A UK Meeting and

Problem Workshop on

Quantitative Systems Pharmacology

14th to 17th September 2015

AstraZeneca, Alderley Park, UK.

Welcome!

It gives me utmost pleasure to welcome you to this UK Workshop on Quantitative Systems Pharmacology (QSP).

If QSP is to realise its goal of integrating subcellular genetic and protein-protein interaction networks with body scale information and clinical data to assist in early stage pharmaceutical development, it needs to bring together researchers working in both the life and theoretical sciences from academia and industry. This meeting is one step in that direction.

This week you will be exposed to the current state of QSP, both internationally and within the UK, given the opportunity to meet with funders interested in funding this new area of emerging science, discuss (and hopefully begin to solve!) problems brought by industrialists who wish to see QSP approaches applied to their problems and have the opportunity to interact with theoretical and life scientists from varied career backgrounds in both academia and industry, at different stages of their career.

The success of this week is very much down to you, the delegates. Please do get involved in the discussions, the problem solving and most of all enjoy yourselves and have fun!

Finally, I and the UK QSP Organising Committee are particularly grateful to AstraZeneca, Pfizer and Unilever for their financial support in making this meeting possible.

On behalf of the UK QSP Organising Committee we hope you enjoy this meeting and welcome your input and feedback.

Marcus Tindall (on behalf of the Organising Committee)

Organising Committee
Prof Leon Aarons (Manchester)
Dr Mike Chappell (Warwick)
Dr Lourdes Cucurull-Sanchez (GlaxoSmithKline)
Prof Gianne Derks (Surrey)
Dr Pinky Dua (Pfizer)
Dr Marcus Tindall (Reading)
Prof Ben Whalley (Reading)
Dr James Yates (AstraZeneca)

Meeting Venue
All activities will take place in the Helix Rooms (2 and 3) at the AstraZeneca Alderley Park Conference Centre, Alderley Park, UK, SK10 4TG.

Meeting Programme
A copy of this programme can be downloaded from
www.reading.ac.uk/~sas07mt/meetings.html
by clicking on "Programme".

A few copies of the programme have been made available at the registration desk. It is assumed most delegates will wish to access the programme via the above website. If you require a paper copy and none are available please contact Marcus Tindall or James Yates who will ensure copies are made.

Hotel Accommodation & Taxi transport
If you are staying at the Alderley Edge Hotel (http://www.alderleyedgehotel.com/) transport to and from the hotel is by shuttle taxi which is included in your accommodation. Each accommodation delegate has been scheduled a place to depart the hotel at either 8.15am, 8.30am or 8.45am on the Tuesday, Wednesday and Thursday mornings of the meeting. A taxi schedule can be obtained from the registration desk.

Please note all rooms are pre-paid and delegates, unless otherwise agreed with the conference organisers, will only need to pay for extra costs (e.g. mini-bar) on their departure.

Food and drink
Your attendance at the conference includes all daytime food and refreshments (morning tea, lunch and afternoon tea). Please see the meeting programme for further details on meal and refreshment times. Lunch, morning and afternoon teas will be served in the atrium area of the conference centre just outside the Helix rooms.

Evening meals
For delegates with accommodation at the Alderley Edge Hotel, your evening meals will be provided for you on the evenings of Tuesday 15th and Wednesday 16th September. All other delegates may purchase a meal from the Alderley Park Conference Venue café on these evenings. Delegates eating in the café should be accompanied by an AstraZeneca member of staff. If you have any queries please contact Marcus Tindall or James Yates in the first instance.

Conference dinner
The Workshop Dinner will be held on the evening of Monday 14th September in the Main Restaurant of the conference centre. Delegates will be able to purchase their own pre-dinner drinks from the bar. Wine will be provided during the meal.

If you are staying at the Alderley Edge Hotel, a shuttle taxi service has been arranged for you from 8.30pm onwards after the meal so guests can return to their room and check in to the hotel.

Wifi Access
Wifi is readily available throughout the conference centre. Please select "Alderley Park CC". No password is required.

Parking permit
If you have driven to the Alderley Park Conference site please ensure you have obtained a parking permit. Please contact James Yates for further details.

Posters
If you are displaying a poster please ensure this is placed on the poster display boards prior to the poster session at lunch on Monday 14th September. Please contact Marcus Tindall or James Yates for further details. Velcro is available for attaching your poster to the poster boards.

Delegate e-mail addresses
Delegate e-mails have not been included in this programme given it will appear on the Internet. A separate delegate e-mail list is available from the registration desk.

Meeting queries
If you have any queries during the meeting please contact Dr Marcus Tindall or Dr James Yates in the first instance. We will do our utmost to accommodate any requests.

Programme

Monday 14th September

11.00-11.30	Registration
11.30-11.40	Welcome: Meeting introduction, objectives and funding opportunities in QSP *Dr Marcus Tindall*
11.40-12.10	"Quantitative Systems Pharmacology: Phase 2 panacea or the emperor's new clothes?" *Prof Piet van der Graaf* (Leiden Academic Centre for Drug Research)
12.10-12.40	"Implementation and application of Quantitative and Systems Pharmacology in large pharma" *Dr Sandra Visser* (Merck)
12.40-13.00	"Mathematical design of optimal treatment strategies for atopic dermatitis" *Dr Reiko Tanaka* (Imperial College, London)
13.00-14.00	Lunch & Posters
14.00-14.20	"Are systems models any better than simple models at prediction" *Dr Hitesh Mistry* (University of Manchester)
14.20-14.50	"Experimentally-based computational models of human electrophysiology for pharmacology: from ion channel to the electrocardiogram" *Prof Blanca Rodriguez* (University of Oxford)
14.50-15.05	Form breakout discussion groups
15.05-16.30	Breakout discussion
16.30-17.00	Afternoon tea
17.00-17.20	"Mechanism based modelling for translational safety assessment" *Miss Teresa Collins* (AstraZeneca)
17.20-17.40	"A combined method of model reduction for Quantitative Systems Pharmacology" *Mr Tom Snowden* (University of Reading)
17.40-17.50	Summary of day one.
17.50-18.30	Pre-dinner drinks
18.30-20.30	Workshop Dinner
20.30-21.15	Transport for accommodation delegates to Alderley Edge Hotel

Tuesday 15th September

8.00-9.00	Transport for accommodation delegates to Alderley Park Conference Venue
9.00-9.45	Open discussion on breakout group discussions of previous day
9.45-10.15	"Systems pharmacology modelling in drug research and development: case studies from oncology and type 2 diabetes/obesity therapeutic areas" *Prof Oleg Demin* (Institute for Systems Biology Moscow)
10.15-10.45	Morning tea
10.45-11.00	Introduction to the problem solving part of the workshop
11.00-11.30	Problem 1: "An abstract modelling framework for adverse outcome pathways" *Dr Alistair Middleton* (Unilever)
11.30-12.00	Problem 2: "Understanding the polypharmacology of antibodies: what are the benefits of using a bispecific vs combination of monospecifics?" *Dr Armin Sepp* (GlaxoSmithKline)
12.00-12.30	Problem 3: "Modelling cancer immunotherapy" *Dr James Yates* (AstraZeneca)
12.30-12.45	Forming problem discussion groups
12.45-13.45	Lunch
13.45-15.45	Work on problems
15.45-16.15	Afternoon tea
15.45-16.15	Afternoon tea
16.15-16.30	5 minute update on problems
16.30-17.00	Work on problems
17.00-17.30	Work in café
17.30-18.00	Transport for accommodation delegates to Alderley Edge Hotel
19.00-20.00	Dinner for Alderley Edge Hotel delegates

Wednesday 16th September

8.00-9.00	Transport for accommodation delegates to Alderley Park Conference Venue
9.00-10.30	Work on problems
10.30-11.00	Morning tea
11.00-11.30	"A UK Quantitative Systems Pharmacology Network" *Dr Marcus Tindall*
11.30-12.45	Work on problems
12.45-13.00	5 minute updates on problem progress
13.00-14.00	Lunch
14.00-16.00	Work on problems
16.00-16.30	Afternoon tea
16.30-17.45	Work on problems
17.45-18.45	Transport for accommodation delegates to Alderley Edge Hotel
19.00-20.00	Dinner for Alderley Edge Hotel delegates

Thursday 17th September

8.00-9.00	Transport for accommodation delegates to Alderley Park Conference Venue
9.00-10.30	Work on problems
10.30-11.00	Morning tea
11.00-12.15	Work on problems
12.15-13.00	Lunch
13.00-13.30	Problem 1 report presentation
13.30-14.00	Problem 2 report presentation
14.00-14.30	Problem 3 report presentation
14.30-14.45	Workshop close

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Talk Abstracts

Quantitative Systems Pharmacology: Phase 2 panacea or the emperor's new clothes?

Prof Piet van der Graaf [1,2]
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A large proportion of drug development projects fail, predominantly in phase II and mainly because of an unacceptable safety profile or lack of efficacy. Arguably, the fundamental origin of attrition is a lack of understanding of the complexity of disease biology, which makes predicting the impact of perturbing the system with a drug very difficult. This would also mean that efforts to make the existing drug discovery processes more cost efficient may only result in failure that costs less. The need to experiment with truly innovative approaches in drug discovery could not be clearer, or more urgent.

Many see model-based drug discovery as a way of tackling attrition, arguing that pharmaco-statistical pharmacokinetic-pharmacodynamic (PKPD) methods have been able to positively influence phase III survival [1]. However, it was also recognised that in order to tackle phase II attrition additional steps are required. One such step may include implementation of translational PKPD reasoning in early drug discovery since by addressing attrition as early as possible, before the major clinical costs are incurred, the greatest potential efficiencies can be realised. However, to date, the discipline focusing on integrating PKPD has been data driven, with emphasis on statistical approaches such as non-linear mixed effect modelling with empirical models. These have significant limitations when it comes to extrapolating PK and PD properties between species. Hence, PKPD has evolved towards a more mechanistic approach, and indeed there are some limited data showing that PD parameters can be scaled. Overall though, the success rate for predicting clinical efficacy from animal models of disease is limited. This has led to the emergence of quantitative systems pharmacology [QSP; 2, 3, 4] which has been defined as the quantitative analysis of the dynamic interactions between drug(s) and a biological system; thus, systems pharmacology aims to understand the behaviour of the system as a whole, as opposed to the behaviour of its individual constituents. It applies the concepts of systems biology and PKPD to the study of complex biological systems through iteration between computational and/or mathematical modelling and experimentation. The opportunities and challenges of implementing QSP in drug discovery and development [5] will be discussed and illustrated with case studies.

1. Milligan PA, Brown MJ, Marchant B, Martin SW, Van Der Graaf PH, Benson N, Nucci G, Nichols DJ, Boyd RA, Mandema JW, Krishnaswami S, Zwillich S, Gruben D, Anziano RJ, Stock TC, Lalonde RL: Model-based drug development: a rational approach to efficiently accelerate drug development. *Clin. Pharmacol. Ther.* 93(6), 502-514 (2013).
2. Benson N, Van Der Graaf PH: The rise of systems pharmacology in drug discovery and development. *Future Med. Chem.* 6(16), 1731-1734 (2014).
3. Van Der Graaf PH: CPT: Pharmacometrics and Systems Pharmacology. *CPT: Pharmacometrics Syst. Pharmacol.* 26(1), e8 (2012).
4. Benson N, Van Der Graaf PH: Systems Pharmacology: bridging systems biology and pharmacokinetics-pharmacodynamics (PKPD) in drug discovery and development. *Pharm. Res.* 28(7), 1460-1464 (2011).
5. Vicini P, Van Der Graaf PH: Systems pharmacology for drug discovery and development: paradigm shift or flash in the pan? *Clin. Pharmacol. Ther.* 93(5), 379-381 (2013)

Implementation and application of Quantitative and Systems Pharmacology in large pharma

Dr Sandra Visser
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Quantitative and systems pharmacology concepts and tools are the foundation of the model-informed drug development paradigm at Merck for integrating knowledge, enabling decisions, and enhancing submissions. Quantitative and systems pharmacology can enable understanding of key compound properties for optimization, streamline research operating plans, improve trial design, set PKPD targets for human dose predictions and safety margins, select doses and regimens, and informs labels. Critical factors for the successful implementation, key concepts, impact examples, and challenges are discussed.

Mathematical design of optimal treatment strategies for atopic dermatitis

Dr Reiko Tanaka
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Atopic dermatitis (AD) is a most common chronic skin disease affecting almost 20% of the paediatric population worldwide, and predisposes to other atopic diseases such as asthma and hay fever. Despite its prevalence and high socioeconomic impact, its pathogenic mechanisms remain only partially understood, and there is a lack of clear consensus about the best and safest way of using the current main treatment (corticosteroids and emollients).

To gain a quantitative, systems-level understanding of the AD pathogenesis that is necessary to develop novel, patient-specific and effective treatment strategies for AD, we have developed the first mathematical model to understand the AD pathogenesis. The model describes the dynamically-changing interactions between tissue-level epithelial barrier function and cellular-level immune responses, both of which are known to be relevant for AD development. This multi-scale ODE-based mechanistic model provides a mathematical framework to integrate the information from clinical and biological studies, reproduces and predicts the different clinical phases of AD, and elucidates the roles of different genetic and environmental triggers in its pathogenesis.

The dynamical systems analysis of the proposed ODE model, from a control engineering perspective, further allows us to design patient-specific optimal treatment regimens that can prevent the disease progression. The optimal treatment is achieved by balancing the tissue-level epithelial barrier homeostasis and cellular-level immune responses, depending on the patient's potential genetic and environmental factors and the severity of the symptoms. This work exemplifies the impact of Quantitative Systems Pharmacology in the design of effective treatment strategies for complex diseases and can be applied to other disease such as asthma.

Joint work with Elisa Domínguez-Hüttinger[1] and Yuzuru Sato[2,3].
[1]Department of Bioengineering, Imperial College London, United Kingdom. [2]Department of Mathematics, Imperial College London, United Kingdom. [3]Division of Mathematical Sciences, Hokkaido University, Japan.

Are systems models any better than simple models at prediction?

Dr Hitesh Mistry
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All models are an abstraction of reality. The level of abstraction is dependent on the question being asked which in the case of QSP models involves accurate predictions of some future experiment given prior knowledge. There is a growing trend within the Pharmacokinetic and Pharmacodynamic (PKPD) modelling and simulation community to move to more detailed models (Systems Biology) with the hope that the more biological detail that is included the better the model will become at making accurate predictions of future experiments. However by including more detail you are increasing the number of parameters that need to be estimated as well as increasing structural uncertainty. The latter being something that is rarely discussed and seen as a taboo subject amongst all modelling communities. Here we look at this issue within the field of ion-channel cardiac safety assessment where there is a well-defined question relating to prediction and where both simple statistical and large-scale biophysical (Systems Biology) models have been used to answer them. We also present how these simple statistical models can form the basis of a QSP model for assessing ion-channel cardiac toxicity within the pharmaceutical industry.

Experimentally-based computational models of human electrophysiology for pharmacology: from ion channel to the electrocardiogram

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The electrophysiological activity of hearts from individuals of the same species is qualitatively similar under physiological conditions, but they can exhibit significant inter-subject differences following pharmacological action. The causes and modulators of inter-subject variability are however unknown. In this presentation, I will describe how we have developed and used advanced computational modelling of the heart to augment experimental and clinical investigations with the main aim of identifying key factors underlying the inter-subject variability of human hearts in the response to pharmacological action and disease.

Mechanism based modelling for translational safety assessment

Miss Teresa Collins
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Safety related attrition remains a large driver of compound failures during the development pipeline, particularly during late preclinical and early clinical development. A clearer picture of how early preclinical safety signals translate into man would allow a more accurate assessment potentially lowering attrition and resulting in safer drugs. Two common questions in safety assessment relate to mechanism identification and prediction of clinical effect. When an unexpected safety finding is observed, mechanism identification can to help in interpreting the implications of the signal or to identify methods of avoiding the toxicity.

Prediction of clinical effect magnitude can assist in understanding whether a sufficient therapeutic margin will exist for the compound under investigation. Mechanism based models provide a powerful tool for interrogation of drug activity and clinical extrapolation because of their ability to be easily adjusted to new biological and physiological situations. Here we will explore these applications through two case studies. The first will be on use of literature models cardiovascular effects from in vivo functional data, and the second will illustrate how to construct mechanism based models for common on-target toxicities through a model of the gastrointestinal crypt. In both case studies, we will illustrate how the mechanistic models allow for exploration of drug mechanism of action as well as translation to clinical effect.

A combined method of model reduction for Quantitative Systems Pharmacology

Mr Tom Snowden
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Quantitative Systems Pharmacology seeks to create detailed models of drug action bridging the gap between Systems Biology and pharmacokinetic-pharmacodynamic modelling. One issue that must be tackled in the development of such an approach is that of model complexity; biochemical systems involved in drug action are often highly detailed and their modelling typically produces complex systems of stiff, nonlinear ordinary differential equations. Model reduction methods offer a possible solution to the issue of complexity and represent the primary topic of the research presented in this talk.

Here a combined model reduction methodology that seeks to simultaneously reduce models of biochemical reaction networks and models of physiologically based pharmacokinetics is introduced; by linking reduced versions of both systems it is possible to construct highly simplified models for application within the context of quantitative systems pharmacology. At its core, the method brings together versions of proper lumping and empirical balanced truncation to reduce nonlinear and stiff dynamical systems that are typical in the modelling of biochemical networks. The algorithm is here demonstrated via application to a model of extracellular signal-regulated kinase (ERK) activation mediated via the extracellular growth factor (EGF) and nerve growth factor (NGF) pathways. It is shown that the model can be reduced from 99 to 8 dimensions whilst maintaining a high degree of accuracy in predicting the effect of administering an EGFR inhibitor on ERK activation.

Joint work with Piet van der Graaf[1,2] and Marcus Tindall[3,4].
[1]Leiden Academic Centre for Drug Research, Universiteit Leiden, Leiden, Netherlands. [2] Pfizer Pharmacometrics, Global Clinical Pharmacology, Sandwich, UK. [3]Department of Mathematics and Statistics, University of Reading, Reading, UK. [4]Institute for Cardiovascular and Metabolic Research, University of Reading, Reading, UK.

Systems pharmacology modelling in drug research and development: case studies from oncology and type 2 diabetes/obesity therapeutic areas

Prof Oleg Demin
Institute for Systems Biology Moscow
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Quantitative Systems Pharmacology (QSP) is an emerging modeling technique that combines the flexibility of systems biology and tractability of compartmental pharmacokinetic–pharmacodynamic modelling techniques. In my presentation the impact of QSP within drug research and development is considered by discussing case studies illustrating how systems

modeling can address questions arising in framework of projects in oncology and diabetes therapeutic areas. One of the case studies presents an application of QSP model of hypomethylating agents decitabine and SGI-110 for evaluation of acute myeloid leukemia treatment by targeting the S-phase with prolonged pharmacokinetic exposures. Other one is focused on type 2 diabetes therapeutic area.

A UK Quantitative Systems Pharmacology Network

Dr Marcus Tindall
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Quantitative Systems Pharmacology (QSP) brings a systems approach to the development of pharmaceuticals, using quantitative approaches such as mathematical modelling and data analysis to integrate subcellular genetic and protein-protein interaction networks with body scale information and clinical data. For pharmaceutical development this means the advantage of traditional pharmacokinetic pharmacodynamic (PKPD) modelling approaches, often used in clinical trial design, to the earlier stages of drug development. To fully realise its potential QSP requires input from academics and industrial researchers working in the life and theoretical sciences. In this talk I will outline the structure of a recently (September 2015) commenced network in QSP in the UK. The network brings together researchers in these areas, via a series of core workshops (one per year) and smaller satellite meetings. The combined dissemination and problem based focus of the workshops will be discussed and ways in which people can become involved outlined.

Problem Descriptions

An abstract modelling framework for adverse outcome pathways

A.M. Middleton, B. Nicol, S. Cooper, Y. Adeleye, A.J. White, C. Mackay, C. Westmoreland, P. Russell

SEAC, Unilever, UK

Problem Overview

To develop a top-down modelling framework for Adverse Outcome Pathways (AOPs), that will be complementary to current bottom-up mechanistic models, with a view to using a combination of these approaches for risk assessment of chemical exposure to humans.

Background

Within toxicology there is a significant shift from qualitative descriptors of adverse endpoints in surrogate species, to quantitative models based on human biology. This shift was precipitated by, in large part, the National Research Council report 'Toxicity Testing in the 21st Century' (TT21C) [1]. One strategy, proposed in the TT21C report, is to recognise that toxic responses are generated through a limited number of so-called AOPs. These are normal gene regulatory and signalling networks that, when perturbed by a chemical (for example, by the chemical binding to a particular receptor or protein), lead to adverse health effects.

While the details of each AOP will differ, it is largely thought that for low levels of chemical exposure, AOPs will elicit an adaptive response, ensuring that normal cell function is maintained. However, at higher exposure levels, adaptation will fail and cells will switch to an adverse response (such as programmed cell death). Thus, from a safety-assessment perspective a key goal is to be able to identify the exposure of a chemical at which the adaptive-adverse switch occurs in humans. Of course, the dynamics of AOPs can only be studied to a limited extent in humans. Instead, TT21C strategy requires that the AOPs are experimentally characterised *in vitro*, and then these observations are used to determine safe levels of chemical exposure *in vivo*.

Several AOPs have been identified in the literature, including ones for oxidative stress, DNA damage and heat shock response [1]. Mathematical models of these pathways are typically based on known or hypothesised interactions within the networks (and are hence mechanistic in nature and are developed bottom-up). While these models have been successfully used to elucidate specific experimental observations on AOPs [2-4], such an approach typically requires that the relevant networks are experimentally well-characterised. In reality, this requirement will only be met by a few AOPs, and even for these, many network components or interactions will be missing. While simple mechanistic models can be used in concert with experiments to first hypothesise and then validate specific network components and interactions, this can be a slow and resource-intensive process. Moreover, since the networks will be incomplete, such an approach may not lead to good predictions on what exposure scenarios might cause cells to switch from an adaptive response to an adverse one, and therefore not be 'useful' from the perspective of safety assessment. Nevertheless, these approaches do allow for experimental data to be related back to model outputs for validation

purposes, and the additional insight they yield (providing they are simple enough) can help increase confidence in a particular safety assessment.

Motivation: could abstract models be used to compliment mechanistic ones?

We wish to explore strategies that could help complement the 'bottom-up' approach offered by purely mechanistic models. In other fields of biology, various complex phenomena have been studied very effectively using so-called 'abstract' models. Here, rather than have the model composed of variables representing specific molecular players and interactions, state variables will represent abstract concepts and in this sense provide a 'high-level' description of the system. For example, in environmental toxicology, Dynamic Energy Budget (DEB) models are used to study how chemicals effect the growth, maturation and reproduction of organisms at the population or eco-system scale [5]. Importantly, the state variables in DEB models are abstract concepts such as (energy) reserve and (organismal) structure, rather than individual molecular players, and are used to assess the impact of chemical exposure on the environment [5]. In the case of developmental biology, abstract models have been used to study phyllotactic patterns in plants (how leaves are organised along a stem). These patterns are thought to be driven by complex interactions between plant hormones and downstream regulatory networks, which are only partially understood. However, Douady and Couder [6] demonstrated that these patterns could be understood by assuming a few simple rules: new leaf primordia emerge at the stem apex, primordia emit an inhibitory field on other nearby primordia, and that as the stem grows the leaf primordia move out radially. This simple model is able to capture the complex phyllotactic patterns observed in nature in a quantitatively accurate manner. Vernoux and co-workers have since extended this approach so that the state variables and parameters of the abstract model can be related back to specific molecular players [7]. By doing so, the abstract model was then used to elucidate complex mutant phenotypes and identify new molecular mechanisms important to the patterning process [8]. Other examples include the work Riedel-Kruse et al. [9], wherein the segmentation of vertebrate embryos was studied using an abstract system of coupled oscillators, leading to new insights on how specific mutations cause complex developmental phenotypes to form. Thus, combining top-down abstract models with bottom-up mechanistic ones can provide a powerful tool for studying complex biological processes.

Problem specifics: oxidative stress and DNA damage

We are interested to explore whether an abstract modelling approach could be applied to studying AOPs. For simplicity, we wish to focus on two well-characterised pathways: oxidative stress and DNA damage. For example, with the oxidative stress pathway, alterations in the levels of reactive oxygen species (ROS) are detected by KEAP1-NRF2 complexes as follows. In normal cells, KEAP1 binds to NRF2 to form a stable complex, preventing NRF2 from entering the nucleus. However, for excess levels of ROS, KEAP1 is oxidised, causing NRF2 to unbind and translocate to the nucleus, allowing it to activate downstream genes and thereby promote a complex repertoire of antioxidant responses. Mechanistic models of this homeostatic aspect of the oxidative stress pathway have appeared in the literature (see for example [10]). However, excess ROS can also lead to increased lipid peroxidation, abnormal protein aggregation, and other adverse effects such as activation of inflammation pathways (via NF-κB signalling), or potentially programmed cell death (via P62 signalling). Thus, as with other AOPs, the oxidative stress pathway is potentially very large and complex, and any model

developed bottom-up will likely be incomplete. The DNA damage AOP involves a similarly complex set of feedback loops involving p53, ATM and γH2AX (among others; see for example [2,3,11]).

Although the composition of both AOPs are quite distinct, the networks are similar from an abstract perspective in that cells: 1) sense the damage caused by a chemical insult; 2) induce mechanisms to repair the damage and possibly remove the chemical (adaptive response); 3) in the event that damage incurred is too great, an adverse response is initiated. A key challenge is to identify whether these or other abstract concepts can be used to form the basis of a model for studying the adaptive-adverse switch in these AOPs. A long term goal would then be to explore whether these ideas can be generalised so that they may be applied to other networks that are less well-characterised. It is desirable that, as with the abstract modelling examples from developmental biology and environmental toxicology given above: 1) we can use our existing, incomplete, knowledge of the underlying biology to relate the abstract state variables back to known molecular players and processes; 2) the models enable one not only to predict certain responses, but also to understand how they are generated from conceptual perspective, which can then help better inform our mechanistic modelling efforts or direct future experiments.

Available data and resources

- Single cell measurements (flow cytometry and fluorescence -based imaging) on the key molecular players associated with DNA-damage and oxidative stress, taken for multiple chemicals at different concentrations and timepoints.
- End-point assays on responses to chemical stimuli (apoptosis, micronuclei etc), which provide information on level of chemical exposure at which the adverse-adaptive switches occurs.
- Data on transcriptomic responses (RT-PCR and microarray).
- Existing mechanistic models of DNA-damage [11] and oxidative stress pathways [10], which capture certain aspects of how the pathways respond to chemical insult.

Question to be addressed

1. From a high-level perspective, what are the commonalities and what are the differences between the oxidative-stress and the DNA-damage AOPs?
2. Can abstract models be used in combination with existing mechanistic ones to better understand what molecular mechanisms drive the adaptive-adverse switch?
3. Is it possible to use an abstract model to accurately predict AOP responses to chemical stimuli? What are the limitations of such an approach?
4. How can different chemical molecular initiating events (MIEs; i.e. how different chemicals might interact with the AOPs) be incorporated in the models? Can abstract models be used to systematize how MIEs are explored experimentally?

References

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Understanding polypharmacology of antibodies: what are the benefits of using a bispecific vs combination of monospecifics.

Armin Sepp and Adam Taylor
GlaxoSmithKline

Project outline

Our aim is to understand the scenarios where using a bispecific monoclonal antiboides (mAb) would be preferential to using a combination of monospecific mAbs.

Background

Antibodies can provide highly specific high affinity binding to almost any molecule. While most therapeutic mAbs are monospecific, protein engineering has allowed to create bispecific varieties (bs-mAb) that can bind two different target molecules simultaneously. Many alternative formats for bs-mAbs exist but in this instance we shall only consider two of them: those with one binding site per mAb molecule for either target (two in total, A on Figure 1) and those where there are two for either target (four in total, B on Figure 1).[1]

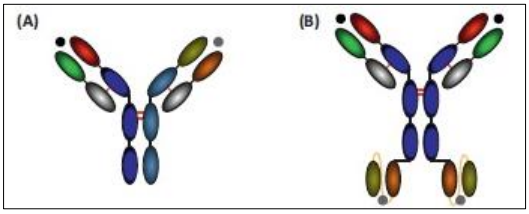

Figure 1: Bispecific antibody formats. Taken from Byrne *et al* 2013.[1]

Traditional antibodies have 2 binding sites, but typically only bind to a single molecule of a soluble target due to high molar excesses when used as a therapeutic. However, when the target is membrane-bound, bivalent interaction may occur that results in improved binding through the avidity effect[2,3]. In the case of bispecific mAbs, it is conceivable that two different targets present on the surface of the same cell may be cross-linked in similar manner.

Aims of project

There are 2 primary aims of this project and 2 secondary aims. For the first two, we are using simulation to understand if there are benefits (reduced dose, reduced dosing frequency, target engagement, etc) in using a bispecific molecule over a combination of monospecific antibodies when the targets are in solution or expressed on the same cell. The last two are concerned with situation when the interacting proteins are on different cells: bs-mAb mediated cell-cell cross-linking and TCR-pMHC interactions.

Primary Aim 1: 2 independent soluble targets: for example TNFα and IL17

Soluble targets are considered to be well mixed (equilabrated) within a given volume. The output from this aim will be:

1. Understand whether there are concentration dependent scenarios where it is preferential to use a bispecific mAb over a combination of monospecific ones
2. Model the probability of bivalent binding to occur with bispecific molecules
3. Model how the concentration of different targets affects the require affinities of a bispecific molecule

Primary Aim 2: Two independent membrane targets on same cell surface

Membrane targets are considered to be anchored on the surface of a cell. The output from this aim will be to understand whether there are scenarios where it is preferential to use a bispecific molecule over a combination of two monospecifc ones. Model the scenarios when the effect of antibody binding is agonistic as well as when the effect is antagonistic.

1. Compare the target engagement of bivalent binding to occur with bispecific molecules
2. Model how receptor density and mobility of different targets affects the required affinities of a traditional antibody
3. Model how receptor density and mobility of different targets affects the require affinities of a bispecific mAb

Consider two cell populations: The first one carries membrane-bound targets A and B both at 100000 per cell while the other one has just target A at the same level. The output would be target A engagement as a concentration-response curve for both cell populations. Is the lateral diffusion of target molecules on cell surface expected to be of any significance?

Secondary Aim 1: Two independent membrane targets on the surface of two different cells. Cross-linking of these two cells by a bispecific mAb

Cell-cell interactions lie at the heart of immune response. Bispecific antibodies have the potential to bind to 2 targets simulatenously that are expressed on independent cells and hence can facilitate this interaction. The output from this aim will be:

1. Model the dose-response curve for cell-cell crosslinking and target engagement by a bispecific antibody when the respective 2 targets are expressed on 2 independent cells. Analyse the effect of bispecific mAb affinities and differences in target densities.

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Modelling Cancer Immunotherapy

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Cancer is a multi-faceted disease that is well characterised by the "Hall Marks Of Cancer" (Hanahan & Weinberg, 2011). An important hallmark that has emerged is the ability of solid tumours to evade detection by the host's immune system. This has resulted in the discovery and development of new anti-cancer treatments targeted to enable the immune system to attack the tumour based upon the cancer immunity cycle (Chen & Mellman, 2013). The approaches range from vaccines to targeting tumour cells ability to inhibit local T-cell response. This former approach aims to reset the immune system whereby the immune system acquires and retains the ability to "see" the tumour and effectively kill tumour cells. Some of these approaches have seen encouraging results in the clinic: although only a minority of patients respond to these agents those that do see their tumours disappear with few cases of relapse observed.

Given these encouraging results for these Immunotherapy agents (Hence forth IO for Immuno-Oncology) treatments, clinical investigations are expanding to combine with established standards of care (SoCs) as well as novel targeted small molecule inhibitors. These small molecules take advantage of other aspects of the hallmarks of cancer by inhibiting aspects of cell proliferation, survival and signalling. The best way to dose these combinations results in a number of questions.

The immune system is complex, however there are a number of useful publications as primers for modellers (Hawse & Morel, 2014).

There are a number of example models in the literature

1. Interaction of tumour and T-cells (Robertson-Tessi, El-Kareh, & Goriely, 2012)(dePillis, Eladdadi, & Radunskaya, 2014)
2. Determining optimal schedules (Cappuccio, Antonio ; Castiglione, Filippo ; Piccoli, 2007)(Piccoli & Castiglione, 2006)
3. The role of cytokines (Cappuccio, Elishmereni, & Agur, 2006)
4. Integration of multiple models into one system (Palsson et al., 2013)

Questions

Based upon the above background the following is a summary of the questions surrounding the best use of these IO agents in combination with other treatments. It is suggested to consider some case studies of combinations in the literature as motivating examples (Cooper, Reuben, Austin-Breneman, & Wargo, 2015) (Twyman-SaintVictor et al., 2015)(Parra-Guillen, Berraondo, Grenier, Ribba, & Troconiz, 2013)(Kakavand et al., 2015). It is clear that the immune system has a threshold like behaviour whereby sufficient stimulus is required before it decides to act. For combinations of immune therapies and other treatments this will be dependent upon a number of factors, importantly what the SoC or small molecule inhibitor "does" to cancer cells and the immune system.

1. What is the optimal relative sequencing of agents (immune therapy + other anti-cancer treatments) with different mechanisms? Some topics to consider/issues to consider in order of importance
    a. Short sharp burst of cell kill vs longer low level for the “targeted” or “kinase inhibitor” type drugs. How important is it to increase the antigenicity of the tumour by killing cells with a targeted agent or chemotherapy versus reducing proliferation of cells (a maintenance effect)? This situation is analogous to a vaccine.
    b. Some small molecules kill or inhibit T-cells: What would the impact of a preferential effect on T-regs vs T-effector cells?
    c. Would a decreased dose of immune therapy be adequate in the presence of small molecule? Or shorter duration of treatment?
    d. How long do we have to do treat for: or how would we know when enough is enough? The hypothesis behind immune therapy is to reset the immune system in the tumour – therefore continued treatment should not be necessary.
2. Impact of model assumptions
3. Key data/experiments to inform model?

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Poster Abstracts

Underlined names indicate those delegates exhibiting the poster.

Mechanistic Model to Predict DDIs in the Liver

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Objectives: To generate a mechanistic dynamic model for the prediction of Drug-Drug Interactions (DDIs), which results from time-processes within hepatocytes, taking into account the spatial distribution of the drugs in a lobule, the uptake at the sinusoidal membrane, the enzyme inhibition/induction [1] and the up-regulation of the enzyme gene within the hepatocytes.

Methods: Over 70 clinical DDIs [2,3], including inhibitors, inducers and mixed interactions, were compared with the prediction using a static model and the new dynamic model. This was implemented in MATLAB® and inserted into a PBPK model with 4 compartments (Blood/Gut/Liver/Rest).

The Blood and Rest compartments are simple compartments with a physiological volume and a partition coefficient. The Blood compartment has a partition coefficient of one, whereas the Rest compartment depends on the drug.

The Gut compartment comprises two sub-compartments: the first represents the gut wall with a first order absorption for the oral dose and takes into account DDIs within the enterocytes assuming a well-stirred compartment; and the second represents the portal vein.

The estimations of the drug parameters (inhibition/inactivation/induction/uptake) were obtained with in vitro experiments and adjusted for the human liver size. The PK parameters (clearance/absorption rate) were obtained from the literature [4,5].

For each clinical case, the AUC ratio of the victim drug was estimated with the dynamic model and compared to the static model along with the clinical outcome.

Results: The preliminary results show that the model accurately predicts the DDI of the compounds which are purely inhibitors (reversible or time-dependent) or inducers. For compounds which are both, the prediction is less accurate. Overall, more than 60% of the DDIs have been predicted within 2-fold and more than 89% within 4-fold. The Geometric mean fold error (GMFE) has been estimated as 1.91, which is in the same range as the current static model ([2,3]: GMFE=1.7-2.5).

Conclusion: The model is consistent with those in the literature. It also provides a dynamic description of the DDIs, such as the enzyme level and spatial distribution within a lobule. Furthermore, the perpetrator dose regimen can be changed to observe its influences on the AUC ratio.

Finally, as in the static model [2,3], the DDIs prediction of compounds demonstrating inhibition and induction in-vitro is poor. These could be the result of a more complex mechanism occurring in the liver and/or intestine as an MDR1 induction or the perpetrator metabolite playing a role in the DDI.

Computational modelling of placental amino acid transport as an integrated system

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Placental amino acid transport is essential for fetal development and impaired transport has been associated with poor fetal growth. Amino acid transport is mediated by a broad array of specific membrane transporters with overlapping substrate specificity. However, it is not fully understood how these different transporters work together, while this cooperation is essential for the transfer of all required amino acids from mother to fetus.

Therefore the aim of this study was to develop a computational model to describe how placental amino acid transport functions as an integrated system.

Briefly, to pass from mother to fetus, amino acids need to cross the two membranes of the placental syncytiotrophoblast barrier, each of which contains a variety of specific active and passive transporters. These include System A accumulative transporters (SLC38), which use secondary active transport driven by the sodium electrochemical potential, System L exchangers (antiporters) such as LAT2 (SLC7A8) and efflux transporters operating via facilitated diffusion such as TAT1 (SLC16A10).

A compartmental modelling approach was combined with a carrier based modelling framework to represent the kinetics of the individual accumulative, exchange and facilitative classes of transporters on each membrane. Modelling results clearly demonstrated how increasing the transport of certain classes of amino acids comes at the price of decreasing the transport of others, which could have potential implications for developing new clinical treatment strategies.

Combined with ex-vivo human perfused placenta and placental membrane vesicle experiments, this integrated modelling approach will help us to achieve an improved quantitative understanding of placental amino acid transport at the systems level. In addition, this approach has wider applications to predict drug-drug and drug transporter interactions in pregnancy.

Mathematical modelling of transdermal pharmacokinetics: a mechanistic approach

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We present the application of the principles of quantitative systems pharmacology (QSP) to transdermal pharmacokinetics. The focus is on mechanistic modelling of the complex effects of drug diffusion in, and its interactions with, the heterogeneous structure of the skin. A general interfacial mass transfer model has been developed to simulate the diffusion of drugs across heterogeneous layers from the vehicle to the stratum corneum consisting of brick-and-mortar structure of lipid and corneocyte, and from the stratum corneum to the underlying viable epidermis and dermis. The key parameters determining the pharmacokinetics, i.e. the diffusion and partition coefficients in skin, are obtained based on the physico-chemical properties of the drug, the human skin physiology, and thermodynamic principles. This microscopic model of skin is further integrated with a macroscopic model of drug transport into blood circulation, which allows the quantification of plasma concentration following topical application of the drug. Such a mechanism-based and multi-scale modelling approach provides the capability of quantitatively predicting the pharmacokinetics of drugs and the delivery scenarios that have not been experimentally studied (i.e. extrapolation). We demonstrate the excellent agreement between the model prediction and the data from experimental and clinical studies, without fitting to these data. We argue that further research along this line could lead to more mechanistic understanding of transdermal pharmacology, and thus a more systems approach to the design of transdermal pharmaceuticals and other chemicals in terms of efficacy and safety.

Data-driven inference of cell-line specific signalling networks in cancer

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A good knowledge of cell-line specific signalling networks is essential in order to understand response to drugs and to design efficacious combination treatments in a given cell-line and, ultimately, in a given cancer patient. The aim of this work is to infer mathematical models representing cell-line specific signalling networks to help understand differential response to drugs targeting the PI3K/PTEN/Akt pathway in different cancer subtypes.

We used a data-driven combined experimental/computational method. After building a generic literature-based signalling/transcriptional network in breast cancer, we performed a pair-wise drug combination experiment measuring the time-dependent response of a set of 30 proteins and phospho-proteins to a panel of 9 anticancer drugs targeting the PI3K pathway and related pathways (PI3Kα, Akt1/2, mTOR1/2, PI3Kβ, PARP1/2, MEK1, ERBB1/2/3, ER, JAK1/2) for three cell lines representing three breast cancer subtypes: BT474 (ER+/HER+, PI3Kα K111N mut), MCF7 (ER+, PI3Kα E545K mut), HCC70 (TNBC, PTEN-). Measurements were done using Reverse–phase Protein Micro Array (RPMA). This dataset has been used to refine the generic literature-built network into three distinct cell-line specific ones and to automatically build mathematical models describing the dynamic behavior of those cell-line specific signalling networks using penalized linear regression. The inferred models mathematically are described by a set of ordinary differential equations, and can be represented graphically as cell-line specific networks describing the type (positive or negative), direction and strength of influences between proteins, and the relative amounts of each protein marker.

This type of network models can be viewed as a tool to: (i) consolidate existing knowledge (i.e. verify if an experiment confirms known behaviours, feedbacks, differential responses to drugs, …); (ii) aid the interpretation of large experimental datasets (i.e. put diverse signaling endpoints into a mechanistic context); and (iii) generate new hypotheses (e.g. uncover novel interactions, feedbacks, activation routes, suggest drug combinations, …).

ATR inhibitor and cancer: a mathematical investigation

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DNA Damage Response (DDR) mechanisms enable cells to sense and repair DNA damage, which occurs as result of a variety of endogenous and exogenous effects. Defects in the DDR lead to genome instability - which is a hallmark of cancer - and several tumours have a clear link with specific DDR dysfunctions [1]. At the same time, this mis-regulation provides therapeutic opportunities and, in fact, several drugs targeting specific DDR components have been developed recently [2].

ATR is a critical component of the DDR mechanisms, and it has a key role in the DNA replication stress response pathway. Loss of ATR function leads to the accumulation of DNA damage and DNA double strand breaks, and it represents an appropriate target for cancer therapies [3]. Although the DDR and its therapeutic potential have been intensively studied, they are not completely understood; much progress can be made using a systems pharmacology approach that combines mathematical modelling with experimental data.

We have designed a mechanistic model of the cell cycle, which reproduces the growth of a population of cancer cells and that enables simulation of mono therapy with an ATR inhibitor. The model was trained with *in vitro* data measuring cell growth, DNA damage and cell cycle transitions of the ATM deficient colon cancer cell line *LoVo*. Our *in silico* experiments reproduced the results observed *in vitro* and were used to understand and characterize the effects of ATR inhibitor on tumour growth. The model has a robust and mechanistic structure that can be adapted to: (i) reproduce the effects of ATR inhibitor on several cell lines, and (ii) describe the effects of other DDR inhibitors on tumour growth. Moreover, our model is also adaptable to reproduce *in vivo* growth, and *in silico* results will be used as prior modelling knowledge for *in vivo* experimental design. Model predictions will then used to better understand the efficacy of combination treatments of ATR inhibitor with other DDR inhibitors and with DNA damaging agents.

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PK TOOL; freeware for clinical PK and dose prediction

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Extrapolation of pharmacokinetics (PK) from preclinical data to human is a key process in early drug discovery. A range of methods are used including for example allometry, single species scaling, in vitro, physiologically based PK and hybrid approaches. However, in order to enable dose estimation, all of these methods require calculations with multiple parameter inputs that ultimately need to be related to a measure of efficacious concentration. Currently there are a limited number of free software tools that provide a framework for these calculations and dose estimates. We present here 'PK Tool' a free, intuitive software tool that is intended to help drug discoverers make the most of their preclinical data and optimise dose selection for initial clinical trials. The tool is flexible in that systems pharmacology models linking to drug PK to can be included and used in the calculation of dose and regimen.