the enterocyte intestinal apical membrane. This has led to designs of peptide-loaded particles that be tailored to alter their surface characteristics during transit across mucus to the epithelium.

1. Brayden, D. J., Hill, T. A., Fairlie, D. P., Maher, S., Mrsny, R. J. (2020). **Systemic delivery of peptides by the oral route: formulation and medicinal chemistry approaches**. Adv. Drug Deliv. Rev. 157, 2-36. https://doi.org/10.1016/j.addr.2020.05.007

2. Hristov, D., McCartney, F. Beirne, J., Mahon, E., Reid, S., Bhattacharjee, S., Penarier, G., Werner, U., Bazile, D., Brayden, D. J. (2020). **Silica-coated nanoparticles with a core of zinc, L-arginine and a peptide designed for oral delivery**. ACS Applied Materials & Interfaces. 12(1):1257-1269.



In vivo and phantom imaging of cyclotron produced ^{133}La as a theranostic radionuclide for ^{225}Ac and ^{135}La

B.J.B. Nelson[1], J. Wilson[1], J.D. Andersson[1,2], F. Wuest[1]

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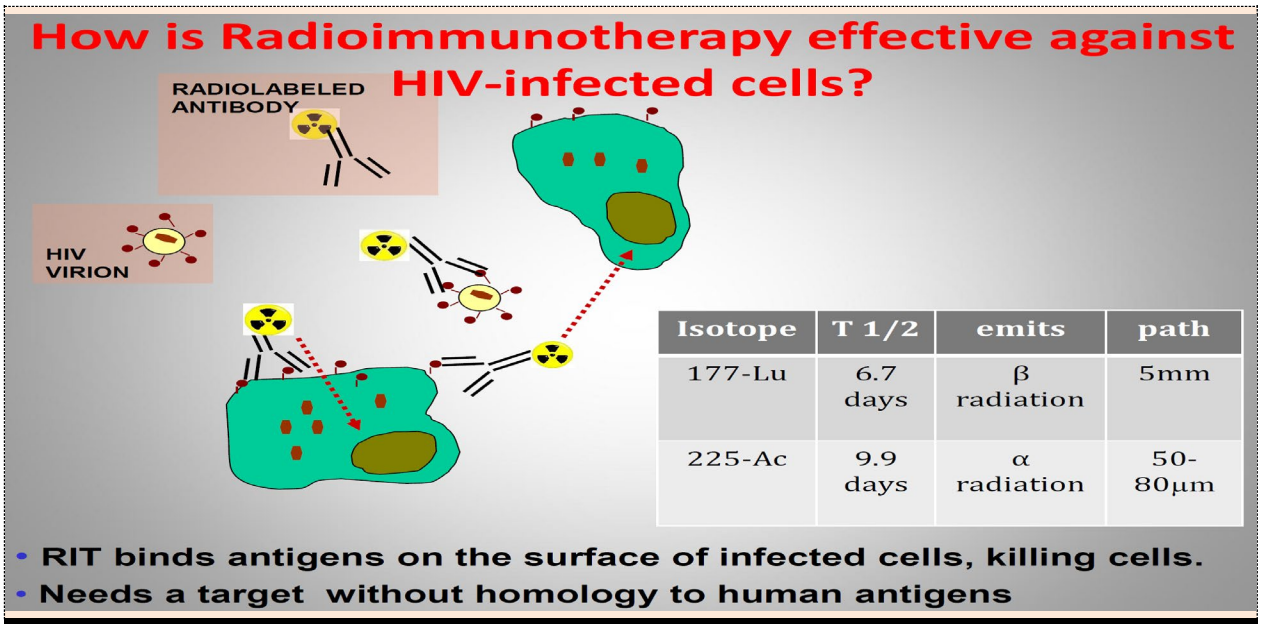
[2]Edmonton Radiopharmaceutical Center, Alberta Health Services, 11560 University Ave, Edmonton,

Theranostic isotope pairs have gained clinical interest as they can be labeled to the same tracer and applied for diagnostic and therapeutic purposes. The goals of this study were to a) investigate cyclotron production of clinically relevant ^{133}La activities using natural and isotopically enriched barium target material, b) compare fundamental positron emission tomography (PET) phantom imaging characteristics of ^{133}La with common PET radionuclides, and c) demonstrate in vivo preclinical PET tumor imaging using ^{133}La-PSMA-I&T.

^{133}La was produced on a 24 MeV cyclotron using an aluminum-indium sealed target with 150-200 mg of isotopically enriched $^{135}BaCO_3$, $^{nat}BaCO_3$, and ^{nat}Ba metal. A NEPTIS Mosaic-LC performed Ba/La separation. DOTA, PSMA-I&T, and macropa were radiolabeled with ^{133}La. Derenzo and NEMA phantom imaging was performed with ^{133}La and ^{132}La and compared with ^{18}F, 68Ga, ^{44}Sc, and ^{64}Cu, and ^{89}Zr. In vivo preclinical imaging was performed with ^{133}La-PSMA-I&T in LNCaP tumor-bearing mice.

Proton irradiations for 100 µA·min at 23.3 MeV yielded 214 ± 7 MBq ^{133}La and 28 ± 1 MBq ^{135}La using $^{135}BaCO_3$. At 11.9 MeV, ^{135}La yields were: 81 ± 2 MBq, 6.8 ± 0.4 MBq, and 9.9 ± 0.5 MBq for ^{135}BaCO3, ^{nat}BaCO3, and ^{nat}Ba metal. NEMA and Derenzo phantom imaging demonstrated ^{133}La PET spatial resolution, and scanner recovery coefficient were superior compared to ^{68}Ga and ^{132}La, and comparable to ^{89}Zr. The apparent molar activity was 130 ± 15 GBq/µmol with DOTA, 73 ± 18 GBq/µmol with PSMA-I&T, and 206 ± 31 GBq/µmol with macropa. Preclinical PET imaging with ^{133}La-PSMA-I&T provided high-resolution tumor visualization with a SUV_{60min} of 0.97 ± 0.17. ^{132}La represents a promising radiometal candidate to provide high-resolution PET imaging as a PET/alpha therapy theranostic pair with ^{225}Ac, or a PET/Auger electron therapy theranostic pair with ^{135}La.



Comparison of various radioactive payloads for a human monoclonal antibody to glycoprotein 41 for elimination of HIV-infected cells

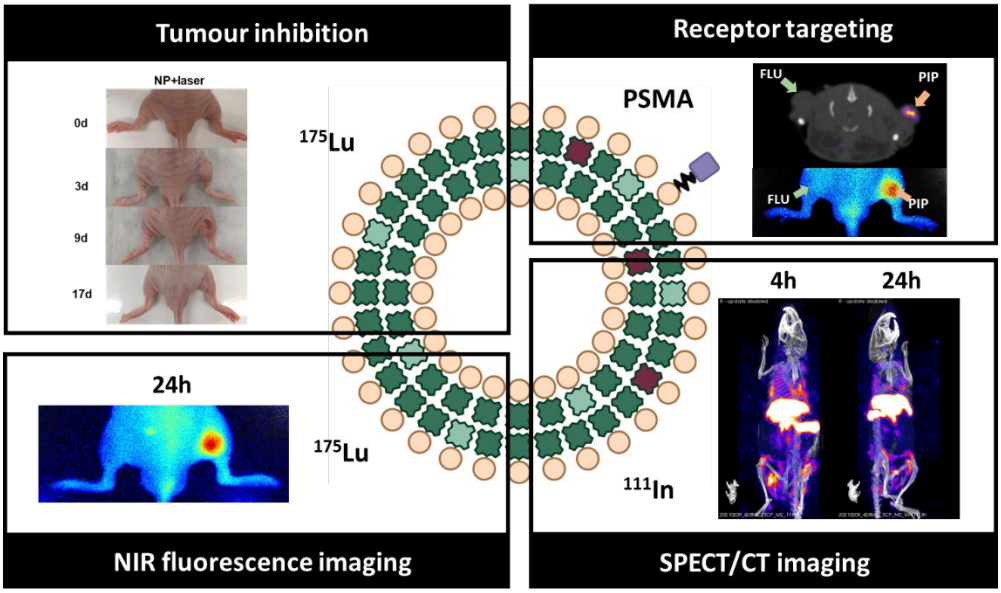
Ravendra Garg[1], Kienna Mills[1], Kevin J.H. Allen[1], Patrick Causey[2], Randy W. Perron[2], Denise Gendron[2], Stephen Sanche[3], Joan W. Berman[4], Miroslaw K. Gorny[5] and Ekaterina Dadachova[1]

[1]College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, SK, Canada; [2]Canadian Nuclear Laboratories, Chalk River, ON, Canada; [3]College of Medicine, University of Saskatchewan, Saskatoon, SK, Canada; [4]Albert Einstein College of Medicine, Bronx, NY, USA; [5] Department of Pathology, New York University School of Medicine, New York, NY, USA

Antiretroviral therapy has greatly improved the life expectancy of people infected with HIV. Unfortunately, it cannot cure HIV as it fails to eliminate the long-lived reservoir of latent HIV-infected cells. Radioimmunotherapy (RIT) relies on antigen-specific monoclonal antibodies (mAbs) for targeted delivery of lethal doses of ionizing radiation to cells (**Figure 1**). In the past we showed that human mAb 2556 to HIV gp41 conjugated with short lived alpha-emitter ^{213}Bi radionuclide selectively killed HIV-infected cells [1]. ^{225}Actinium ($t_{1/2}$ =9.92 d, alpha-emitter) and ^{177}Lutetium ($t_{1/2}$ =6.7 d, beta-emitter) are two long-lived radionuclides currently used for cancer treatment which might be more effective in killing infected cells systemically and in central nervous system. In this work we demonstrated that 2556 mAb when labeled with ^{213}Bi (4-20 μCi), ^{225}Ac (20-100 nCi) and ^{177}Lu (4-50 μCi) significantly reduced viral replication in HIV infected cells 7 days post-treatment in comparison with the control non-specifc mAb [2]. These results prove that RIT is a promising novel treatment option for the eradication of HIV-infected cells in combination with anti-retrovirals and possibly latency reactivation drugs.

1. Tsukrov D, McFarren A, Morgenstern A, Bruchertseifer F, Dolce E, Gorny MK, et al. (2016) **Combination of Antiretroviral Drugs and Radioimmunotherapy Specifically Kills Infected Cells from HIV-Infected Individuals.** Front Med (Lausanne);3:41.

2. Garg R, Mills K, Allen KJH, Causey P, Perron RW, Gendron D, Sanche S, Berman JW, Gorny MK, Dadachova E. (2020) **Comparison of various radioactive payloads for a human monoclonal antibody to glycoprotein 41 for elimination of HIV-infected cells**. Nucl Med Biol. 82-83:80-88

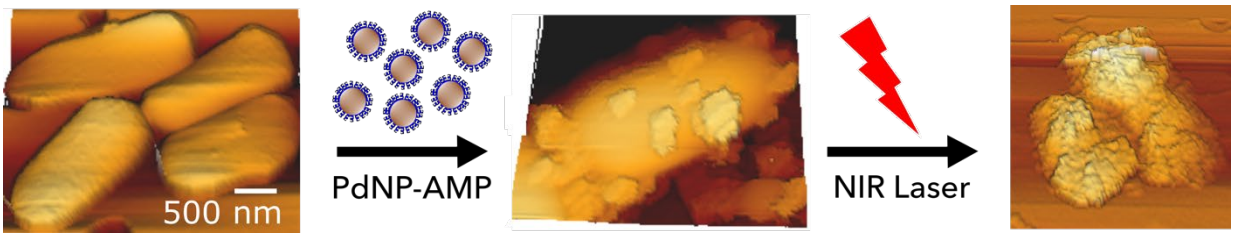


Customizable multifunctional metal nanotexaphyrin as a radiotheranostics agent for cancer imaging and therapy

M. H. Y. Cheng[1], M. Overchuk[1,2], M. A. Rajora[1,2], J. W. H. Lou[1,3], J. Chen[1], Y. Chen[4], M. G. Pomper[4], G. Zheng[1,2,3]

[1]Princess Margaret Cancer Centre, University Health Network, 101 College Street, PMCRT 5-354, Toronto, Ontario M5G 1L7, Canada. [2]Institute of Biomedical Engineering, University of Toronto, 101 College St., Toronto, ON M5G 1L7, Canada. [3]Department of Medical Biophysics, University of Toronto, 101 College St., Toronto, ON M5G 1L7, Canada. [4]Johns Hopkins Medical School, 1550 Orleans Street, 492 CRB II, Baltimore, Maryland 21287, United States.

Multifunctional nanoparticles are excellent theranostics platforms that can significantly improve diagnostic and therapeutic efficacies. To enable targeted imaging-guided therapy, we present a novel multifunctional nanotexaphyrin as a non-invasive tool for prostate-specific membrane antigen (PSMA) targeted radionuclide imaging and focal photodynamic therapy (PDT). Through the chelation of metal isotopes (In, Lu), metallated texaphyrin-lipid self-assembled into metallo-nanotexaphyrin with 'cold' Lu for PDT and 'hot' ^{111}In for single-photon emission computed tomography (SPECT) imaging. Radiolabelling method for ^{111}In/Lu-nanotexaphyrin was established using a microfluidic system and achieved a high radiochemical yield (>90%). This mixed and matched approach of different metals enabled the evaluation of the radiopharmaceutical profile of ^{111}In/Lu-nanotexaphyrins. We observed that ^{111}In/Lu-nanotexaphyrins had a preferential tumour accumulation over surrounding organs/tissues (1-2% ID/g) at 48 h in various preclinical tumour models and a moderate plasma circulation half-life in healthy mice ($t_{1/2}$ = 6.62 h). We further investigated the targeting potentials of the small molecule PSMA ligand decorated ^{111}In/Lu-nanotexaphyrin in PSMA overexpressed tumours. The PSMA-^{111}In/Lu-nanotexaphyrin showed a selective and enhanced PSMA+ tumour accumulation (3.01 ± 0.27 %ID/g) at 48h visualized by near-infrared fluorescence imaging and SPECT/CT imaging. In combination with light irradiation, the PSMA targeting nanotexaphyrin had shown a potent PDT effect and successfully inhibited PSMA+ tumour growth in a subcutaneous xenograft model. These results highlighted the hybrid metallo-nanotexaphyrin as customizable and multifunctional nanomedicine in radiation oncology and demonstrated its utility as cancer radiotheranostics.



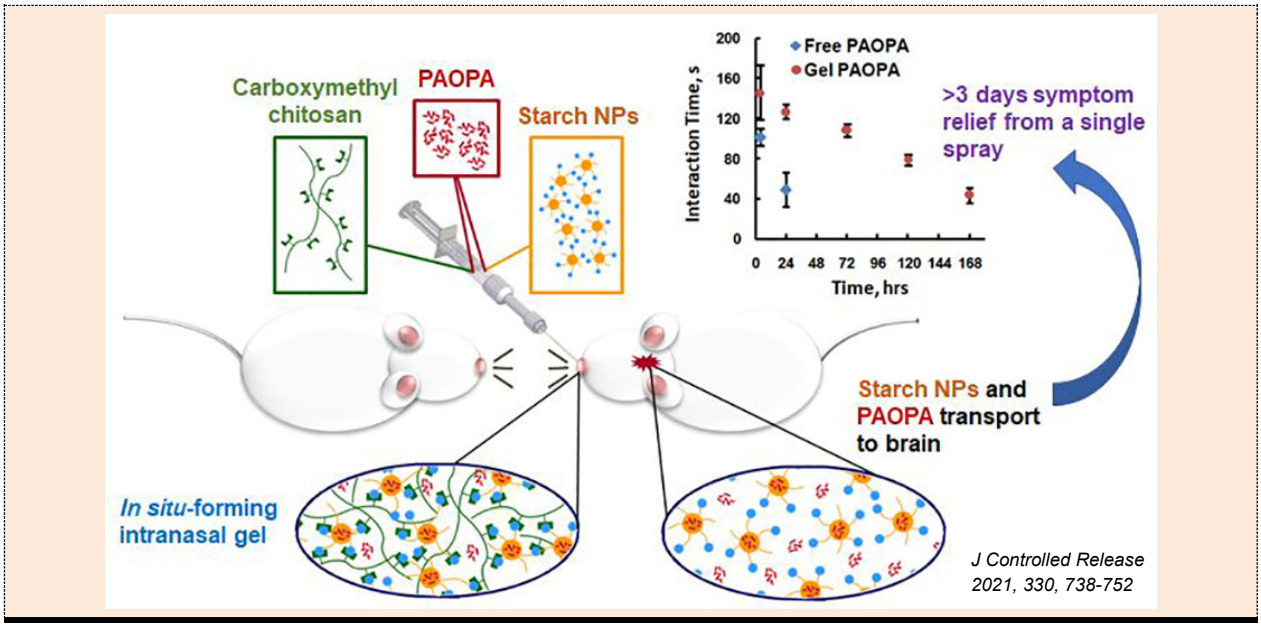
Advanced Functional Materials, 2020, 2004503.

Smart nanomaterials for multi-pronged strategies against bacteria

Nesha May O. Andoy [1], Keuna Jeon [1,2], Christian T. Kreis [1], Ruby May A. Sullan [1,2]*

[1]Department of Physical and Environmental Sciences, University of Toronto Scarborough, Toronto, ON M1C 1A4, Canada; ruby.sullan@utoronto.ca [2]Department of Chemistry University of Toronto, Toronto, ON M5S 3H6

The rising threat of antimicrobial resistance, especially in a biofilm environment, warrants new strategies. In this talk, I will highlight our recent progress in engineering smart nanomaterial-based therapeutics (nanotherapeutics) designed to destabilize bacteria via multiple and synergistic biocidal mechanisms. By combining the intrinsic laser-induced activity of a bioinspired nanomaterial, along with the targeting and lytic action of an antimicrobial peptide, we have shown that the resulting nanotherapeutic platform is more effective in tackling a drug-resistant pathogen. I will also present the quantitative imaging platform we developed to simultaneously image biofilm morphology and its mechanical properties at the nanoscale—under physiological conditions. As interactions between various antimicrobial agents and biofilms occur at the nanoscale, understanding heterogeneities of the biofilm interface with nanometer resolution is important. Considering the different sectors where biofilm-related problems arise, and its ever-increasing role in the development of bacterial resistance, understanding the action of nanomaterial-based antimicrobials as well as how mechanical factors influence biofilm interfacial properties is critical in devising effective strategies to combat biofilm-related fouling and infections.



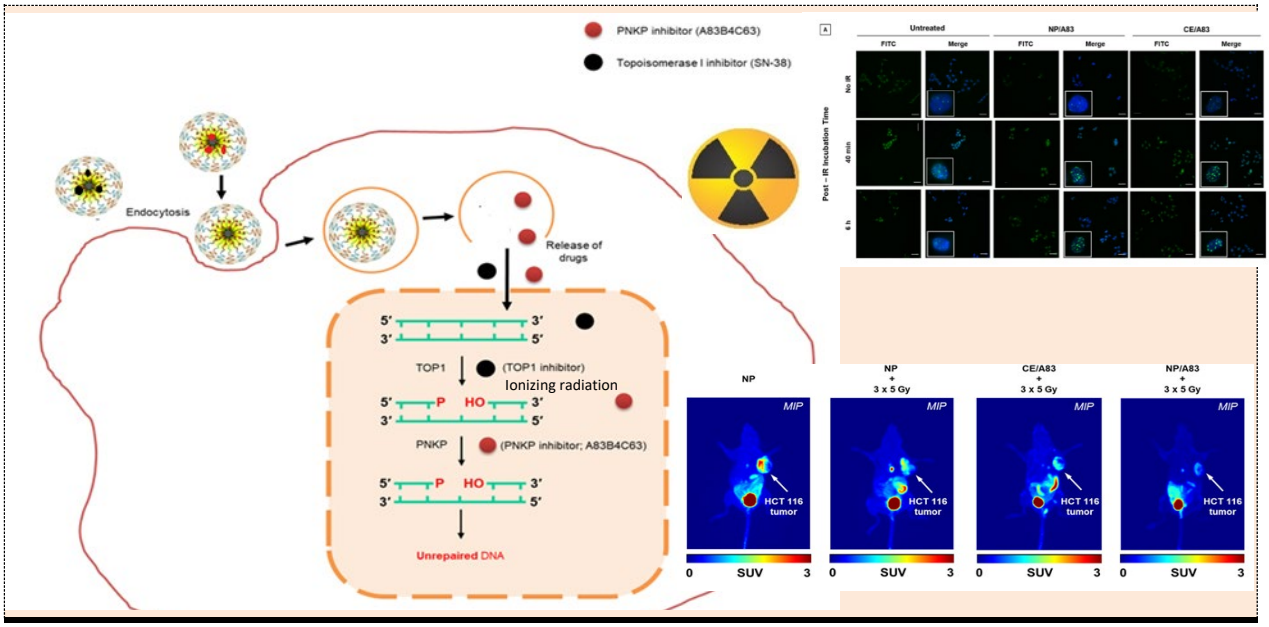
Sprayable Nanoparticle Network Hydrogels for Promoting Intranasal Drug Delivery to the Brain

Michael J Majcher[1], Ali Babar[2], Andrew Lofts[2], Fahed Abu-Hijleh[3], Bhagwati Gupta[4], Ram K Mishra[3], and Todd Hoare[1,2]

[1]Department of Chemical Engineering, [2]School of Biomedical Engineering, [3]Department of Psychiatry and Behavioural Neurosciences, and [4]Department of Biology, McMaster University, Hamilton, ON L8S 4L7; hoaretr@mcmaster.ca

Oral delivery of antipsychotic drugs is limited by the blood-brain barrier, first-pass metabolism, and the gut microbiota, thus requiring larger drug doses that result in often severe side-effects. Intranasal delivery circumvents many of these barriers but poses other challenges in how to administer and retain the vehicle in the nose and overcome mucosal/nasal epithelial barriers. In response, we have developed sprayable in situ-gelling bulk hydrogels based on oxidized starch nanoparticles (SNPs) and O-carboxymethyl chitosan (CMCh) [1] that facilitate mucoadhesion, slow release of small (20-50 nm) SNPs for transport to the brain, and controlled release of the anti-psychotic peptide (3R)-2-oxo-3-[[(2S)-2-pyrrolidinylcarbonyl]amino]-1-pyrrolidineacetamide (PAOPA) or levodopa (L-Dopa). Bulk gels can be designed to gel in 10s-30min, degrade in hours to days, and mechanically match the nasal mucosa (G' ~500-2000 Pa). PAOPA-loaded gels alleviate negative schizophrenic symptoms induced by dizocilpine (MK-801) for >72 hours at half the total dose required for one-day symptom alleviation with PAOPA alone, with biodistribution studies indicating high retention of SNPs in the nose and transport into the brain. *C. elegans* electrotaxis studies in which Parkinson's-like symptoms were induced using 6-OHDA followed by the application of L-Dopa-loaded hydrogels enabled full motility recovery for >72 hours (compared to <5 hours with L-Dopa alone) and significantly improved drug stability. As such, the use of starch nanoparticle-based sprayable hydrogels enables the use of lower drug doses and frequencies of administration, both beneficial to improve mental health clinical outcomes.

1. Majcher MJ*, Babar A*, Lofts A, Li X, Leung A, Smeets NMB, Mishra RK, Hoare T (2021) **In Situ-Gelling Starch Nanoparticle (SNP)/O-Carboxymethyl Chitosan (CMCh) Nanoparticle Network Hydrogels for the Intranasal Delivery of an Antipsychotic Peptide**. J Controlled Release 330, 738-752.



Nano-delivery of novel inhibitors of DNA repair for targeted chemo- and radio-sensitization of solid tumors

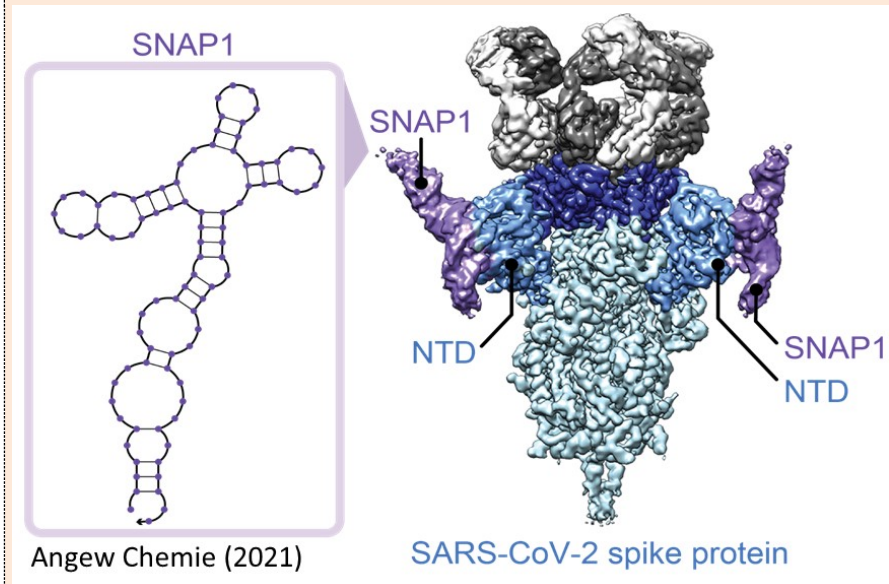
Sams Sadat[1], Melinda Wuest[2], Michael Weinfeld[2], Dennis Hall[3], Afsaneh Lavasanifar[1]*

[1]Faculty of Pharmacy and Pharmaceutical Sciences, [2] Faculty of Medicine, [3] Faculty of Science, University of Alberta, Edmonton, AB, Canada

Inhibition of a DNA repair enzyme known as human polynucleotide kinase/phosphatase (PNKP) makes cancer cells sensitive to DNA damage by ionizing radiation and topoisomerase I inhibitors. Systemic delivery of PNKP inhibitors, however, may sensitize both cancer and normal cells to DNA damage. Preferential delivery of PNKP inhibitors to tumor by nanoparticles (NP) was proposed to reduce the side effects PNKP inhibitors to normal tissue, particularly when combined with DNA damaging therapies.

We have developed NPs based on methoxy poly(ethylene oxide)-*b*-poly(α-benzyl carboxylate-ε-caprolactone) (mPEO-*b*-PBCL) encapsulating a novel inhibitor of PNKP, i.e., A83B4C63 (NP/A83). The radio-sensitization effect of NP/A83 following fractionated tumor irradiation by an image-guided Small Animal Radiation Research Platform (SARRP), with 24 h pre-administration of A83 (25 mg/kg × 3/week) was compared to that of A83B4C63 solubilized by Cremophor EL: ethanol (CE/A83) in HCT116 bearing mice. Significantly higher retardation of tumor growth in mice treated with a combination of IR and NP/A83 than those treated with IR plus CE/A83 or IR alone was observed by caliper, luminescence or [^{18}F]FLT PET imaging. We have also developed NPs for the delivery of the potent topoisomerase I inhibitor, SN-38, to be used in combination with NP/A83 to CRC cells. Overall, the results evidenced the activity of NP/A83 as a radio- and chemo-sensitizer for CRC treatment.

1. N K Bernstein, F Karimi-Busheri, A Rasouli-Nia, R Mani, G Dianov, J N M Glover, M Weinfeld, **Polynucleotide kinase as a potential target for enhancing cytotoxicity by ionizing radiation and topoisomerase I inhibitors**. Anticancer Agents Med Chem, 2008. 8(4): p. 358-67.
2. Zahra Shire, Mohammad Reza Vakili , Timothy D R Morgan, Dennis G Hall, Afsaneh Lavasanifar, Michael Weinfeld, **Nanoencapsulation of Novel Inhibitors of PNKP for Selective Sensitization to Ionizing Radiation and Irinotecan and Induction of Synthetic Lethality**. Mol Pharm, 2018. 15(6): p. 2316-2326.



Discovery and application of novel SARS-CoV2-binding aptamers

Nataly Kacherovsky[+], Lucy F. Yang[+], Ha V. Dang[+], Emmeline L. Cheng, Ian I. Cardle, Alexandra C. Walls, Matthew McCallum, Drew L. Sellers, Frank DiMaio, Stephen J. Salipante, Davide Corti, David Veesler[b*], Suzie H. Pun[a*]

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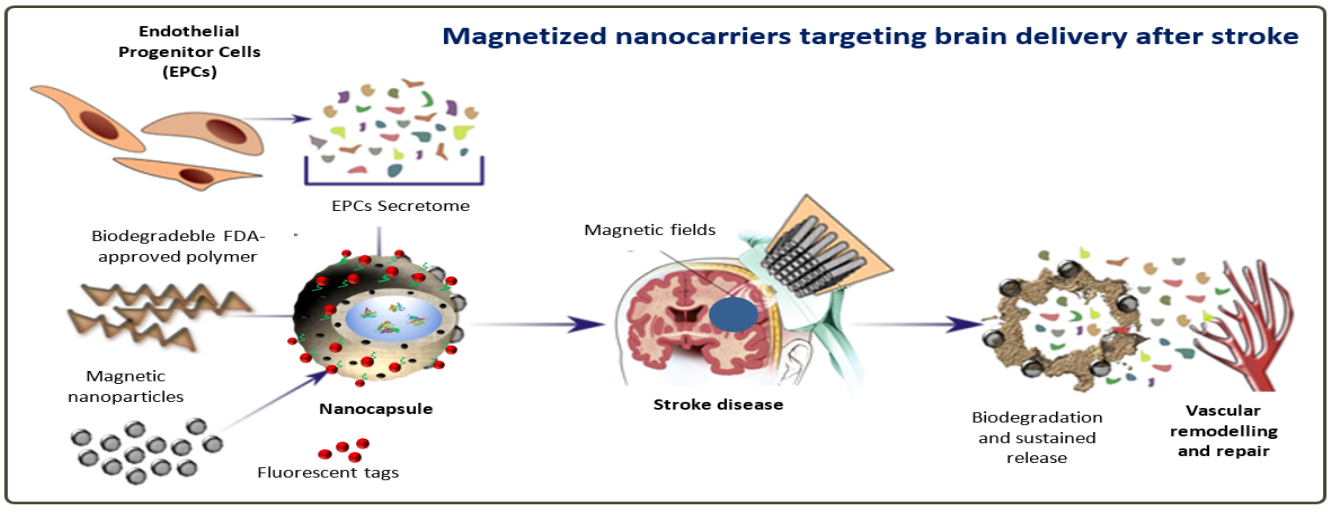
Early detection is an important component of disease control in the COVID-19 pandemic. We used library selection to identify a novel DNA aptamer that binds with high affinity and specificity to SARS-CoV-2 Spike protein. We characterized the binding of this aptamer to target through flow cytometry and biolayer interferometry binding studies and visualized target interactions directly by high resolution cryo-EM. We then applied this aptamer in ELISA format and lateral flow assay and demonstrated sensitive detection of UV-inactivated SARS-CoV-2 down to 5 x 10^5 copies/mL.

Reference: Kacherovsky, N.,* Yang, L.F.,* Dang, H.V.,* Cheng, E.L., Cardle, I.I., Walls, A.C., McCallum, M., Sellers, D.L., DiMaio, F., Salipante, S.J., Corti, D., Veesler, D., [†] and Pun, S.H. [†] (2021) Discovery and characterization of spike N-terminal domain-binding aptamers for rapid SARS-CoV-2 S detection. *Angew Chemie*, accepted.



Magnetized nanocarriers targeting brain delivery after stroke

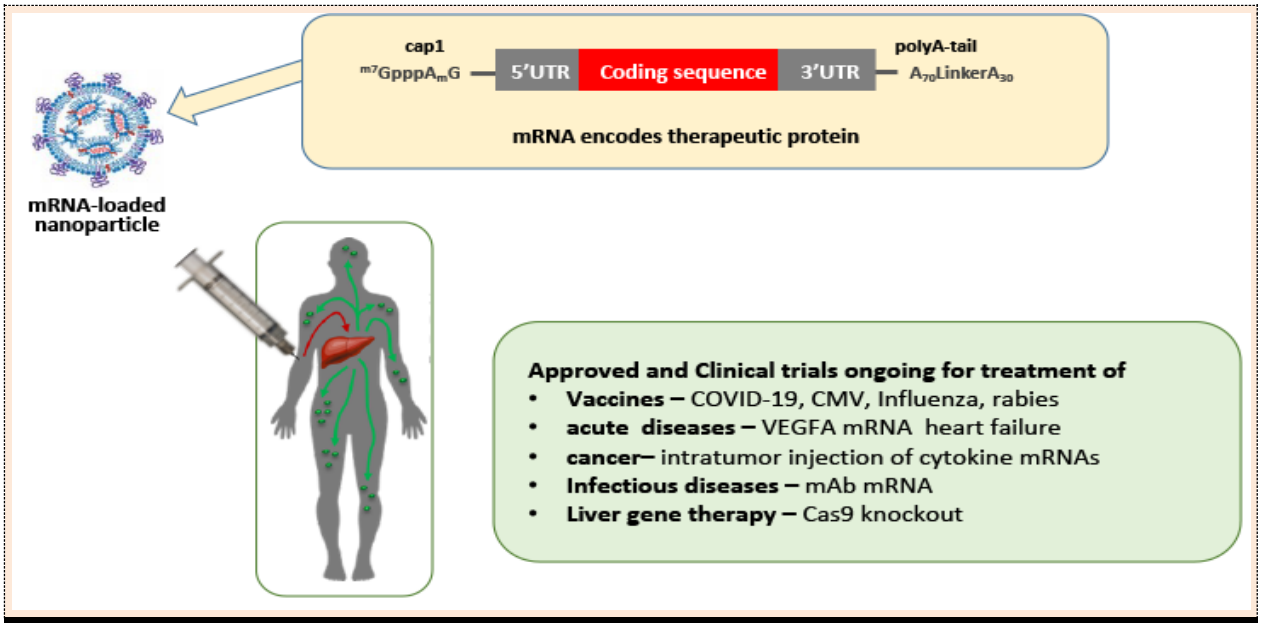
Anna Rosell - Vall d'Hebron Research Institute VHIR, Neurovascular Research Laboratory, Barcelona, Spain

Co-authors: Alba Grayston[1], Miguel Garcia-Gabilondo[1], Anna Roig2, Yajie Zhang[2], Andrea Stephany[2], Fabien Gosselet[3], Rodrigo Azevedo[3], Milan Timko[4], Jozef Kovac[4], Peter Kopcansky[4], Laura Castellote[5], Jiahui Li[6], Marc Ribó[6], Sara Belloli[7], Rosa Maria Moresco[7], Maria Picchio[7], Agnieszka Kowalska[8], Maciej Mazurek[8]

[1]Vall d'Hebron Research Institute VHIR, Neurovascular Research Laboratory, Barcelona, Spain. [2]Institute of Materials Science of Barcelona ICMAB-CSIC, Group of Nanoparticles and Nanocomposites, Bellaterra, Spain. [3]Blood-brain barrier laboratory, Sciences Faculty Jean Perrin at Artois University. [4]Institute of Experimental physics, SAS, Kosice, Slovakia. [5]Department of Clinical Biochemistry, Clinical Laboratories, Vall d'Hebron University Hospital, Barcelona, Spain. [6]Stroke Laboratory, Vall d'Hebron Research Institute, Barcelona, Spain. [7]Nuclear Medicine Department, IRCCS San Raffaele Scientific Institute, Milan, Italy. [8]Pure Biologics S.A., Wroclaw, Poland

Fifteen million persons suffer a stroke worldwide each year becoming one of the principal causes of death and disability in adults. However, the only available treatments are the acute thrombolytic therapies (pharmacological or mechanical) which are live-saving but are being administered to less than 10% of stroke patients due to strict selection criteria. In contrast, during post-stroke recovery only rehabilitation programs are approved and new neuro-repair treatments could offer the opportunity to treat more stroke patients by extending the therapeutic time window, however targeted brain delivery has challenged the implementation of advanced therapies such as cell therapies. With this background, factors secreted by endothelial progenitor cells (EPCs), with proved potential to induce tissue repair, can be encapsulated in multiple biomaterials to successfully and safely deliver them into the damaged brain tissue. Our collaborative investigations have been conducted in a pre-clinical mouse model of stroke using PLGA nanocapsules and retained by an external magnetic field with a focused magnet in the cortical vasculature with the aim to induce tissue repair. We have continuously produced PLGA-NC batches for the functional testing and robustly produced EPCs secretome proving its functionality after the lyophilization and encapsulation process and the standardized production protocols as a therapeutic agent. In parallel the magnetic targeting was achieved with a magnet prototype built for the mouse implantation and a prototype for the human use both designed with appropriate anatomical and functional characteristics. First in vivo studies showed the incorporation of the PLGA-NC into vessel-like structures in cortical areas under the influence of the magnetic fields and PLGA-NC were in vivo imaged by MRI and molecular imaging techniques. In vitro, we have proved the uptake of the PLGA-NC inside endothelial cells of the Blood Brain Barrier, the therapeutic actions of the encapsulated EPCs secretome have been tested to demonstrate vascular remodeling actions (proliferation, migration and tube formation) and its additional protection on the BBB model after oxygen-glucose-deprivation injury. Finally, in vivo PLGA-NC have been successfully administered in a mouse model of cerebral ischemia with successful brain targeting in the damaged area when administered intraarterially in clinically-relevant endovascular interventions when compared to classical intravenous administration. This intraarterial approach has proved its safety when administered shortly after ischemia into the internal carotid artery while increasing the amount of PLGA-NC in the targeted injured brain. A similar approach has been tested with the human magnet prototype using 3D vascular models of the human supra-aortic arterial circulation proving the translational approach of our proposed therapy.

1. **Endovascular administration of magnetized nanocarriers targeting brain delivery after stroke.** Grayston A, Zhang Y, Garcia-Gabilondo M, Arrúe M, Martin A, Kopcansky P, Timko M, Kovac J, Strbak O, Castellote L, Belloli S, Moresco RM, Picchio M, Roig A, Rosell A. **J Cereb Blood Flow Metab. 2021** Jul 6. doi: 10.1177/0271678X211028816.
2. **PLGA protein nanocarriers with tailor-made fluorescence/MRI/PET imaging modalities.** Zhang Y, García-Gabilondo M, Grayston A, Feiner IVJ, Anton-Sales I, Loiola RA, Llop J, Ramos-Cabrer P, Barba I, Garcia-Dorado D, Gosselet F, Rosell A, Roig A. **Nanoscale. 2020** Feb 27;12(8):4988-5002. doi: 10.1039/c9nr10620k.

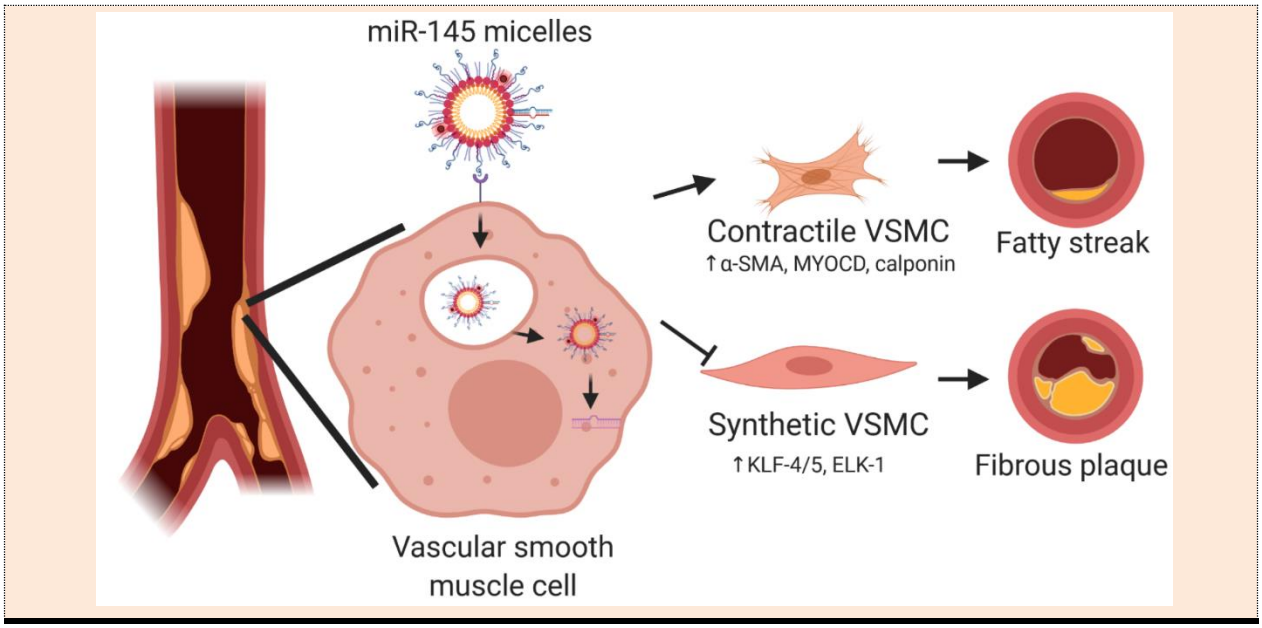


Nucleoside-modified mRNA-LNP therapeutics

Drew Weissman

Department of Medicine, University of Pennsylvania, Philadelphia, PA, US, dreww@pennmedicine.upenn.edu

Vaccines prevent 4-5 million deaths a year making them the principal tool of medical intervention worldwide. Nucleoside-modified mRNA was developed over 15 years ago and has become the darling of the COVID-19 pandemic with the first 2 FDA approved vaccines based on it. These vaccines show greater than 90% efficacy and outstanding safety in clinical use. The mechanism for the outstanding immune response induction is the prolonged production of antigen leading to continuous loading of germinal centers and the adjuvant effect of the LNPs, which selectively stimulate T follicular helper cells that drive germinal center responses. Vaccine against many pathogens, including HIV, HCV, HSV2, CMV, universal influenza, coronavirus variants, pancoronavirus, nipah, norovirus, malaria, TB, and many others are currently in development. Nucleoside-modified mRNA is also being developed for therapeutic protein delivery. Clinical trials with mRNA encoded monoclonal antibodies are underway and many other therapeutic or genetic deficient proteins are being developed. Finally, nucleoside-modified mRNA-LNPs are being developed and used for gene therapy. Cas9 knockout to treat transthyretin amyloidosis has shown success in phase 1 trials. We have developed the ability to target specific cells and organs, including lung, brain, heart, CD4+ cells, all T cells, and bone marrow stem cells, with LNPs allowing specific delivery of gene editing and insertion systems to treat diseases such as sickle cell anemia, Nucleoside-modified mRNA will have an enormous potential in the development of new medical therapies.



microRNA-145 delivery by targeted peptide micelles for atherosclerosis therapy

Deborah Chin [1], Christopher Poon [1], Eun Ji Chung [1,2,3]*

[1]Department of Biomedical Engineering, University of Southern California, Los Angeles, CA, United States; [2]Department of Chemical Engineering and Materials Science, University of Southern California, Los Angeles, CA, United States; [3]Department of Surgery, Division of Vascular Surgery and Endovascular Therapy, University of Southern California, Los Angeles, CA, United States

Atherosclerosis is characterized by the buildup of plaques in the arteries that can severely exacerbate blood flow. These plaques consist of lipids, calcium, and a heterogenous population of cells including macrophages, foam cells, osteogenic cells, and vascular smooth muscle cells (VSMCs). However, more recent studies have identified that up to 70% of the cells found in atherosclerotic plaques are derived from dedifferentiated and transdifferentiated VSMCs [1]. Notably, microRNA-145 (miR-145), a short, non-coding RNA that is the most abundant in the vasculature, is a key regulator of the dedifferentiation of healthy, contractile VSMCs into the synthetic and disease-propagating phenotypes [2]. Specifically, miR-145 maintains healthy contractile VSMC phenotypes by downregulating synthetic genes: KLF4/5, and ELK-1. Thus, we hypothesize that miR-145 therapy can mitigate atherosclerotic plaque growth by promoting healthy VSMC maintenance.

To facilitate miR-145 delivery to atherosclerotic plaques, we utilize monocyte chemoattractant peptide-1 (MCP-1) that binds to C-C chemokine receptor 2 (CCR2) expressed on synthetic VSMCs. These peptides are incorporated into micelles that contain covalently attached miR-145 (miR-145 micelles) for the targeted delivery to plaques. In atherosclerotic mice, miR-145 micelles demonstrate accumulation in plaques and upregulation of contractile VSMC phenotypes through miR-145 therapy. Subsequently, plaque size was reduced in the aorta by up to 49% compared to non-treated controls and stability improved due to enhanced extracellular collagen production. Overall, we demonstrate the potential of miR-145 micelles as a therapy for atherosclerosis.

[1] Shankman, Laura S et al. “KLF4-dependent phenotypic modulation of smooth muscle cells has a key role in atherosclerotic plaque pathogenesis.” Nature medicine vol. 21,6 (2015): 628-37. doi:10.1038/nm.3866
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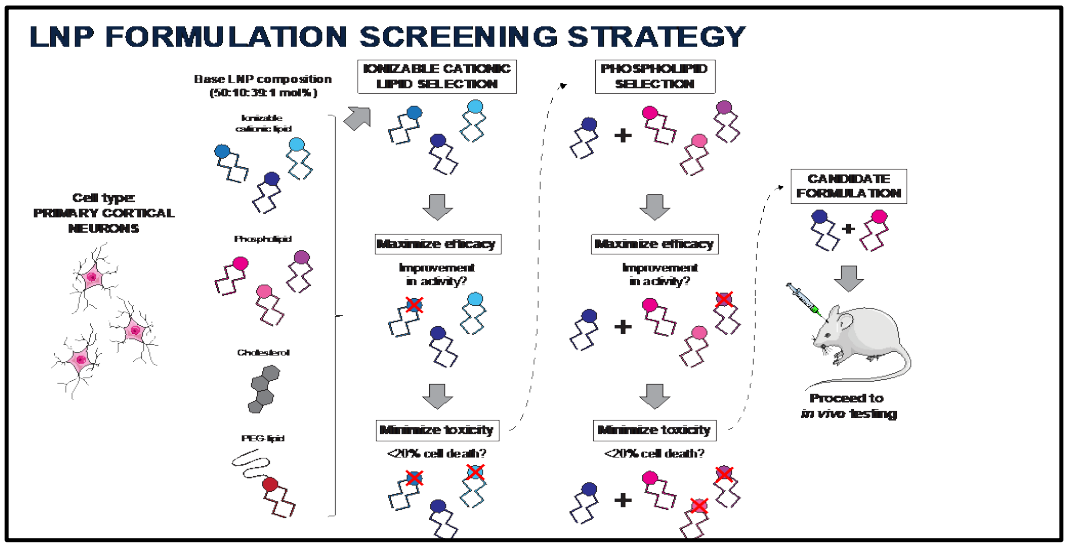

Development and Optimization of LNP-based Gene Therapy Approaches in the Brain

Sarah Thomson, Terri L. Petkau, and Blair R. Leavitt

Centre for Molecular Medicine & Therapeutics and Department of Medical Genetics, UBC and Children's and Women's Hospital, 980 West 28th Avenue, Vancouver, BC, Canada V5Z 4H4

Brain diseases, particularly age-related diseases such as Huntington's disease, Frontotemporal dementia, Alzheimer's and Parkinson's disease, are a significant burden to the Canadian health care system and with our aging population the prevalence of these diseases is increasing. Treatment of genetic brain diseases, including neurodevelopmental and neurodegenerative disorders, is severely limited by the lack of accessibility of most genetic therapies to the brain due to the presence of the blood-brain barrier. Gene therapy is a viable option for the treatment of brain diseases provided the therapeutic agents can be delivered to neurons, the primary cells of interest in the brain. Current approaches to gene therapy in the brain are centered around the use of antisense oligonucleotides (ASOs) and adeno-associated viral (AAV)-mediated gene delivery. There are numerous limitations to these approaches, leaving abundant space for novel and/or improved gene therapy delivery methods.

Lipid nanoparticle (LNP) based gene therapy approaches hold great promise for the future clinical development of brain disease treatments for two main reasons. First, we and others have shown that neurons, either isolated *ex vivo* or *in vivo*, are highly amenable to transfection by LNPs carrying gene therapy agents. This is in stark contrast to other methods of transfection. Second, LNPs have been proven safe and effective in clinical trials for the treatment of other conditions, with many LNP-based drugs now approved by the FDA. I will present an update on our efforts to identify optimal brain-specific LNP formulations for the delivery of two key gene therapy payloads, siRNA and mRNA. These optimized formulations will ultimately be adapted for the treatment of genetic brain diseases. To do this, we established a pipeline for screening LNP formulations in primary neuronal cultures (*ex vivo*) followed by validation via direct brain injections (*in vivo*). We performed screening assays for the delivery of mRNA using luciferase as a reporter gene and GFP for siRNA. We have identified specific optimal LNP formulations, doses, and modes of administration for LNP delivery of siRNA and mRNA payloads in cultured neurons and have begun to test these optimized formulations *in vivo*, setting the stage for future development of target-specific siRNA and mRNA payloads to treat genetic brain diseases.

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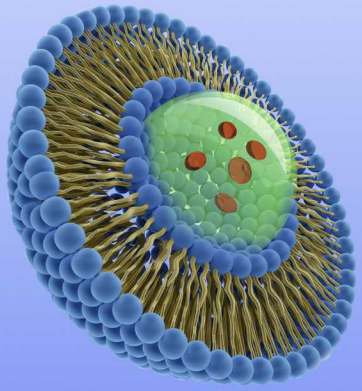

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Tenure-Track Assistant Professor/Tier 2 Canada Research Chair Position

The University of British Columbia (UBC) is one of the world's top public universities. The UBC Faculty of Pharmaceutical Sciences is undergoing major expansion and investment to meet our ambitious goal of being one of the leading academic centres internationally in the pharmaceutical sciences within the next decade. As part of this ongoing strategic development program, research activity in the Faculty is focusing on themes that reflect areas of existing strength, opportunities for new partnerships, and the potential for delivering long-term impact, with an emphasis on the application of state-of-the-art concepts and methodologies to address clinically important issues in pharmacotherapy.

We now invite applications for a full-time tenure-track Assistant Professor position in either of the following areas of the Faculty's research focus: Molecular and Systems Pharmacology, and **Nanomedicines and Chemical Biology**. The incumbent will be nominated for a prestigious Tier 2 Canada Research Chair (CRC). Applicants for this position must possess a PhD or equivalent doctoral qualification, with research expertise in one of the following priority areas: molecular and systems pharmacology including genomics/proteomics and human health (particularly as it relates to pharmacogenomics, toxicogenomics, or chronic diseases); chemical biology; or drug delivery and nanomedicine. Relevant postdoctoral research experience, demonstrated research skills, an outstanding publication record, potential for excellence in teaching, well-developed mentoring and communication skills, and a strong commitment to professional, graduate, and post-doctoral education are essential. The successful candidate will have a track record, or demonstrated potential, for success in attracting national and/or international research funding (e.g., CIHR, NSERC, NIH). The major focus of this position will be the development of a cutting-edge, externally-funded, world-class research program. Other responsibilities will include educating students in the BPSc, PharmD, MSc/PhD, and postdoctoral programs, as well as new programs under development.

The Faculty of Pharmaceutical Sciences is located in a state-of-the-art $150-million, 23,000-square-metre facility on UBC's Vancouver campus underpinned by world-class infrastructure and equipment. The building also houses one of the Faculty's key partners, adMare BioInnovations (https://www.admarebio.com/) The incumbent will have ample opportunities for collaboration with basic and clinical researchers in the Faculty, other major basic science and health science faculties, core research facilities, and clinical centres. Salary is competitive, negotiable, and commensurate with experience and is subject to final budgetary approval. UBC is committed to attracting outstanding faculty members and offers competitive compensation and benefits packages, including support for housing and relocation (http://www.hr.ubc.ca/housing-relocation/fhop/).

The Chair is equally open to individuals of all nationalities. The Chair is subject to review and final approval by the CRC Secretariat. Applicants must meet the eligibility requirements for a CRC Tier 2 position. Tier 2 Chairs are intended for exceptional emerging scholars with less than 10 years of experience as an active researcher in their field at the time of nomination. Applicants who are more than 10 years from having earned their highest degree may have their eligibility for a Tier 2 Chair assessed through the program's Tier 2 justification process; please contact the UBC CRC office (ubc.crc@ubc.ca) for more information. Please consult the Canada Research Chairs website (www.chairs.gc.ca) for full program information, including further details on eligibility criteria.

Applicants should submit a curriculum vitae, a five-year research program plan (up to 4 pages), a statement of teaching interests and accomplishments (up to 2 pages), copies of up to five key publications (summarizing briefly for each publication the significance, impact, and your contribution) and the names and contact information of five referees. In your application package, please also include a brief statement describing your experience of, and your contributions to, creating/advancing a culture of equity and inclusion in your workplace or within your discipline. Applications must be submitted by e-mail to pharmsci.hr.recruitment@ubc.ca.

The anticipated start date for this position is July 1, 2021 or upon a date to be mutually agreed. Inquiries about the position may be addressed to the chair of the search committee, Dr. Larry Lynd, Professor and Associate Dean, Research at larry.lynd@ubc.ca. For more information, see here.

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Postdoctoral Fellow (PDF) Position in Targeted Drug Delivery and Nanomedicine

One full-time postdoctoral position is available in the lab of Dr. Shyh-Dar Li at the Faculty of Pharmaceutical Sciences, University of British Columbia (Vancouver, BC, Canada). Expected start date is negotiable, although a start date as early as possible is preferred.

Research in the Li lab focuses on employing chemical approaches to engineer innovative drug delivery systems such as lipid- or polymer-based nanoparticles to enhance drug targeting. For more information about the Li lab and current research, please check: http://lilab-tddn.pharmsci.ubc.ca/

Dr. Li is the Chair of the Faculty's Nanomedicine and Chemical Biology Research Theme as well as the Training Program. He is one of the research leaders at the Nanomedicine Innovation Network (NMIN), a newly established National Centre of Excellence co-funded by the Government of Canada and industry, focusing on clinical translation and commercialization of nanomedicines (https://www.nanomedicines.ca/). Trainees in the Li lab are exposed to a rich and unique training environment, ranging from chemistry, pharmaceutics, drug formulation, nanoparticle engineering, drug development, animal study, to entrepreneurship. Trainees from the Li lab are highly competitive for highly skilled jobs, including scientists in innovative biotech companies and tenure-track faculty.

Qualifications: Applicants must:

- Have a PhD in Chemistry
- Have published peer-reviewed articles as the first author
- Have excellent synthetic and analytical skills in organic chemistry
- Have experience with bioanalytical techniques including HPLC and MS
- Have excellent communication skills
- Be self-motivated and interested in drug delivery research
- Preference will be given to those who have experience in cell culture, biological assays, or in vivo studies.

Responsibilities: The successful candidate will:

- Take the lead of a major project in the lab
- Synthesize novel small molecules, peptides, prodrugs, polymer-drug conjugates, and lipids
- Perform drug formulation as well as characterization in vitro and in vivo.
- Lead organization and maintenance of the Li lab
- Train junior lab members
- Publish research results and assist in grant writing
- Present their data at conferences and lab meetings.
- Teaching opportunity is available if interested.

Pay will be commensurate with level of experience and subject to UBC regulations for postdoctoral stipends. The contracted term will be for one year, from which further extensions will be possible. For further information, please email shyh-dar.li@ubc.ca.

Review of applications will start immediately, and will continue until the position is filled.

Please send a curriculum vitae and the names of three referees to:

Dr. Shyh-Dar Li, Angiotech Associate Professor
Faculty of Pharmaceutical Sciences, The University of British Columbia

Email: shyh-dar.li@ubc.ca

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- Hands on experience with quantitation analysis techniques on HPLC, LC/MS/MS and ELISA
- Experience in the setup, development and validation of bioanalytical assay
- Experience using Waters and/or Sciex LC/MS/MS for quantitation
- Demonstrated problem-solving and troubleshooting abilities
- General knowledge of drug disposition processes
- Strong written and verbal communication skills
- Strong planning and organization abilities
- Strong with computers skills, like MS Word, MS Excel
- Competent and self motivated individual able to work independently.

Duties and responsibilities will include:

- Perform bioanalytical assays utilizing HPLC, LC/MS/MS and MSD
- Develop and validate bioanalytical assays for small molecule, large molecule and biomarkers
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- Provide advanced technical input to the sales process, for our instrumentation and contract services.
- Provide high level application support for our customers in the pharmaceutical industry.
- Develop and document Malvern Panalytical and Concept Life Science applications knowledge and expertise in pharmaceutical sciences.
- To aid in solving non-routine customer measurement problems and to provide advanced training to customers and our sales organisations.

What do you need to be successful in this role?

- Drive and enthusiasm to understand our customers challenges, and the solutions Malvern Panalytical provides.
- Ph.D. in a relevant field, such as Drug Discovery, Small Molecule Drug Development and Manufacture, API Characterization, or M.S. / B.S. with 2 years direct experience in the pharmaceutical industry sector
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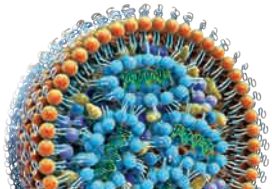

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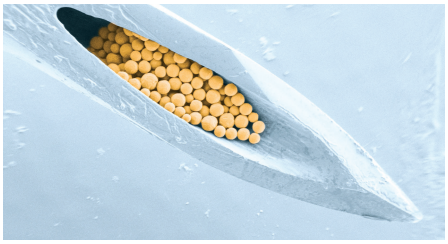

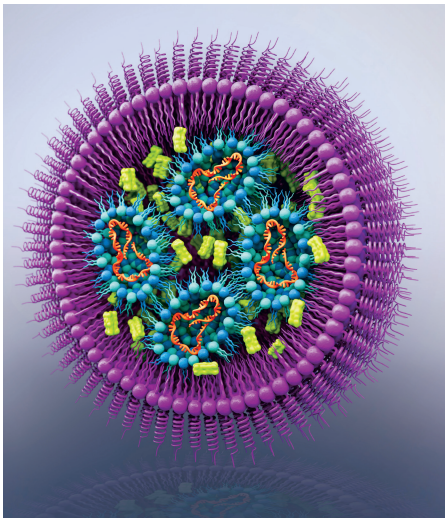

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Job Postings: Positions open for Industrial Postdoctoral Research Fellows in Synthetic & Medicinal Chemistry areas in our Chemistry R&D site in Vancouver.

PHARMA INVENTOR INC., is a Vancouver (Canada) based rapidly growing drug discovery contract research & development organization. Our company offers a dynamic and collaborative work environment where scientific excellence, innovation and matching salary & benefits are at the forefront.

Job Summary: We are seeking a highly motivated PhD and MSc level synthetic organic and/or medicinal chemists to join our drug discovery team. Candidates are expected to have experience in modern organic synthesis with good laboratory skills and a record of high productivity. Key requirements of the role include, being able to work within a team structure, propose new targets, execute synthetic routes, engage in troubleshooting exercises as needed, and effectively communicate with biology, pharmacology and DMPK colleagues. Candidates are expected to demonstrate laboratory and scientific proficiency, creativity, and a willingness to work in a dynamic group environment. Candidates are expected to carry out multistep organic synthesis, purification, and characterization of new molecules. The candidates will be part of a research team and will be expected to interpret SAR and ADME data and contribute to the design of new targets and to the chemistry strategy.

Key Duties and Responsibilities:

- Proficiency in modern organic synthesis and ability to independently perform complex, multi-step procedures.
- Experience in the purification of small molecules using a variety of methods such a flash chromatography, HPLC purification, distillation and others as needed.
- Structural characterization of small molecules using modern spectroscopic instruments and techniques such as LC-MS, 1 and 2D NMR methods and others.
- Contributes significantly to patent and/or publication preparation.
- Independently prepares project presentation and presents experimental conclusions at Group/Department or Project Team research meetings.
- Interprets SAR and ADME data and able to propose new targets to address chemistry and/or project issues
- Stays abreast of scientific literature and incorporates new methods and technologies in his/her research. Performs other duties as assigned.

Education and Experience: * Ph.D. in chemistry or medicinal chemistry, with 0-2 of relevant employment experience. Open work permit holders or LMIA exempt candidates are welcome to apply.

Website: www.pharmainventor.com

Job Types: Full-time, Contract, Permanent

Benefits:

- On-site parking
- Paid time off

Schedule:

- Monday to Friday

Education:

- Master's Degree (preferred)

Work remotely:

- No

JOB TITLE: Research Associate / Scientist – Synthetic Chemistry

YOU: A committed professional with experience in synthetic organic and/or medicinal chemistry looking to develop further in an innovative, fast paced biotech environment.

US: Leading innovators in the lipid nanoparticle (LNP) field, looking for a talented individual to join our collaborative, passionate, diverse pharmaceutical focused team.

ROLE SUMMARY:

Acuitas Therapeutics is seeking a highly skilled MSc or PhD level scientist with expertise in synthetic organic and/or medicinal chemistry to work in the Chemistry Group, reporting to the Director, Chemistry. The role holder will be responsible for the design, synthesis and characterization of novel compounds in support of our ongoing development of state-of-the-art LNP formulations for nucleic acid delivery. They will work as part of a cross-functional team, regularly interacting with our analytical chemistry, formulations and preclinical research groups.

JOB DESCRIPTION:

The Research Associate/Scientist will work at the bench performing research related to the design, synthesis and characterization of novel lipids for use in LNP formulations. They will contribute to the understanding of the structure activity relationship (SAR) of these compounds and suggest further iterative improvements to the compounds to provide optimal performance of our LNP formulations.

Working with the Director, Chemistry, the responsibilities would include:

1. Synthesis, purification and characterization of a variety of lipids and small molecules.
2. Contribute to the design of new compounds based on current understanding of the SAR and feedback from colleagues in other disciplines across the organization.
3. Work effectively in a cross-functional team and contribute to team, departmental and organizational meetings.
4. Assist in technology transfer related to the scale up of compounds discovered in our labs.
5. Keep detailed lab notes at industry standards.
6. Participate in drafting the technical portion of intellectual property filings and research papers.
7. Lab management duties as required.
8. Collaborative analytics with other departments including Formulation Development, Process Development and Pre-Clinical.
9. Maintain familiarity with relevant scientific knowledge and advancements.

QUALIFICATIONS AND SKILLS:

- MSc with 8+ years' experience or a PhD with 5+ years' experience in a drug discovery/synthetic chemistry/medicinal chemistry organization.
- Current and comprehensive knowledge of modern synthetic organic chemistry, purification and characterization techniques.
- Experience in optimizing discovery scale chemical reactions to enable multi-gram synthesis is an asset.
- The ability to develop and master new techniques quickly and to be able to work independently.
- Familiarity with industry standard chemistry-specific software and cheminformatics tools.

ABOUT ACUITAS THERAPEUTICS

ACUITAS
THERAPEUTICS

Acuitas Therapeutics is a private biotechnology company based in Vancouver, British Columbia, Canada. We are the premier global provider of LNP delivery systems for nucleic acid therapeutics. Acuitas is partnered with multiple international, biotechnology and pharmaceutical partners who are focused on bringing new vaccines and drugs into clinical development and to the marketplace. As an organization, we focus on fostering an inclusive and supportive work environment reflecting our values of honesty, integrity, innovation and openness. We strive to work internally and with our partners in an ethical, collegiate and respectful manner.

We are an early-stage start-up that's growing rapidly.

WE ARE CURRENTLY HIRING:

RNA biologist

Formulation scientist

Synthetic chemist

Contact us at info@nanovationtx.com
or directly via LinkedIn.

NANOVATION therapeutics

nanovationtx.com