Development and optimisation of liposome loaded bone cements

Outline
Approximately 110,000 cemented knee and hip replacements were performed in England and Wales in 2014. Failure as a result of infection is a major problem due to the complex treatment required, higher morbidity rates and risk of subsequent failure and complications. To overcome the limitations of existing antibiotic-loaded cements, a patented liposomal delivery system was developed at the Arthritis Research UK Centre of Bioengineering and Biomechanics at Cardiff. This system releases a higher percentage of the incorporated antibiotic in a controlled and prolonged manner, without compromising mechanical strength.

This PhD studentship is an interdisciplinary project between the Schools of Pharmacy and Pharmaceutical Sciences, Dentistry and Engineering at Cardiff University. The project will build upon previous work by further investigating the characteristics of drug release from the cement and establishing the mechanisms of action of liposomal antibiotic formulations against potentially resistant clinically isolated bacteria. The project will also optimise the technology towards clinical translation, enhancing its potential for commercialisation in terms of appropriate and synergistic antibiotic combinations, drug dosage, product stability and potential manufacturing processes using novel microfluidic manufacturing methods in collaboration with an industrial partner. The cytotoxicity of the system will also be determined against a variety of mammalian cells in preparation for future clinical trials.

Supervisors: Professor James Birchall, Dr Wayne Ayre & Professor Sam Evans

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Developing and testing a novel percutaneous delivery system for the glutamate receptor antagonist NBQX to treat joint pain and disease

Outline
Osteoarthritis (OA) affects 8.5 million people in the UK; however, no cure exists. Injury induced joint degeneration (e.g. tennis elbow, shoulder pain, ACL rupture, disc degeneration) is far more common. Synovial fluid glutamate concentrations are increased in human arthritis, and in animal models of inflammatory pain. Glutamate receptors (GluR) mediate joint pain, inflammation and degeneration, representing new drug targets for treatment of joint disease. We have demonstrated that AMPA/KA GluRs expressed in arthritic joints cause pain, inflammation and pathology and can be successfully inhibited by intra-articular injection of the GluR antagonist, NBQX in inflammatory arthritis (Bonnet et al 2013) and in 2 models of injury-induced OA (unpublished).

This project will test the hypothesis that the GluR antagonist NBQX can be modified for percutaneous delivery to treat joint pain, inflammation and degeneration. We will (i) determine whether NBQX is amenable to percutaneous penetration as a unionised molecule using rational drug design to achieve physicochemical parameters (ii) assess percutaneous and synovial fluid drug delivery in porcine skin and joint models, respectively, (iii) assess percutaneous drug delivery in human skin model and (iv) test the optimal topical formulation for effects on inflammation, pain and pathology in our in vivo model of ACL rupture.

Human trials and pharmacokinetic studies of drugs targeting AMPA/KA receptors show them to be well tolerated, revealing an opportunity for rapid translation (patent PCT/GB2014/052030: National Phase in Europe US and China). The topical formulations designed and tested in this grant will provide opportunities for new Intellectual property and improved therapeutic options.

Supervisors: Dr Deborah Mason, Dr Charles Heard & Professor James Birchall

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