FYP Projects (AY18/19)

Prof Subbu Venkatraman’s Biogroup
Self-assembled PEG-PLA nanostructures for drug delivery

• **Background**
  There is growing interest in making use of nanoparticles for drug delivery due to unique properties such as EPR and large surface to volume ratio. One such way of forming nanoparticle is through molecular self-assembly of polymers. This makes use of weak interaction between molecules (such as hydrophilic) to form supramolecular structures which can then be used as drug delivery vehicles. Such structures have advantages such as enhanced stability, chemical tunability and shape control.

  This project aims to further fundamental understanding of the self-assembly and drug delivery capabilities of self-assembled amphiphilic di-block co-polymers, which will be important when translating this carrier for clinical applications.

• **Objective**
  To understand factors that affect the formation of various self-assembled PEG-PLA and study its effect on the drug loading and release capabilities of these nanostructures.

• **Scope**
  • Fabricate various PEG-PLA nanostructures
  • Investigate factors that affect the formation of the nanostructures
  • Characterize nanostructures using light scattering and electron microscopy techniques
  • Evaluate drug loading and release from various nanostructures

Image adapted from Figg et al (2017)
Developing nanocarriers for hydrophilic drugs (small molecules, peptides, proteins etc.) is challenging due to low drug loading, burst release etc. Polymersomes are self-assembled vesicles formed by amphiphilic block co-polymers; careful selection of the co-polymer blocks in terms of hydrophobicity, charge, molecular weight etc. could then potentially improve hydrophilic drug loading and release. To this end, the overall goal of this project is to study the viability of polymersomes (based on different block copolymers) as nanocarriers for hydrophilic drugs.

**Equipment:**
- Rotary evaporator, Microfluidics; Extruder, DLS Nanosizer, Brookhaven SLS; HPLC; LCMS; MicroBCA

**Steps:**
1. Load hydrophilic model drugs into nano-sized polymersomes using various techniques
2. Characterize size, morphology, stability, drug encapsulation efficiency etc.
3. Carry out in-vitro experiments to understand release profiles
4. Identify parameters affecting drug loading and release => develop optimal drug delivery systems for hydrophilic drugs
Microfluidics driven nanoparticles for delivery of hydrophilic drugs

Aims: Explore microfluidics system as a fabrication method for the loading of hydrophilic drugs into liposomes
Efficiency of the self assembled system will be discussed

What skills student will learn:
Size measurement: DLS
Drug encapsulation: HPLC, UV-Vis spectrometer
Particle Morphology: TEM

Objective of this FYP:
• Generation of sub 200nm liposomes
• Investigate effects of physical properties on size, PDI and drug loading
Microfluidics as a potential platform for nanolipogel and drug delivery

**Background:** The development of sustained release formulations for hydrophilic drugs is currently one of the most important challenges in pharmaceutical research. Inspired by the cells, we proposed novel “nanolipogels” with a hydrogel-core and a lipid-shell for encapsulation of hydrophilic drugs.

**Objective:** To explore microfluidics system as a platform for nanolipogel fabrication and drug delivery

**Scope:** 1. Fabrication of nanolipogels using microfluidics machine
   2. Characterize size, morphology, stability, drug encapsulation and release

Challenges for protein delivery:
1. Low encapsulation and loading efficiency
2. Fast leakage
3. No sustain release

Inspired by cell cytoplasm (hold proteins inside cell)
Cell-mimicking nanolipogels for encapsulation & delivery of proteins

**Background:** The development of sustained release formulations for proteins and hydrophilic drugs is currently one of the most important challenges in pharmaceutical research. Inspired by the cells, we proposed novel “nanolipogels” with a hydrogel-core and a lipid-shell.

**Objective:** To study and characterize nanolipogels for the controlled release of proteins

**Scope:**
1. Fabrication of nanolipogels
2. Measure the release and bioactivity of proteins
3. Characterize the size of nanolipogels and the degradation of hydrogel core
Transdermal liposomes for treatment of atopic dermatitis

Atopic dermatitis (AD), also known as eczema, is a skin inflammation condition that affects more than 18 million American adults. Oral methotrexate is given to patients with moderate-to-severe AD but is limited by hematological, hepatic and gastrointestinal side effects. This project aims to use novel transdermal delivery carriers to provide localized treatment to the skin.

**Objective**

Formulation of methotrexate in liposomes and nanocarriers for eczema application.

**Scope**

1. Formulation, fabrication, and characterization of liposome and/or nanocarriers
2. Investigate the in vitro performance and release behavior of the carriers
3. Understand the skin permeability of methotrexate-loaded carriers in a porcine model.

https://www.nationaljewish.org/conditions/eczema-atopic-dermatitis/what-causes-eczema
Formulation and in vitro release study of drug-loaded polymer coatings for arteriovenous hemodialysis stents

Introduction

- What is Arteriovenous Hemodialysis Grafting (AVG)?
  - Surgically created artificial conduits that connect an artery to a vein
  - Failure of vascular access includes patient compliance and increase rates of hospitalization
- Current treatment involves Thrombectomy and Access Re-creation
- This project is aimed at studying drug-loaded polymer coatings for direct vascular delivery to prevent restenosis following AVG procedures

Scope of project

- Prepare drug-loaded polymer coatings
- Study the release profiles of the drugs from coating layers

Selected by Reuben Wong Wen Loong
A bilayer swellable drug-eluting stent for the treatment of urological diseases

The ureteric tract in humans are subject to disorders including carcinoma and strictures. Such conditions can benefit greatly from localized drug administration that enhances efficacy while reducing side-effects. Unfortunately, the urothelium can present a formidable barrier to drug retention and penetration. It has been reported that the problem can be overcome by increasing the duration of direct contact between the abnormal tissue and drug.

We hypothesize that, by placing a bilayer hydrogel-swellable drug-eluting stent in the ureter post-operatively, there can be enhancement of the localized delivery of an anti-fibrotic drug (Mitomycin C) into the proximate ureteric disease area with sustained drug delivery over the period of time when the stent is left in-situ. Our previous studies have shown promising results with the use of Mitomycin C.

The scope of this FYP work will focus on the use of an alternative anti-proliferative drug, namely paclitaxel. Parameters to study involve the effect of polymer thickness, drug concentration and hydrogel on drug release. Also, delivery carrier such as liposomes may also be adopted.

Some of the Lab Skills that can be acquired at the end of the FYP:
- Drug release (HPLC, LCMS)
- Hydrogel fabrication and characterization
- Liposomes fabrication and drug loading

Selected by Yee Zhen Lin
Core-shell electrospun fibers for delivery of hydrophilic drugs

We have previously achieved electrospinning of polymeric core-shell nanofibers. The idea is to be able to control the delivery of hydrophilic drugs by tuning the composition of the ‘shell’ material.

Objective
Fabrication of core-shell fibers using a co-axial electrospinning setup for the controlled delivery of therapeutic doses of hydrophilic drug/model drug

Scope
• Prepare core-shell fibres for the loading of fluorescence-tagged drug into fiber core
• Investigate the materials used in fiber core to achieve optimum loading of drug in the fiber core
• Measure the release of drug from fibers
Influence of nanoparticle properties on trans-epithelial transport

The transport of biodegradable nanoparticles across epithelial cell barriers is important for many applications in drug delivery. This project involves the investigation of nanoparticle physical and chemical properties on transport across epithelial layers.

**Objective**
Fabrication and characterization of various polymeric- and liposome-based nanoparticles

**Scope**
- Fabrication of poly(lactic-co-glycolic acid) (PLGA), hybrid lipid-coated PLGA nanoparticles, and lipo-nanogels with different sizes and surface charge.
- Characterization of nanoparticle properties (size, surface charge)
- Working with others, attempt transport studies in epithelial cell layers
Biodegradable stents with nano-materials for treating heart disease

Selected by Muhammad Azril Bin Idris

- Heart Disease claimed 17.7 million lives globally
- Coronary stents targeted to treat occluded coronary arteries with atherosclerotic plaque
- Metallic stents and drug-eluting stents used but presented their own set of problems
- Concept of bioresorbable stents brings advantages but limited by weak mechanical properties

Student will scope his/her FYP according:

- Study of nanofiller loading in improving mechanical properties
- Investigate the effect of functionalisation in improving dispersion of nanofiller to improve mechanical properties
- Study the mechanism of functionisation of nanofillers

Nanotechnology for oral delivery of insulin

Selected by Wee Shi Ting

Objective: To investigate the characteristics of a carrier system that delivers therapeutically relevant quantities of insulin across the intestinal epithelial cells while preserving its bioactivity

Scope:
1. Liposome fabrication
2. In vitro cell culture
3. Enteric coating of capsule

Enteric coating protects capsule from harsh acidic environment in the stomach
Enteric coating dissolves when pH changed to alkaline in small intestine, releasing liposome encapsulated insulin
Insulin gets transported across intestinal epithelial cells entering systemic circulation
Liposomes for the sustained-release of nitric oxide

The therapeutic effects of nitric oxide (NO) include the inhibition of platelet aggregation, stimulating angiogenesis and prohibiting intimal hyperplasia. These make NO an ideal candidate for cardiovascular intervention but it is plagued by a short half life. This project aims to explore liposome encapsulation as a possible platform for a localized and sustained release of NO to prolong its therapeutic effects.

Objective: Formulate NO liposomes for stent coating application

Scope:
1. Encapsulate NO in liposomes
2. Study the NO release profile based on liposome size, charge and rigidity

By the end of FYP, student will be able to:
1. Fabricate and load liposomes with NO drug
2. Characterize the liposomes
3. Conduct drug release study
Development of a robust amphiphilic coating for drug-coated balloons

Drug-eluting balloons (DCB) have been considered as a non-stent approach to treat occluded vessels with clinical data suggesting their favorable use in coronary in-stent restenosis (ISR) and peripheral artery diseases (PAD). Current commercial DCB platforms lack a balanced drug coating matrix that can result in a low drug loss, high tissue transfers and little/zero particulate generation. In this project, biomolecules with amphiphilic properties are proposed as a potential DCB coating.

Briefly, to achieve the development of a novel amphiphilic biomolecular coating for DCB application, the project will involve:
1. Optimization and surface modification of the amphiphilic coating
2. Fabrication and evaluation of the novel coating in terms drug release and stability
3. Evaluation of drug loss, drug transfer and particulate generation in in vitro bench top models

The development of a robust coating matrix that can enhance the transfer and retention of drug can potentially improve the clinical outcome of using a non-stent strategy for the treatment of coronary ISR and PAD. With improved efficacy and safety of this treatment, it can improve the cost of healthcare for treatment of occluded vessels, decreasing the healthcare expenditure.

Supervisor: Prof. Subbu Venkatraman
Co-Supervisor: Dr. Huang Ying Ying/Dr. Ang Hui Ying (NHCS)
The fabrication of a β islet cell encapsulating scaffold by 3D bioprinting

Selected by Sean Wong Qui Long

The aetiology of type 1 diabetes involves the autoimmune destruction of the patients own insulin secreting islet cells. The implantation of immunologically isolated insulin secreting islet cells, using protective polymer coating, has been proposed to be a potential therapy for the condition. The use of 3D bioprinting will allow the design of an implantable construct with predetermined architecture that confers immunoprotection to the therapeutic cells.

The project will involve optimizing the 3D bioprinting process to increase the viability of printed cells both during printing and subsequent culturing. The cellularized scaffold will be assessed for glucose responsive insulin release. The polymers forming the printing bioink, the hydrogel bioink crosslinking processes and printing parameters (speed and pressure) can be varied to produce the most precise scaffold with greatest cell viability.

Project will involve polymer handling and characterization, hydrogel crosslinking, cell studies and 3D bioprinting

3D printed hydrogels

Back pressure robotic system used for 3D bioprinting
Tuning the material compliance of elastomeric small diameter vascular prosthesis using 3D printing

There is currently the need for a clinically effective small diameter vascular prosthesis to meet the demand for coronary artery and peripheral artery bypass operations. The current synthetic polymers used in vascular devices are overly stiff and thus unable to match the material compliance of host vasculature to allow them to function as small diameter vascular prosthesis. Small diameter prosthesis fabricated from these materials tend to fail within months of implantation due to the disturbance in blood flow caused by the mismatch. The vasculature non linear elasticity, in that the blood vessels become stiffer at higher pressure to limit the rate of distention. Biomaterial elastomers such as polyurethanes have been considered as potential materials to form a small diameter prosthesis, however they do not stiffen at higher pressure.

In this project, 3D printing will be used to produce structures of a stiffer material to limit the expansion of an elastomeric tube thus conferring a matching compliance between the vasculature and prosthesis. The project will include polymer handling and characterization, dip coat fabrication, extrusion 3D printing and vascular compliance assessment.

Compliance apparatus

Small diameter vascular prosthesis assessed for compliance

Implanted prosthesis
We have previously found that by using a gelatin hydrogel bioinks crosslinked with transglutaminase, we can 3D print cell guiding microchannels that orientate vascular smooth muscle cells (vSMCs) towards the desired contractile phenotype.

The extracellular matrix around the cells has also been found to influence the behavior of cells. Elastin, a major protein present in blood vessels, is believed to also promote the desired contractile phenotype in vSMCs. The advantage of using transglutaminase crosslinking is that additional protein components such as elastin can be included into the printing bioink without any monomer modification.

In this project, elastin will be included into a gelatin bioink to 3D biprint cell guidance features. The effect of including elastin on seeded vSMC phenotype will be assessed. This study will help advance the understanding of using 3D bioprinting for the fabrication of cellularized vascular grafts for regenerative medicine.

Techniques will include hydrogel handling and characterization, 3D bioprinting, and cell culture and studies.
Characterizing and quantifying biologic-release from electrospun core shell fibers

• Electrospun-fibres (un-compacted and compacted) loaded with different concentrations of avastin would be prepared for biologic-release studies

• Blank and avastin-loaded samples would be incubated in media and mass changes recorded at pre-determined time-points (up to possibly 6 months)

• Additional biologic-release studies from avastin-loaded samples would be conducted from collected media at pre-determined time-points, via Elisa for bioactivity and SEC/LC-MS for total avastin content

The aim of this project will be to investigate the bioactivity of fiber encapsulated avastin and the duration of release.

Figure (left to right)
- Formation of a hollow core shell fiber during electrospinning.
- SEM of polycaprolactone fibers.
- Hollow fiber consisting of PCL shell and PEO core.