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Quantitative systems pharmacology modeling of biotherapeutics in oncology

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Section VI.
Appendices

Curriculum vitae

Alison Betts (1972, Edinburgh, Scotland) began her scientific career in 1990 at the University of St. Andrews in Scotland. She graduated in 1994 with a first-class honors degree in Biochemistry (BSc.) and was recipient of the class prize in Biochemistry. This course included an internship in an immunology research group at St. Andrews. In 1994, Alison moved from Scotland to the south of England to start her career at Pfizer in the department of Drug Metabolism. Here she gained extensive hands on experience of drug metabolism and pharmacokinetics and supported many small molecule drug discovery projects across diverse therapeutic areas.

From 2002-2004, Alison completed a secondment in the clinical pharmacometrics group at Pfizer. Here she learned the art and science of modeling, providing PK/PD support to the Pain research unit. In 2005, Alison joined the newly formed preclinical PK/PD group under the leadership of Dr. Piet van der Graaf. In this role she supported the Genitourinary and Obesity research units, using PK/PD modeling in the design and interpretation of experiments for small molecule drugs and performing PK and PK/PD predictions to human.

In September 2007, Alison moved to the USA with her family, to take up a new opportunity working in the Translational Modeling and Simulation (TMS) group in the department of Pharmacokinetics, Dynamics, and Metabolism (PDM) in Groton, CT. In this role, Alison had a diverse and extensive modeling career, supporting small and large molecule mathematical modeling across many research areas. Highlights included her role as TMS team leader supporting the antibacterial research group. In this role she was responsible for the successful execution of PK/PD modeling and translational strategy across the antibacterial portfolio including projects from exploratory stage through to Phase 1 clinical development. Here, Alison implemented mechanism-based PK/PD, PBPK and QSP models to predict efficacy and emergence of resistance and used these to develop novel strategies for clinical dose predictions of antibacterial drugs. In this work, Alison's team was awarded a Pfizer Leadership Team Excellence Award 2009. A particular focus was the establishment of *in vitro*: *in vivo* correlations so that *in vitro* models could be used to replace *in vivo* experiments. This work resulted in a reduction in *in vivo* animal spend by 40% and was awarded Pfizer Animal Care and Welfare Board 'Reduce, Re-use and Refine' award in 2010.

In 2010, Alison assumed responsibility as TMS team leader supporting the biotherapeutics division of the Oncology research unit at Pfizer. Alison's team supported a diversity of novel biotherapeutic modalities including proteins, peptides, antibodies, antibody drug conjugates (ADCs), bispecific antibodies, T cell engagers, cytokine conjugates and nanoparticles. Highlights of this work included providing modeling and simulation support to progress two ADCs to the market (Mylotarg® and Besponsa®) and many others to clinical studies. In this time, Alison was leader of the ADC working group at Pfizer, defining the quantitative analytical and predictive strategy for ADCs at Pfizer from preclinical stage through to clinical studies and she completed a

successful external partnership with Prof. Dane Wittrup's lab at the Koch Institute for Integrative Cancer Research, MIT to model intracellular trafficking of ADCs.

During this time, Alison became leader of the preclinical modeling and simulation discipline for the biotherapeutics division of PDM, including TMS teams in Cambridge MA, Groton CT and La Jolla CA. This included overseeing TMS support to Immunology & Inflammation, Oncology, Rare Diseases, Cardiovascular metabolic diseases, Neuroscience, and the Center for Therapeutic Innovation. Here she was responsible for leading scientific vision, defining strategy and for day-to-day process management of the group, including technical, infrastructure, resourcing (internal and outsourcing) and budgetary requirements. In this time, Alison's role and team transitioned from Groton, CT to Cambridge, MA.

In 2017, during her time at Pfizer, Alison started her PhD research on quantitative systems pharmacology modeling of biotherapeutic drugs in oncology at the Leiden Academic Centre for Drug Research (LACDR), under the supervision of Prof. dr. Piet H. van der Graaf. This gave Alison the opportunity to further explore her passions for using mechanistic modeling to enable quantitative decision making in oncology drug discovery, for preclinical to clinical translation, to optimize clinical dosing regimens and address precision medicine questions.

After 25 years at Pfizer, Alison started a new career path with Applied Biomath in 2019. Alison is Senior Director of Scientific Collaborations and Fellow of Modeling and Simulation at ABM, where she collaborates with partners to introduce mechanistic system pharmacology modeling approaches at preclinical and clinical stages to de-risk drug programs within the pharmaceutical and biotechnology industry. She maintains a hands-on approach as project leader for several modeling collaborations across therapeutic modalities. She is also recipient and Principal Investigator of an NIH SBIR Grant to build a platform QSP model for ADCs (ADC Workbench) capable of predicting efficacy and toxicity with the aim of reducing TI.

In her diverse and extensive modeling and simulation career, Alison has published 31 manuscripts and has given 40 invited presentations at conferences.

List of Publications

1. Spinosa, P., Musial-Siwek, M., Presler, M., **Betts, A.**, Rosentrater, E., Villali, J., Wille, L., Zhao, Y., McCaughy, T., Subramanian, K., & Liu, H. (2021). Quantitative modeling predicts competitive advantages of a next generation anti-NKG2A monoclonal antibody over monalizumab for the treatment of cancer. *CPT: pharmacometrics & systems pharmacology*, 10(3), 220–229. <https://doi.org/10.1002/psp4.12592>
2. Root, A.R., **Betts, A.**, et al. (2021). Discovery and optimization of a novel anti-GUCY2c x CD3 bispecific antibody for the treatment of solid tumors. *MABs*, 13(1):1850395. doi:10.1080/19420862.2020.1850395
3. **Betts, A.**, Clark, T., Jasper, P., Tolsma, J., van der Graaf, P. H., Graziani, E. I., Rosfjord, E., Sung, M., Ma, D., & Barletta, F. (2020). Use of translational modeling and simulation for quantitative comparison of PF-06804103, a new generation HER2 ADC, with Trastuzumab-DM1. *Journal of pharmacokinetics and pharmacodynamics*, 47(5), 513–526. <https://doi.org/10.1007/s10928-020-09702-3>
4. **Betts, A.**, & van der Graaf, P. H. (2020). Mechanistic Quantitative Pharmacology Strategies for the Early Clinical Development of Bispecific Antibodies in Oncology. *Clinical pharmacology and therapeutics*, 108(3), 528–541. <https://doi.org/10.1002/cpt.1961>
5. **Betts, A.**, Haddish-Berhane, N., Shah, D. K., van der Graaf, P. H., Barletta, F., King, L., Clark, T., Kamperschroer, C., Root, A., Hooper, A., & Chen, X. (2019). A Translational Quantitative Systems Pharmacology Model for CD3 Bispecific Molecules: Application to Quantify T Cell-Mediated Tumor Cell Killing by P-Cadherin LP DART®. *The AAPS journal*, 21(4), 66. <https://doi.org/10.1208/s12248-019-0332-z>
6. Jones, H. M., Zhang, Z., Jasper, P., Luo, H., Avery, L. B., King, L. E., Neubert, H., Barton, H. A., **Betts, A. M.**, & Webster, R. (2019). A Physiologically-Based Pharmacokinetic Model for the Prediction of Monoclonal Antibody Pharmacokinetics From In Vitro Data. *CPT: pharmacometrics & systems pharmacology*, 8(10), 738–747. <https://doi.org/10.1002/psp4.12461>
7. **Betts, A.**, Keunecke, A., van Steeg, T.J., van der Graaf, P.H., Avery, L.B., Jones, H., Berkhout, J. (2018) Linear pharmacokinetic parameters for monoclonal antibodies are similar within a species and across different pharmacological targets: A comparison between human, cynomolgus monkey and hFcRn Tg32 transgenic mouse using a population-modeling approach. *MABs*, 10(5):751-764. doi: 10.1080/19420862.2018.1462429.
8. Shah, D.K., Loganzo, F., Haddish-Berhane, N., Musto, S., Wald, H.S., Barletta, F., Lucas, J., Clark, T., Hansel, S., **Betts, A.**, (2018) Establishing in vitro-in vivo correlation for antibody drug conjugate efficacy: a PK/PD modeling approach. *J Pharmacokinetic Pharmacodyn*, 45(2):339-349 (ISSN: 1573-8744)
9. Damelin, M., **Betts, A.**, et al. (2017) A PTK7-targeted antibody-drug conjugate reduces tumor-initiating cells and induces sustained tumor regressions. *Sci Transl Med*, 9(372). doi: 10.1126/scitranslmed.aag2611.
10. **Betts, A.M.**, Haddish-Berhane, N., Tolsma, J., Jasper, P., King, L.E., Sun, Y., Chakrapani, S., Shor, B., Boni, J., Johnson, T.R. (2016) Preclinical to Clinical Translation of Antibody-Drug Conjugates Using PK/PD Modeling: a Retrospective Analysis of Inotuzumab Ozogamicin. *AAPS J.*, 18(5):1101-1116. doi: 10.1208/s12248-016-9929-7.
11. Chen, X., Haddish-Berhane, N., Moore, P., Clark, T., Yang, Y., Li, H., Xuan, D., Barton, H. A., **Betts, A. M.**, & Barletta, F. (2016) Mechanistic Projection of First-in-Human Dose for Bispecific Immunomodulatory P-Cadherin LP-DART: An Integrated PK/PD Modeling Approach. *Clinical pharmacology and therapeutics*, 100(3), 232–241. <https://doi.org/10.1002/cpt.393>

12. Maass, K. F., Kulkarni, C., **Betts, A. M.**, & Wittrup, K. D. (2016) Determination of Cellular Processing Rates for a Trastuzumab-Maytansinoid Antibody-Drug Conjugate (ADC) Highlights Key Parameters for ADC Design. *The AAPS journal*, 18(3), 635–646. <https://doi.org/10.1208/s12248-016-9892-3>
13. Singh, A. P., Maass, K. F., **Betts, A. M.**, Wittrup, K. D., Kulkarni, C., King, L. E., Khot, A., & Shah, D. K. (2016) Evolution of Antibody-Drug Conjugate Tumor Disposition Model to Predict Preclinical Tumor Pharmacokinetics of Trastuzumab-Emtansine (T-DM1). *The AAPS journal*, 18(4), 861–875. <https://doi.org/10.1208/s12248-016-9904-3>
14. Maass, K. F., Kulkarni, C., Quadir, M. A., Hammond, P. T., **Betts, A. M.**, & Wittrup, K. D. (2015) A Flow Cytometric Clonogenic Assay Reveals the Single-Cell Potency of Doxorubicin. *Journal of pharmaceutical sciences*, 104(12), 4409–4416. <https://doi.org/10.1002/jps.24631>
15. Singh, A. P., Krzyzanski, W., Martin, S. W., Weber, G., **Betts, A.**, Ahmad, A., Abraham, A., Zutshi, A., Lin, J., & Singh, P. (2015) Quantitative prediction of human pharmacokinetics for mAbs exhibiting target-mediated disposition. *The AAPS journal*, 17(2), 389–399. <https://doi.org/10.1208/s12248-014-9690-8>
16. **Alison M. Betts**, Oliver Ackaert, Kristin Bergmann, Nahor Haddish- Berhane, Jian Lin, Sharon Ripp, John O’Donnell, and Deb Hanna. ‘Use of a PK/PD Modeling and Simulation Approach to Predict Clinical Efficacy of Macrolide Antibiotics Telithromycin and PF-04287881 versus Streptococcus pneumonia’. In preparation.
17. Shah, D. K., King, L. E., Han, X., Wentland, J. A., Zhang, Y., Lucas, J., Haddish-Berhane, N., **Betts, A.**, & Leal, M. (2014). A priori prediction of tumor payload concentrations: preclinical case study with an auristatin-based anti-5T4 antibody-drug conjugate. *The AAPS journal*, 16(3), 452–463. <https://doi.org/10.1208/s12248-014-9576-9>
18. Sapra, P., **Betts, A.**, & Boni, J. (2013). Preclinical and clinical pharmacokinetic/pharmacodynamic considerations for antibody-drug conjugates. *Expert review of clinical pharmacology*, 6(5), 541–555. <https://doi.org/10.1586/17512433.2013.827405>
19. Shah, D. K., Barletta, F., **Betts, A.**, & Hansel, S. (2013). Key bioanalytical measurements for antibody-drug conjugate development: PK/PD modelers' perspective. *Bioanalysis*, 5(9), 989–992. <https://doi.org/10.4155/bio.13.78>
20. Haddish-Berhane, N., Shah, D. K., Ma, D., Leal, M., Gerber, H. P., Sapra, P., Barton, H. A., & **Betts, A. M.** (2013). On translation of antibody drug conjugates efficacy from mouse experimental tumors to the clinic: a PK/PD approach. *Journal of pharmacokinetics and pharmacodynamics*, 40(5), 557–571. <https://doi.org/10.1007/s10928-013-9329-9> Experimental Tumors to the Clinic: a PK/PD Approach’.
21. Shah, D. K., & **Betts, A. M.** (2013). Antibody biodistribution coefficients: inferring tissue concentrations of monoclonal antibodies based on the plasma concentrations in several preclinical species and human. *mAbs*, 5(2), 297–305. <https://doi.org/10.4161/mabs.23684>
22. Shah, D. K., Haddish-Berhane, N., & **Betts, A.** (2012). Bench to bedside translation of antibody drug conjugates using a multiscale mechanistic PK/PD model: a case study with brentuximab-vedotin. *Journal of pharmacokinetics and pharmacodynamics*, 39(6), 643–659. <https://doi.org/10.1007/s10928-012-9276-y>
23. Shah, D. K., & **Betts, A. M.** (2012). Towards a platform PBPK model to characterize the plasma and tissue disposition of monoclonal antibodies in preclinical species and human. *Journal of pharmacokinetics and pharmacodynamics*, 39(1), 67–86. <https://doi.org/10.1007/s10928-011-9232-2>
24. Attkins, N., **Betts, A.**, Hepworth, D., & Heatherington, A. C. (2010). Pharmacokinetics and elucidation of the rates and routes of N-glucuronidation of PF-592379, an oral dopamine 3 agonist in rat, dog, and human. *Xenobiotica; the fate of foreign compounds in biological systems*, 40(11), 730–742. <https://doi.org/10.3109/00498254.2010.514961>

25. **Betts, A. M.**, Clark, T. H., Yang, J., Treadway, J. L., Li, M., Giovanelli, M. A., Abdiche, Y., Stone, D. M., & Paralkar, V. M. (2010). The application of target information and preclinical pharmacokinetic/pharmacodynamic modeling in predicting clinical doses of a Dickkopf-1 antibody for osteoporosis. *The Journal of pharmacology and experimental therapeutics*, 333(1), 2–13. <https://doi.org/10.1124/jpet.109.164129>
26. Blasi, E., Bamberger, M., Knight, D., Engwall, M., Wolk, R., Winter, S., **Betts, A.**, John-Baptiste, A., & Keiser, J. (2009). Effects of CP-532,623 and torcetrapib, cholesteryl ester transfer protein inhibitors, on arterial blood pressure. *Journal of cardiovascular pharmacology*, 53(6), 507–516. <https://doi.org/10.1097/FJC.0b013e3181a8184c>
27. Mantell, S. J., Gibson, K. R., Osborne, S. A., Maw, G. N., Rees, H., Dodd, P. G., Greener, B., Harbottle, G. W., Million, W. A., Poinard, C., England, S., Carnell, P., **Betts, A. M.**, Monhemius, R., & Prime, R. L. (2009). In vitro and in vivo SAR of pyrido[3,4-d]pyrimidin-4-ylamine based mGluR1 antagonists. *Bioorganic & medicinal chemistry letters*, 19(8), 2190–2194. <https://doi.org/10.1016/j.bmcl.2009.02.106>
28. **Betts, A.**, Atkinson, F., Gardner, I., Fox, D., Webster, R., Beaumont, K., & Morgan, P. (2007). Impact of physicochemical and structural properties on the pharmacokinetics of a series of alpha1L-adrenoceptor antagonists. *Drug metabolism and disposition: the biological fate of chemicals*, 35(8), 1435–1445. <https://doi.org/10.1124/dmd.107.015180>
29. Harrison, A., **Betts, A.**, Fenner, K., Beaumont, K., Edgington, A., Roffey, S., Davis, J., Comby, P., & Morgan, P. (2004). Nonlinear oral pharmacokinetics of the alpha-antagonist 4-amino-5-(4-fluorophenyl)-6,7-dimethoxy-2-[4-(morpholinocarbonyl)-perhydro-1,4-diazepin-1-yl]quinoline in humans: use of preclinical data to rationalize clinical observations. *Drug metabolism and disposition: the biological fate of chemicals*, 32(2), 197–204. <https://doi.org/10.1124/dmd.32.2.197>
30. Beaumont, K., **Harper, A.**, Smith, D. A., & Abel, S. (2000). Pharmacokinetics and metabolism of a sulphamide NK2 antagonist in rat, dog and human. *Xenobiotica; the fate of foreign compounds in biological systems*, 30(6), 627–642. <https://doi.org/10.1080/004982500406453>
31. Beaumont, K., **Harper, A.**, Smith, D. A., & Bennett, J. (2000). The role of P-glycoprotein in determining the oral absorption and clearance of the NK2 antagonist, UK-224,671. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*, 12(1), 41–50. [https://doi.org/10.1016/s0928-0987\(00\)00144-5](https://doi.org/10.1016/s0928-0987(00)00144-5)

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Finally, this thesis is dedicated to and inspired by my mother, Susan Harper, who died of metastatic breast cancer at the age of just 50. In her abbreviated time on this earth, she achieved a lot and has been a continuous source of inspiration. Working in cancer research has been an honor and a privilege, and this thesis is dedicated to her memory.

Thank you,

Alison