Integration of sub-cellular imaging and systems modelling to optimise breast cancer treatment

Proposers:
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Lay Summary: One in eight women will suffer from breast cancer during their lifetime. Despite advances in therapy, the survival rate is still unacceptably low. One reason behind this is that we are, as yet, unable to predict how well drugs enter breast tumours; no drug will work unless it gets to its target. It is thus vital to develop novel technologies to address this important knowledge gap. Using our cutting edge approaches from Medical Physics we can image individual drug molecules in developing tumours. We will couple this with our expertise in mathematical modelling of drug flow in tissues to build the first robust model of drug movement through tumours. This will allow us to design optimal treatment regimens that ensure drugs penetrate tumours most effectively, with the ultimate aim of increasing patient survival.

Scientific Case for Support:

Background: Breast cancer is the most prevalent cancer among women worldwide, with nearly 1.5 million diagnoses in 2010. Despite the development of a range of therapeutics, the mortality rate for breast cancer has remained stubbornly high. One reason for this is that it is still unclear how drugs dispose into tumours, meaning that effective drugs may fail simply because they do not reach the target cells. It is thus imperative to design novel technologies to first measure and then computationally model this drug disposition, allowing prediction of optimal therapeutic regime based upon enhanced understanding of the tumour microenvironment.

Aim: Through integration of distinct, but complementary, established expertise at UoS (mathematical modelling, systems biology of breast cancer) and NPL (tissue and sub-cellular detection of drug disposition) we will build a robust mathematical model of drug disposition within tumours.

Techniques and Methodology: The student will be based primarily in mathematics but be exposed to a wide range of approaches across three disciplines during their training: mathematics, medicine and physics. While it is unreasonable to expect the student to become proficient in all the aspects of the project, we expect them to gain a working knowledge of all aspects. This is an important part of our training ethos, producing the multidisciplinary scientist that will be required to meet society’s grand challenges.

Mouse xenograft experiments are the gold standard to study tumour development in vivo and will be used to mimic the 3D tumour microenvironment. Animals will be inoculated with human breast cancer cell lines, and then treated with anticancer drugs for varying periods of time. Tumours will be excised, tumour volume measured, and then snap-frozen for further analysis (UoS, Biology). Time of flight secondary ion mass spectrometry (ToF-SIMS) will be used to obtain chemical images of the drug dosed tumours. The distribution of the drug, its metabolites and the tissues metabolic response to the treatment will be investigated. Chemical images will be registered to optical image of tissue subjected to histological and immunohistochemical staining methods, in order to correlate chemical changes in the tissue’s metabolic profile with its histology. These two experimental streams will provide the data to generate robust mathematical models of drug distribution and metabolism within tumours (UoS, maths). Finally, these mathematical models will be used to predict the disposition of untried drug treatment regimens, acting as a validation of the predictive ability of the system.

Objective 1: MS: Time of flight secondary ion mass spectrometry (ToF-SIMS) will be used to obtain chemical images of the drug dosed tumours. The distribution of the drug, its metabolites and the tissues metabolic response to the treatment will be investigated. Chemical images will be registered to an optical image of the tissue subjected to immunohistochemical and histological staining methods, in order to correlate chemical changes in the tissue’s metabolic profile with its histology. In a proof of concept experiment, the chemotherapy agent doxorubicin was drop dried on a tissue section (see Figure). In the negative ion mode the deprotonated molecule ion, [M-H]-, of the compound is observed in the region doped with drug. Here, we show that the proposed project is feasible. The student will also be

Figure- ToF-SIMS image (insert) overlaid on the optical image of tissue dosed with chemotherapy agent, doxorubicin. The deprotonated molecule ion of doxorubicin at m/z 540, mapped green in the ion image, maps to the tissue region stained orange in the optical image. Phosphocholine, an endogenous lipid marker, at m/z 184 is mapped in blue.
responsible for establishing and optimizing a post-SIMS sample preparation method that would allow this correlation to be performed on the same tissue section. Currently chemical and optical imaging is performed on adjacent tissue sections. Since the cell type can vary section to section, a method that allow the analysis to be done on the same tissue section would improve the ability to correlate pathology with IMS and reduces the amount of sample required for the overall analysis.

**Objective 2: Mathematical modelling.** Develop the first mathematical model of drug distribution in tumour tissue. Model parameters will be found by fitting to experimental data produced in objective 1, while ensuring that they are constrained within biologically realistic parameters. Next, we will examine the robustness of the model outcomes to model assumptions, both for the training set of compounds, and for a novel test compound. This will have two important deliverables: first, to allow us to refine the model to ensure that it represents closely the observed biological data, without being constrained into local conditions that are not biologically realistic; second, to allow us to use the model to determine the critical factors that determine drug penetration in tumour tissue and predict optimal treatment strategies.

**Integration with ongoing research:**
Dr Plant’s group has worked on Constraint-Based Modelling (CBM) of biological systems for over 10 years, with a proven track record in this area. With a focus on understanding human disease models, we have used an experimental-mathematical systems approach to examine lipid-loading in the liver (BB/008195/1, BB/1014451/1), heterogeneity in breast cancer tumours (BB/K501694/1), breast cancer metabolism (BCNPhD165), and drug metabolism (BB/N503939/1). Dr Skeldon has extensive experience of creating and analysing mathematical models of physical and biological systems. This has included modelling the distribution of oxygen in tumour tissue and the use of pharmacokinetic models to deduce oxygen concentration from tissue activity curves. Prof Derks has a track record of working with pharmacologists on drug deposition modelling. Prof Gilmore’s group focusses on the development of novel imaging technologies for many applications, including medical physics. He has considerable funding in this area, including the 3D-nanoSIMS project to build and optimise the next generation of measurement approaches.

**Suitability for PhD study:**
At the end of this project we will deliver a motivated highly motivated post-doctoral researcher with a cross-disciplinary skill set that will enhance their future career opportunities. While the majority of the student’s time will be spent undertaking mathematical modelling of the generated data, we feel it is important that they gain a full appreciation of both the medical and physical aspects of the project. Hence, the successful student will be based within the mathematics department at Surrey, but it is expected that they will spend time at both NPL and within the School of Biosciences and Medicine (UoS). These periods will both allow learning of transferable skills by the student, and act as focus points for project meetings between all three groups involved in this project. Within the mathematics department at Surrey, all PhD students receive up to £1000 to contribute to travel and the expenses of such collaborative work, ensuring this important part of student development is attainable. The applicants have substantial experience in PhD supervision, with over 30 students successfully submitting their thesis within four years between them. Thus, we are confident in being able to recruit, retain and successfully graduate a highly quality early career scientist within the project timelines.

**Contribution of NPL and UoS:**
Prof Gianne Derks and Dr Anne Skeldon will lead the mathematical modelling of drug disposition within tumours. Prof Ian Gilmore and Dr Melissa Passarelli will lead the MS-based detection of drug levels within tumour slices. Dr Nick Plant will lead the generation of biological samples for imaging and biological interpretation. Prof Derks will act as primary supervisor for the student and chair of the supervisory team. Beyond day-to-day supervisory duties, the entire research team will meet monthly via teleconference and face-to-face every four months to discuss project progression against timelines.

**Project Outcomes and consequent added value:**
This work will have three important deliverables: first, we will substantially extend the current ability of (nano)SIMS to image cellular drug concentrations, an important resource to understand drug-target engagement during drug development; second, we will build the first robust pharmacokinetic (i.e. mathematical) model of drug disposition within tumours in vivo; and, third, generation of a case study for validation of the technological approach. Together, these scientific deliverables will result in the publication of at least two high quality publications, in high impact, multidisciplinary journals. In addition, the technological development and validation case study will act as the preliminary data required for substantial bidding activity. We envisage follow up bids to both RCUK and industry due to the cross-disciplinary and commercially important nature of the developments we will make (the supervisors already extensively collaborate with several pharmaceutical companies, including GSK, Pfizer and AstraZeneca).

**Underwriting of research funding:**
From UoS the most significant cost is that associated with the generation of tissue samples from xenograft mouse models. Use of these models is already in place within FHMS, with samples being generated throughout the life of this proposal (BB/N503939/1 and BCNPhD165). Material beyond that required by these projects is produced by each animal study; excess will be flash frozen and sectioned for the current proposal. Hence, not only will we be able to meet the project requirements from ongoing studies, representing a considerable added value, but will meet the requirements of the 3Rs by leveraging the most value from each animal study. Studies and training at NPL will be supported by the 3D nanoSIMS project.