Project Title: Peptide PEGylation for the optimal prostate cancer treatment outcome	**Code: SPS6**

Host School / Institute: Sydney Pharmacy School

Address: Pharmacy And Bank Building, A15, Camperdown Campus

Primary Supervisor: Dr Hien Duong

Phone: 0432 623 990

Email: hien.duong@sydney.edu.au

Co-Supervisor/team: Dr Bret Church, Senior lecturer, School of Pharmacy

Certificates & Clearances required: No

Project Type: Laboratory based

Project Category: Technology; Cancer

Skills / Attributes of a successful student: The successful student should have an interest in the interface of technology and medicines, how they work, and an interest in chemistry experiments. Student must have done chemistry or biochemistry courses with laboratory classes, in which data is analysed. The student will be trained in all aspects of the required laboratory methods**.**

Project Keywords: PEGylation; prostate cancer; phospholipases; inhibitor; peptide

Project Description: More than 10% of men will develop prostate cancer during their lifetime. The incidence rate of prostate cancer is highest in Australia. Despite potentially curative therapy by surgery or radiation, there has been a 72% increase in metastatic prostate cancer from 2007. Therefore, new treatment strategies for this disease are urgently required.

It has been demonstrated that secretory phospholipase A2-IIa (sPLA2-IIa) is overexpressed in almost all human prostate cancer, therefore this enzyme may potentially serve as a biomarker for prostate cancer (Dong et al, 2010). In our previous study, the pentapeptide, FLSYK (Phe-Leu-Ser-Tyr-Lys) dose-dependently inhibited the activity of human sPLA2-IIA (Church et al, 2001). More importantly, cyclic FLSYK recently entered clinical trials for the treatment of prostate cancer (Australian New Zealand Clinical Trials Registry, 2019). Although the FLSYK peptide was shown to be potent in specifically inhibiting sPLA2-IIa enzyme activity, its low aqueous solubility could hamper any clinical application. Therefore, the aim of this summer project is to enhance the solubility of this specific FLSYK peptide in biological environment for the optimal prostate cancer treatment outcome.

Our so-called PEGylation approach is to functionalise the FLSYK peptide with a PEG-like polymer using the amino group of the peptide. The polymer is comprised of poly(ethylene glycol) methyl ether acrylate (POEGA), a PEG-like polymer. This polymer greatly assists with colloidal stability (Duong, 2011). It also provides many advantages for biological applications including high biocompatibility, low toxicity and immunogenicity, prolonged half-life through reduced renal clearance and no metabolic degradation. We will use two strategies for the conjugation: i) peptide will be permanently conjugated to the polymer and ii) peptide will be conjugated to the polymer through a pH-responsive linkage which will be cleaved in mildly acidic conditions at the tumour site. The solubility of the conjugate will be assessed in comparison with the intact FLSYK peptide and the activity of the peptide conjugate in inhibiting sPLA2-IIa enzyme will be also evaluated using prostate cancer cells. The influence of the conjugation strategy will also be compared.

References: Dong, Z et al (2010). Secretory phospholipase A2-IIa is involved in prostate cancer progression and may potentially serve as a biomarker for prostate cancer. Carcinogenesis 31, 1948-1955.

Church, W.B et al (2001) A Novel Approach to the Design of Inhibitors of Human Secreted Phospholipase A2 Based on Native Peptide Inhibition. Journal of Biological Chemistry 276, 33156-33164.