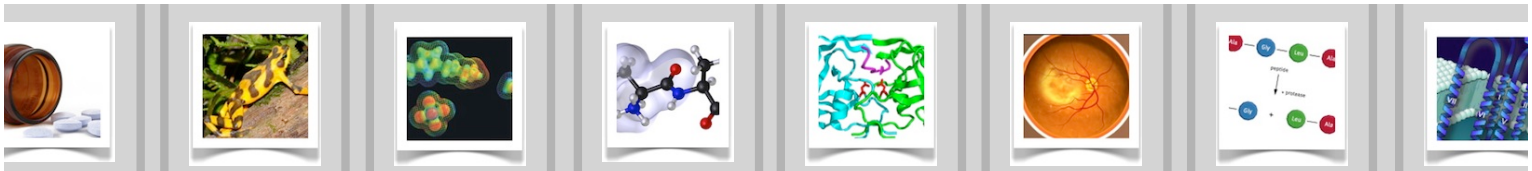

School of Pharmacy PhD Projects 2014

Project Title **Preclinical development of simple and inexpensive depot injectable formulations for combination contraception and HIV prevention**

Supervisors Professor R. Karl Malcolm and Dr. Raj Thakur

Description

a. Background information and rationale
Improving maternal reproductive health, combating HIV/AIDS, and preventing sexually transmitted infections (STIs) are major global health priorities specifically highlighted under the UN Millennium Development Goals. In fact, these three health priorities are often closely interrelated; for example, both pregnancy and genital HSV2 infection increase the risk of acquiring and transmitting HIV. Recently, leading health organizations have emphasized the need for development of new multipurpose prevention technologies (MPTs) that simultaneously address at least two of these health priorities. Although a significant number of agenda-setting, commentary and review articles have now been published on MPTs, there has to date been only limited development of new MPT product concepts. A single, long-acting, highly user-adherent, injectable product that is simultaneously targeted at contraception and HIV prevention has been assigned a high priority as a MPT strategy.

b. Study hypothesis and rationale
Our hypothesis is that inexpensive, long-acting, depot-type, injectable drug formulations can be developed to achieve and maintain in vivo drug concentrations capable of simultaneously providing hormonal contraception and preventing sexual transmission of HIV. Injectable-type hormonal contraceptive products, exemplified by Depo Provera® (DP) and Depo subQ Provera (DSQP), are already well established in reproductive healthcare, particularly in Africa where they are often the preferred choice among women. Given that the drug delivery approaches proposed in the first part of this study are largely based on existing injectable contraceptive technologies, we do not anticipate problems with achieving contraceptive efficacy. Instead, the challenge for an injectable MPT product targeted at both contraception and HIV prevention is primarily concerned with achieving sufficient systemic and/or vaginal drug concentrations of the antiretroviral drug to prevent sexual transmission of HIV. The lack of clinical potency of current antiretrovirals, at least relative to that of hormonal contraceptive drugs, is part of the problem. Only relatively recently have vaginally administered antiretroviral products been shown to provide protection against HIV, although adherence remains a major concern with this approach. Based on the results of the iPrEx study, the FDA has approved oral administration of tenofovir and emtricitabine for HIV prevention in high risk populations, demonstrating that administration of antiretrovirals remote from the site of initial exposure to the virus in women (i.e. the vagina) can be clinically effective. The concept of a long-acting, injectable, antiretroviral formulation for HIV treatment has also been considered. Taken together, these data and observations strongly support investigation into the potential of long-acting injectable formulations for simultaneous hormonal contraception and HIV pre-exposure prophylaxis in women.

c. Study methods
Two different injectable formulation approaches will be assessed in this project. The first will be based upon the commercial depot injection contraceptive products DP and DsQP, both of which take the form of injectable suspensions of micronised medroxyprogesterone acetate (MPA). Specifically, the potential for reformulating these marketed products with the inclusion of a potent, poorly water soluble, small molecule, antiretroviral agent (to be selected) will be investigated.

The second strategy is based on an in situ forming injectable implant. Specifically, we will develop an injectable solution comprising a pharmaceutical-grade, biocompatible and biodegradable polymer (polylactic acid-co-glycolic acid; PLGA), a water miscible solvent (polyethylene glycol diacrylate; PEGDA), the hormonal steroid MPA and a candidate antiretroviral agent (to be selected). Following intramuscular injection, the solvent diffuses from the system and is replaced with the aqueous interstitial fluid. This causes the polymer component to precipitate forming a depot implant that controls the rate of release (and ultimately systemic absorption) of the incorporated drug(s). Such in situ forming, long acting, subcutaneous implants have already been commercialized for treatment of prostate cancer (e.g. Eligard®).

The project will be largely completed as part of a 3-year PhD project at the Queen's University Belfast and will comprise four major activities: (i) in vitro characterisation of commercially available, injectable suspension products for hormonal depot contraception; (ii) development and in vitro characterisation of injectable suspension formulations containing MPA and an antiretroviral agent; (iii) development and characterisation of novel in situ forming, liquid injectable implants containing MPA and an antiretroviral agent; (iv) pharmacokinetic testing of the lead candidate injectable suspension formulation and the lead candidate in situ forming injectable implant in mouse and macaque models.

d. Eligibility criteria and details of award
Candidates should hold a first or upper second class degree in a relevant discipline (Pharmacy, Pharmaceutical Sciences, Pharmaceutical Engineering, Chemistry, or related areas) and must satisfy the eligibility criteria for the award. In addition to the payment of fees (UK/EU) for the duration of the project (3 years), the award includes provision for a student maintenance grant at the rate starting £13,590 pa.

Start Date Between 1st September 2014 and 1st February 2015

Keywords HIV prevention; Hormonal contraception; multipurpose prevention technology (MPT); Long-acting injectable; Drug delivery; Pharmaceutical

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How to Apply
Postgraduate applications should be made using Queen's Online:
http://go.qub.ac.uk/pgapply
Please note that there are two application processes: one for admission to the university and another for postgraduate awards.
Further Information
Additional information for prospective postgraduate students can be found on the School of Pharmacy website:
http://www.qub.ac.uk/pha
and the Queen's Postgraduate website:
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