SHORT TERM SCIENTIFIC MISSION (STSM) – SCIENTIFIC REPORT

The STSM applicant submits this report for approval to the STSM coordinator

Action number: TD1409
STSM title: Modelling dual drug-eluting stents
STSM start and end date: 01/07/2018 to 13/07/2018
Grantee name: Sean McGinty

PURPOSE OF THE STSM/

(max.500 words)

Whilst the rates of restenosis have significantly decreased since the introduction of drug-eluting stents (DES), it is still the case that repeat revascularisation rates are at least 3-5% per year, more than doubling in complex lesions. This amounts to hundreds of thousands of patients globally and the numbers are increasing. Simultaneously, late stent thrombosis (LST) associated with delayed healing remains a major concern and has led to a need for prolonged treatment with expensive dual anti-platelet therapy. An emerging strategy is the coating of stents with two drugs try to reduce restenosis in the early stages but accelerate healing to avoid LST in the latter stages. These are referred to as Dual Drug-eluting stents.

The primary aims of this STSM were to:

1) Develop the first mathematical models of drug release from dual drug-eluting stents in collaboration with Dr Martin Meere at NUI Galway. These will make use of both analytical and numerical methods

2) Discuss our models with

(a) Experimental groups at NUI Galway (The laboratory of Prof Peter McHugh)

(b) Several stent companies based in the Galway area (Boston Scientific, Abbot Vascular, Veryan Medical, Creganna Medical, and others)

3) Assist with the design of drug-release experiments which will inform the mathematical models (with Prof McHugh), and to visit the laboratory where these experiments take place

4) Use our models to inform dual drug release strategies and new stent design

DESCRIPTION OF WORK CARRIED OUT DURING THE STSMS

The initial work focussed on model development. A mathematical model of drug release from dual drug-

eluting stents and subsequent redistribution in the arterial wall was conceived and solved numerically in matlab by implementation of a finite difference approach. There were many fruitful discussions during the visit, these involving colleagues in the School of Mathematics, and also in Biomedical Engineering (Peter McHugh's group). As expected, new problems were uncovered and we spent quite a bit of time thinking about modelling solid dispersions with a view to understanding mixtures of one or more drug with polymer and the subsequent impact on drug release. A preliminary model was developed, making use of Flory-Huggins theory and this was solved both analytically (for simplifying cases) and numerically using finite element software for the 2D geometries. There were discussions with a number of companies during the trip. Dr McGinty gave a presentation entitled "On the influence of non-uniform binding site density in determining arterial drug distribution following stent-based delivery", which was well-received.

DESCRIPTION OF THE MAIN RESULTS OBTAINED

(max. 500 words)

Much of the discussion centred on the coupling between the drug transport model for each drug. For dilute drugs, the coupling of the model equations would only arise in the tissue where competition for binding sites exist. We discovered that, based on the available parameter values in the literature, the non-specific binding site densities were sufficiently high that, in reality, the coupling is weak and almost negligible. We have set out to mathematically derive the conditions under which the system of equations does need to be coupled: these will be conditions on the initial drug doses and release rate and involve asymptotic methods. Work on solid dispersions is ongoing, and we have mathematically derived a number of patterns that we should see in the solutions when we have the numerical method fully up and running.

FUTURE COLLABORATIONS (if applicable)

(max.500 words)

Future collaborative activities have already been planned:

Dr Meere will visit Glasgow in September to continue the work, as will a colleague from Biomedical Engineering at Galway. They will also both attend the workshop being organised by Dr McGinty entitled "Modelling and experiments of drug delivery systems"