Institution: University of Surrey

Unit of Assessment: UOA 10 Mathematical Sciences

Title of case study:

Guiding drug discovery by prediction of in vivo efficacy of monoclonal antibodies

1. Summary of the impact (indicative maximum 100 words)

In the initial stages of the drug-discovery process, a range of synthetic molecules are developed and the most promising ones are selected for further development into potential drugs. The research of the Surrey team in collaboration with a research team at Pfizer sheds new light on how to achieve high efficacy, by using mathematical modelling to speed up this selection process. The research has led the pharmaceutical company Pfizer to terminate a discovery project and redeploy resources in a new direction. This research has generated direct impact in the field of early-stage pharmaceutical research, and indirect impact on the economy and health.

2. Underpinning research (indicative maximum 500 words)

The Surrey team (Dr Philip Aston and Dr Gianne Derks, both Readers in Mathematics) had a combined 33+ years of experience working in applied dynamical systems and mathematical modelling, when they were contacted by a Research Scientist at Pfizer in 2009. Pfizer was interested in using mathematical models consisting of small systems of ordinary differential equations (ODEs) to get a better understanding of fundamental properties of monoclonal antibodies, with an aim to improve and guide the early drug discovery process through modelling.

Pfizer's problems involved monoclonal antibodies and target-mediated drug disposition (TMDD) models that describe their pharmacokinetic-pharmacodynamic (PKPD) interactions. One of the questions was "What is the relation between efficacy of monoclinic antibodies and their affinity and elimination parameters?" Another was "Can rebound occur and if so, what triggers it?" The mathematical underpinning involved systems of ODEs, representing the target-mediated drug disposition (TMDD) models, with coefficients representative of parameters in the pharmacokinetic-pharmacodynamic processes. These models were then extensively analysed both methodologically and rigorously to determine parametric effect and asymptotic behaviour. The principal analysis to address the efficacy question was a study of the relationship between the target affinity of a monoclonal antibody and its in-vivo potency/efficacy. As a measure of efficacy, the minimum level of the free receptor following a single bolus injection of the ligand into the plasma compartment was considered. It is known that the equilibrium dissociation constant K_D, which is the quotient of the dissociation constant k_{off} and the association constant k_{on}, plays an important role in the efficacy. Before this research, the different roles played by the two constants in this quotient had not been realised.

The methodology in the underpinning research involved qualitative analysis of ordinary differential equations, dynamical systems analysis (invariant manifold theory, attracting sets, heteroclinicity), multi-scale asymptotics, and numerical simulation. The initial stage pharmacokinetic-pharmacodynamic implications of the analysis are discussed in [1]. A rigorous mathematical analysis of the system of ODEs, focusing on the full time course and the rebound question is considered in [2] , which is primarily a theorem-proof paper, and uses invariant manifold theory, geometric analysis from dynamical systems, and heteroclinic orbits to give a comprehensive description of the rebound phenomenon

From the ODEs in the model, two expressions for the efficacy were obtained, in terms of the parameters of the problem, one of which is valid over the full range of values of the equilibrium dissociation constant K_D, and the other which is valid only for a large drug dose or for a small value of this constant. Both of these formulae show that the efficacy achieved by increasing the

association constant k_{on} can be very different from the efficacy achieved by decreasing the dissociation constant k_{off}. In particular, there is a saturation effect when decreasing the dissociation constant k_{off}, where the increase in efficacy that can be achieved is limited. There is no such effect when increasing the association constant k_{on}.

Thus, for certain monoclonal antibodies, an increase in efficacy may be better achieved by increasing the association constant k_{on} than by decreasing the dissociation constant k_{off}. This observation sheds new light on the drug-discovery process. The saturation of the dissociation constant k_{off} was an especially unpleasant surprise as that one is easier to manipulate and hence usually the focus of design trials.

While the efficacy question involved mainly the initial stages of the PKPD interaction of the monoclonal antibody with its antigen target, the rebound question involved the full time course. Rebound is a post-dose rise in receptor (antigen/cytokine) levels to higher than pre-dose (baseline). The mathematical research, which involved the study of four different parameter regions, showed that rebound can happen if and only if the elimination rate of the antibody-receptor complex is smaller than the elimination rates of both the antibody and the receptor on their own.

3. References to the research (indicative maximum of six references)

1. P.J. Aston, G. Derks, A. Raji, B.M. Agoram & P.H. van der Graaf ."*Mathematical analysis of the pharmacokinetic-pharmacodynamic (PKPD) behaviour of monoclonal antibodies predicting in-vivo potency*", J. Theoretical Biology 281, 113-121 (2011) doi: 10.1016/j.jtbi.2011.04.030.
2. P.J. Aston, G. Derks, B.M. Agoram & P.H. van der Graaf. "*A mathematical analysis of rebound in a target-mediated drug disposition model: I. Without feedback*", J. Mathematical Biology (published online April 2013) doi: 10.1007/s00285-013-0675-5.

The project was initially funded by a grant from the BioPharma Skills project, which was a joint initiative between the Universities of Surrey and Reading. It was funded by both universities as well as the Higher Education Funding Council for England's Economic Challenge Investment Fund (ECIF) and the South East England Development Agency (SEEDA). The BioPharma Skills project awarded an 11 month internship. The intern worked in 2010-2011 at the Pfizer offices with regular interaction with the Surrey team.

4. Details of the impact (indicative maximum 750 words)

The impact had five facets.

1. It affected a decision pathway at Pfizer: the research gave strong doubts into the viability of an on-going project and on this basis Pfizer decided to terminate this project and redeploy the resources elsewhere. This impact had clear financial implications, but Pfizer has not revealed the value.
2. Pfizer is part of a consortium in the US called the Centre for Protein Therapeutics (which also includes most of the other major pharmaceutical companies). The mathematical analysis, reported in the JTB paper, formed the basis for a proposal by Pfizer for an experimental project by this consortium. The proposal was ranked first out of all the proposals competing for funding in this consortium. The project aims to exploit the theoretical ideas by focusing on techniques to influence the association constant of proteins such as antibodies.
3. The impact has sector-wide implications as the major drug companies such as Pfizer are now aware of the importance of both the dissociation and the association constant in the efficacy of proteins and antibodies. As evidence of this secondary impact, a team at Bristol-Meyers Squibb Co in the USA, has adapted the analysis and simulation techniques from this project to their drug discovery process. They reported their results in one of the highest impact industrial

journals issued by the American Association of Pharmaceutical Scientists: Chimalakonda et al, Amer. Assoc. Pharma. Sci. J. (2013), doi: 10.1208/s12248-013-9477-3.

4. In the design of therapeutics, the question arose as to whether a longer half-life antibody would be more likely to cause rebound in antigen levels after treatment cessation. However, the rebound analysis showed that this was not the case, allowing the Pfizer project to move forward.
5. On a more general level, this project gave new confidence to the idea of using mathematical models as a guide in the early drug-discovery process to develop and identify the most promising candidates.

Pfizer stated;
"*As the pharmaceutical industry strives to improve decision-making at all stages of drug discovery and development, one aspect that has gained attention is the ability to make more objective decisions, especially at an early stage of projects, using quantitative tools. This collaboration is at the forefront of this shift in expectations. A key aspect of the mathematical analysis practiced by Dr Derks and Dr Aston is the ability to draw general conclusions about the "design property space" that is not suitable for a particular project – a conclusion that can elude a purely simulation-based analysis. While being elegant, this aspect has the hidden advantage of condensing a lot of information into simple outputs that can be more easily conveyed to a non-quantitative audience, and hence used in decision-making*. "

The principal impact occurred in the period 2011-2012, with research interaction continuing which will further the mathematical modelling of the discovery process in drug manufacturing. The team is currently working on part 2 of the rebound paper, in collaboration with a new industrial partner, MedImmune, the worldwide biologics research and development arm of the international biopharmaceutical company AstraZeneca, based in Cambridge. Further research and industry interaction: (a) a MMath placement student was embedded in Neusentis (a part of Pfizer) for 7 months in 2013, working on 2 compartment TMDD models; (b) an EPSRC-DTG PhD student will start in October 2013 under the supervision of Drs Aston and Derks, in collaboration with Pfizer (a new team at Pfizer), to work on the analysis of extended TMDD models; (c) funding is being sought for an academic-industry partnership in the area of ``Mechanistic Modelling of Biologics''.

5. Sources to corroborate the impact (indicative maximum of 10 references)

Corroboration has been obtained from the two principal scientists working on the project at Pfizer.

1. Director of Clinical Pharmacology/DMPK, MedImuune. Provided statement.
2. Principal Scientist, Academic Center for Drug Research, University of Leiden. Contact details provided.

In addition, a file with the evidence of the award by the BioPharma Skills project, and the outcome of the proposal to the Centre for Protein Therapeutics (including evidence of its top ranking) is available.