Dose selection rationale for type 1 interferon neutralizing antibody
Project leader: Dr Timothy Nicholas

Background:

Type 1 interferons (α/β) have been suggested as key cytokines in autoimmune diseases (Higgs 2011, Kiefer 2012, Theofilopoulos 2005). These cytokines exert a myriad of effects on the development and function of both B and T lymphocytes. A selective humanized immunoglobulin G1 (IgG1) neutralizing antibody targeting human soluble interferon-alpha (IFNa) is being developed for the treatment of autoimmune disorders such as systemic lupus erythematosus (SLE). Other examples have been shown in which IFNa modulation has impacted IFN gene signatures (Wang 2013).

As part of early clinical development, data have been collected on the drug concentrations in plasma and IFNa modulation. Additionally, data from a proprietary genetic signature, characterizing type 1 IFN activity have become available. To note, the data provided for this workshop are simulated for proprietary reasons. Target-mediated drug disposition (TMDD) occurs in cases in which a drug binds with high affinity to a receptor, enzyme, or other ligand and may show nonlinear pharmacokinetic (PK) behavior (Mager 2001). TMDD has become common in the development of biologic drugs and a series of models have been proposed (Mager 2001, Gibiansky 2008). The type 1 IFN neutralizing monoclonal being developed is expected to be described by TMDD related PK and pharmacodynamics (PD).

A clinical study in SLE with this drug is being proposed and a rationale for the dosing regimen is required.

Objectives:

1. Assess relationship between novel drug and IFNa concentrations (PKPD model).
2. Assess relationship between novel drug and gene signature (expanded PKPD model).
3. Provide dosing rationale for next clinical study in SLE (simulations based on models).

References:

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Response threshold analysis in exposure-response and pharmacogenetictranslational applications
Project leader: Dr Bart Borek

This problem essentially involves finding a threshold for responsiveness across two variables related in some non-linear fashion. It can arise in several pharmacological contexts, which can have distinct implications for QSP modeling. We will explore this in two contexts: exposure-response modeling, and translational modeling informed by pharmacogenetic variation. There are four main parts to the problem, outlined below:

1) R code will be provided including a simulated dataset, example structural model fitting script, and response threshold calculation script. If the data represents exposure-response, what questions could this analysis begin to answer in the context of drug discovery and development?

2) As we ”warm up” in part 1) let’s formally explore functional assumptions/constraints/cases around estimating a threshold for responsiveness. Please derive (analytically or via simulation) confidence or prediction intervals around the response threshold in part 1).

3) Please code and fit the translational main pharmacogenetic dataset from the Benjamin, *et al.* Paper [1]. Treat the in vitro GLP HEK assay outputs as the exposure variable, and the in vivo alpha-GALa as the response variable. What assumptions did you make in estimating threshold for responsiveness in this context? How does your threshold compare to their amenability criteria? Can you predict response of a virtual population of patients with mutations in the study? Is the known prevalence of mutations different than in the study? What other questions could this analysis inform in the context of drug discovery and development?

4) How could response threshold analyses in the two aforementioned applications(exposure response and pharmacogenetic translation) be used to inform QSP modeling efforts? Feel free to discuss this in the context of any particular therapeutic area, or across all of them.

Reference:

1. Benjamin ER, Della Valle MC, Wu X, Katz E, Pruthi F, Bond S, Bronfin B, Williams H, Yu J, Bichet DG, Germain DP, Giugliani R, Hughes D, Schiffmann R, Wilcox WR, Desnick RJ, Kirk J, Barth J, Barlow C, Valenzano KJ, Castelli J, Lockhart DJ. The validation of pharmacogenetics for the identification of Fabry patients to be treated with migalastat. *Genet Med; 19(4):430-438.* 2017. https://www.ncbi.nlm.nih.gov/pubmed/27657681

Cardiovascular QSP Modeling: Virtual Ventricular Cell Case Study
Project co-leaders: Dr Anna Kirpichnikova and Dr Anna Sher

Project description: QSP provides a mechanistic description of a biological system of interest and the effect of drug treatment on system behavior [1]. Some widely used methods/approaches in QSP include parameter sensitivity, model emulation and virtual patient generation and selection studies [2-6]. This project will focus on a cardiovascular case study, specifically on identifying efficacious and safe electrophysiological targets in chronic heart failure [7]. For instance, dysregulation of the sarco(endo)plasmic reticulum calcium ATPase (SERCA2a) function has been implicated in the pathology of heart failure and clinical trials utilized the approach of restoring SERCA2a activity in humans. Yet, the underlying mechanisms of chronic heart failure are still poorly understood. Moreover, heart failure is known to be associated with higher risk of onset of ventricular arrhythmias. Workshop participants will perform simulation studies to analyze one of the existing human ventricular myocyte models [8-10] and to identify efficacious and safe electrophysiological targets in failing cardiomyocytes [11-12] either by helping to gain confidence in the rationale of existing and/or emerging targets or proposing novel heart failure targets.

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Immuno-oncology: Evaluating Strategies for overcoming rituximab resistance via modulation of Antibody-Dependent Cell-mediated Cytotoxicity & Phagocytosis (ADCC & ADCP)

Project leader: Dr Dean Bottino

While the recent successes of immune checkpoint inhibitors have underscored the importance of the adaptive immune system in treating cancer, the innate immune system has been exploited for many years using anti-CD20 antibodies such as rituximab (R) for treating $CD20^+$ cancers such as Non-Hodgkins Lymphoma (NHL). One of the proposed mechanisms of action (MoA) of Rituximab is to coat (opsonize) $CD20^+$ cells, at which point natural killer (NK) cells and macrophages (MP) bind to R's Fc domain via their FcgRIII receptors (AKA CD16). Upon sufficient crosslinking the NK cells release cytotoxic agents to perform ADCC, or alternatively, MPs engulf the target cells to perform ADCP.

Despite the impressive performance of R-containing regimens like R-CHOP in $CD20^+$ NHL, 30-60% of R-naïve NHL patients are estimated to be resistant to rituximab, and approximately 60% of those patients will not respond to subsequent single agent R treatment.[1] Increasing the activation level and/or CD16 expression of NK and MP cells may be one strategy for overcoming R resistance.

In the proposed project, participants will develop and calibrate to literature data[23456789] a quantitative systems pharmacology (QSP) model and -- time and data permitting -- a stochastic differential equation (SDE) based model of ADCC/ADCP to address key questions regarding overcoming R resistance such as:

- Which mechanisms of R resistance[10] could be overcome by increased NK or MP activation and/or increased expression of CD16 by NK and MP cells?
- For example, in the case of CD20 loss as mechanism of resistance, can increasing NK or MP expression of CD16 overcome partial CD20 loss, and if so, how much CD16 increase is required to overcome a given level of CD20 loss?
- Some patients have a single-nucleotide polymorphism (SNP) that decreases the affinity of CD16 to the Fc domain of R, potentially diminishing ADCC and therefore R efficacy. What is the relationship of CD16:Fc affinity to ADCC, and to what extent can it be overcome by increasing CD16 expression?
- How sensitive is ADCC to effector:target (E:T) cell ratio compared to other model parameters?
- Flow cytometry can be used to estimate the CD16 or CD20 expression levels in tens of thousands of individual effector or tumor cells in each clinical blood or tumor sample. Is this statistical distribution of CD20 levels among tumor cells and CD16 levels among effector (NK & MP) cells in the patient important for predicting ADCC potential, or do frequently used summary measures like median fluorescence intensity (MFI) and percent of cells above a threshold (% positive) suffice (and if so, which one)?

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[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3113665/pdf/nihms289495.pdf
[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4254685/pdf/nihms621468.pdf
[3] https://www.jstage.jst.go.jp/article/jslrt/56/2/56_89/_pdf/-char/ja
[4] http://jcb.rupress.org/content/217/9/3267/tab-pdf
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