Competition:

UQUAPS 2017 "Pitching Research" Competition

Submission id:	Date submitted:
UQUAPS-2017-022	**28 Aug 2017 at 07:51 AWST**

Faculty or Institute:	School:
UQ Australian Institute for Bioengineering and Nanotechnology (AIBN)	**Australian institute for Bioengineering and Nanotechnology (AIBN) and Center for Advanced Imaging (CAI)**

Programme:	Load:	Level:
PhD	**Full-time**	**4-6 months**

Name:

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(A) Working Title:

Self-assembled polymeric micelle for hepatic fibrosis - an approach to non-invasive staging and targeted drug delivery

Word count: **994 words**

(A) Working Title	Self-assembled polymeric micelle for hepatic fibrosis - an approach to non-invasive staging and targeted drug delivery
(B) Basic Research Question	Can we address the clinical complications associated with diagnosis and treatment of hepatic fibrosis by utilizing novel techniques?
(C) Key paper(s)	Pellicoro, A., et al. "Liver fibrosis and repair: immune regulation of wound healing in a solid organ." Nat. Rev. Immunol., 2014, 14, 181-194. Wang, H., et al. "Diagnostic imaging and therapeutic application of nanoparticles targeting the liver." J. Mater. Chem. B., 2015, 3, 939-958. Fuchs, B.C., et al. "Molecular MRI of collagen to diagnose and stage liver fibrosis." J. Hepatol., 2013, 59, 992-998.
(D) Motivation / Puzzle	Hepatic fibrosis (HF), a common pathological feature of different liver diseases, cause millions of deaths worldwide. Each year the United States alone spend more than 100 billion dollars on liver-related health issues. During HF, normal liver tissue transforms into a hard-fibrous mass. If unchecked, it progresses to cirrhosis, hepatocellular carcinoma, and ultimately liver failure. Despite better knowledge of HF pathophysiology, the existing diagnostic and therapeutic techniques are not effective in clinical practice. However, recent studies have shown that HF can be managed well with the help of nanomedicine. So, can we build on that notion by exploiting nanoparticles with targeting ability and developing a new way of diagnosis using PET/MRI?
THREE	**Three** core aspects of any empirical research project i.e. the "IDioTs" guide
(E) Idea	Liver biopsy is the standard method for identifying and assessing HF despite the problems associated with this technique. Patient discomfort, sampling error, need of special expertise, and intra-and inter-observer differences demand better tools for these assessments. Recently, several non-invasive approaches including biomarkers based staging, elastography (FibroScan), MRI, and MR-elastography have been proposed as possible alternatives. However, some techniques work well for only few type of liver diseases while most of them fail to pick subtle improvements in fibrosis during the treatment process. On the other hand, therapeutics applied for HF also face various challenges such as uptake by undesired cell types, low drug concentration at target and inability to pass through the distorted liver architecture. To date, there are no FDA approved clinical treatments for HF. We hypothesise that the above issues can be addressed by using polymeric nanoparticles decorated with targeting ligands. For non-invasive diagnosis, agents targeting activated hepatic stellate cells (HPC's) - a cell type that produces excessive ECM - can be used along with those targeting deposited collagen fibers. Through this approach, we can monitor subtle changes in disease state and the sensitivity can be further increased by using hybrid molecular imaging tools like Positron Emission Tomography-Magnetic Resonance Imaging (PET/MRI). Furthermore, the drug delivery can be improved by loading anti-fibrotic drugs into multifunctional nanoparticles containing two or more

	ligands which target the overexpressed receptors on HPC's. It is hypothesized that by this method the treatment for HF can be efficiently given with more specificity.
(F) Data	Initially, data about the chemical structure, molecular weight, stability and physicochemical properties (shape, size, surface charge) of the self-assembled micelles (nanoparticles) will be collected. Then cytotoxicity, targeting ability and receptor-mediated endocytosis of the nanoparticles will be assessed by in vitro and in vivo assays. This will then determine the best combination of ligands for targeting HPC's and deposited collagen fibers in the liver. The collagen content and the HPC's population in the fibrotic liver will be calculated through PET/MRI by using the contrast to noise ratio data between the liver and surrounding tissues. Later, this information will be correlated with corresponding biopsy data to demonstrate the accuracy of multimodal imaging technique (PET/MRI) in staging HF. Finally, the drug encapsulation, degradability, pharmacokinetics and bio-distribution information of the applied anti-fibrotic agent will be acquired to document the ability of synthesized nanoparticles to specifically deliver drugs to HPC's, and the recovery will be monitored using PET/MRI.
(G) Tools	The advanced imaging tool-PET/MRI will be extensively used to acquire various information on the pathophysiology of HF to perform non-invasive staging. Further, it will also play a central role in studying targeting ability, biodistribution and clearance of nanoparticles. The in vitro studies of nanoparticles will be run on rat-derived quiescent and activated HPC's. For non-invasive staging and in vivo studies, rat models with hepatotoxin (carbon tetrachloride) induced fibrosis will be used.
TWO	**Two** key questions
(H) What's New?	1. Utilization of powerful imaging tools such as PET/MRI can increase the reliability of staging performed non-invasively. Further, by taking into account the HPC's population in the liver along with the information on collagen content we can avoid the drawbacks reported in current approaches with monitoring HF resolution. 2. Making use of ligands that correspond to overexpressed receptors on cells during HF, and decorating nanoparticles with multiple ligands as opposed to typical monofunctional drug delivery models. The direct comparison of different targeting agents will reveal potential candidates, which can be adopted in future studies. 3. Unlike conventional nanoparticles, the self-assembled micelles used in this research possess an internal degradation mechanism. This special property along with naturally occurring enzymatic degradation processes inside the human body may facilitate effective clearance of nanoparticles and stimuli responsive release of payloads based on disease state.
(I) So What?	Orthotopic liver transplant is the only available treatment for patients having advanced fibrosis. However, the donor number doesn't match the demand, and the management of HF takes a huge portion of healthcare funding. So by

	detecting and effectively treating HF in its early stages we can save a lot of money and also enhance the life quality of patients.
ONE	**One** bottom line
(J) Contribution?	Positive outcomes may change the way HF is diagnosed and treated in the future. Moreover, it also appeals for more multidisciplinary efforts to address the complications in managing liver diseases.
(K) Other Considerations	Is Collaboration needed/desirable? -Idea: no -Data: yes -multi-disciplinary and multi-institutional - Collaboration will be formed with pathologists having expertise in liver histology to perform the staging through biopsy procedure for comparison with imaging technique. Target journals - Hepatology, Journal of Hepatology, Theranostics, Advanced Healthcare Materials. Risk assessment: "no result"- low, a result is expected due to the nature of the study and the methodology proposed. Proper ethical clearance will be obtained before performing animal studies and risk assessments related to harmful chemical usage will also be completed.