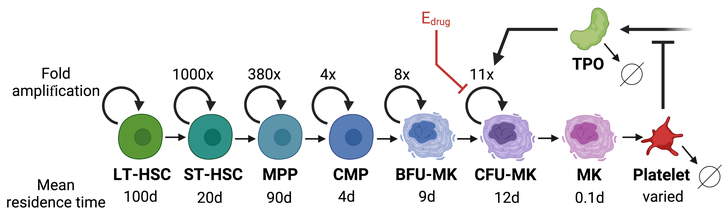
A mechanistic model of ADC-induced thrombocytopenia for predicting therapeutic index

Kimiko McGirr[1], Tracy Kuper[2], Max Nowak[1], Bruna Scheuher[1], Kas Subramanian[1], Joshua F. Apgar[1] and Alison Betts[1]
[1]Applied BioMath, 561 Virginia Road, Suite 220, Concord MA 01742
[2]Department of Chemical Engineering, University of Virginia

BACKGROUND

- Off-target **hematotoxicity** has been reported in the clinic for many antibody-drug conjugates (ADCs); toxicity can limit the maximum tolerated dose in the clinic.
- A **mechanistic model** of hematopoiesis was developed to describe **thrombopoiesis** post Trastuzumab-emtansine (T-DM1) administration, but *could be generalized to other hematopoietic diseases and other therapeutics.*
- **Combining efficacy and toxicity models allows us to explore common therapeutic metrics**, such as therapeutic window and indexes.

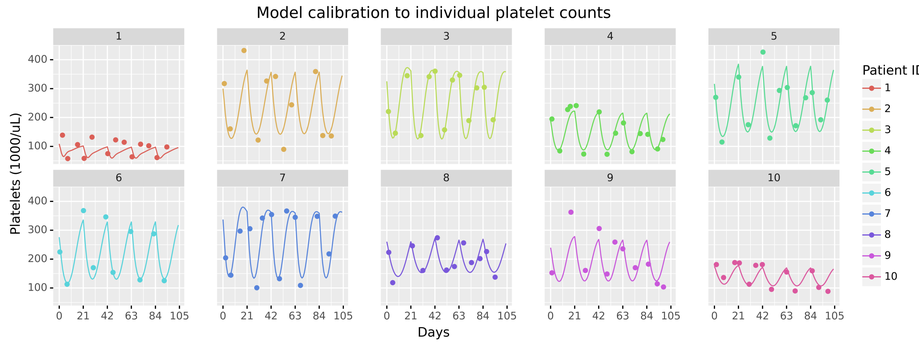
MODEL DIAGRAM



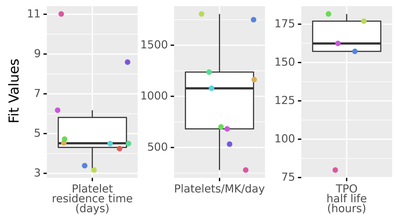
The TCP model contains:

1. **Stem cell to platelet differentiation**
   a. Long and Short Term-Hematopoietic Stem Cells (**LT-HSC** and **ST-HSC**), Multi-Potent Progenitor cells (**MPP**), Common Myeloid Progenitor cells (**CMP**), Burst and Colony Forming Unit Megakaryocyte (**BFU-MK** and **CFU-MK**) can expand (fold amplification) or differentiate (driven by mean residence time). Original structure and values were adapted from *Zheng et. al. (2021).*
   b. Megakaryocytes (**MK**) produce platelets (rate of Platelets/MK/day) and die (not pictured).
   c. **Platelets** can die at a rate determined by the platelet residence time which varied depending on the individual (3 to 11 days). Increased number of platelets reduces the number of TPO.
2. **Thrombopoietin** (**TPO**) tunes the expansion of the CFU-MKs. When platelets are low, TPO can accumulate, amplifying the number of CFU-MKs. This produces the inverse relationship between TPO and platelet count.
3. **Concentration of ADC** in the central compartment ($\mathbf{E_{drug}}$) reduces expansion and kills CFU-MK cells.

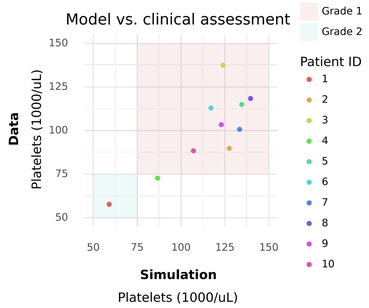
MODEL CALIBRATION & POPULATION BOOTSTRAPPING



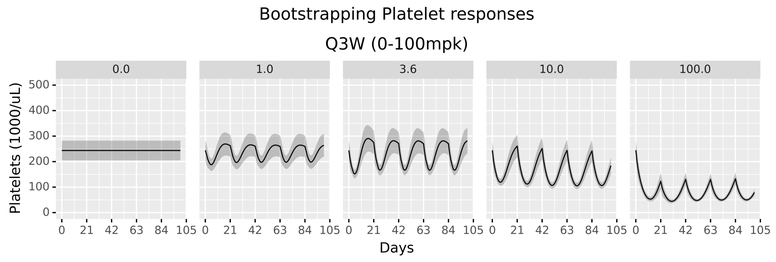
The model was calibrated to **10 individual patients' platelet time series data (3.6 mpk Q3W)** within the first 100 days in a Phase I study of T-DM1 (digitized from *Krop et al. 2010*). A drug effect parameter was globally fit while three other parameters were calibrated to match individual platelet oscillations (see figure below). Model results are generally consistent with the platelet levels and dynamics seen in each individual patient.



Three model parameters were calibrated to observe different patient's platelet response (parameter values plotted in points with color corresponding to a patient ID). Plots without patient values indicate that those values were fixed to nominal values (Platelet residence time = 4 days, Platelets/MK/day = 450, TPO half life = 24 hours) for identifiability.



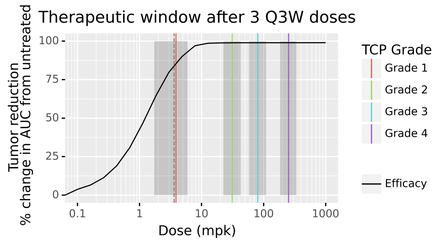
TCP grade (blue and red boxes) was assigned to patient data (y-axis) and simulation (x-axis) based on the minimal platelet level. **9 out of 10 simulated patient responses were assigned the correct TCP grade** (points within colored boxes).



Non-parametric bootstrapping was performed on individual patient simulations at a range of different dose levels Q3W. Average platelet response is plotted (line) with 95% CI of the mean (shaded region).

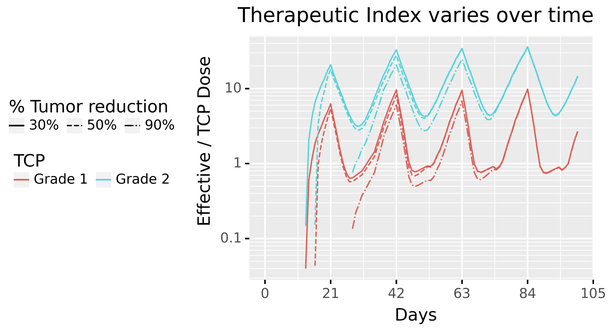
Platelet rebound occurs at low doses but is not observed as T_{trough} is delayed at higher doses.

PREDICTING THERAPEUTIC INDEX



- Efficacy (black line) is defined as the percent tumor reduction in AUC from the untreated control after 63 days.
- Bootstrapped simulations determined the average dose eliciting TCP (95% CI of the mean shaded in gray).
- MTD for T-DM1 (gray dashed line) is 3.6 mpk Q3W.

A nominal patient will experience mild but not severe TCP at the clinical dose.



- TI was simulated as the dose required for a specific target percentage reduction (from baseline) of tumor (different line types) divided by the dose eliciting a particular grade of TCP (separate colors).
- Trough TI values are particularly driven by the timing of the platelet oscillations. TI values converge as dosing sensitivity is compounded over time.

Because TI can vary over time, it is important to select particular time points for efficacy and toxicity measurements.

CONCLUSIONS & FUTURE DIRECTIONS

Conclusions:

- A mechanistic model of hematopoiesis can simulate platelet dynamics in response to therapeutics using *parameters informed by biological measurements*. This model performed just as well as the typical semi-mechanistic "*Friberg*" model (not shown).
- Therapeutic windows can be predicted by combining efficacy and toxicity models, which can be *used to explore different outputs that act on different time scales*.
- While T-DM1 has a high TI index , the *TI value can range over an order of magnitude when observing TI over time*.

The model is built so that different drug effect mechanisms can be included, and other drug parameters (deconjugation rate, DAR, ADC half life) can be explored.

Next Steps:

- Create a virtual population of patients to identify subpopulations that could benefit from fractionated or alternative dosing regimens.
- **Validate model on larger datasets** (hundreds to thousands of patients)
- Assess the model's ability to scale from **in vitro → cyno → human**.