Objective

- To develop an efficient methodology to identify the best drug combinations to be administered to patients with acute myeloid leukemia based on ex-vivo response vs exposure experiments
- Not for dose-selection (so far)
- Compute subject’s specific descriptors to correlate with clinical outcome

Strategy for Data Analysis & Results

Workflow

- PD modelling of data from monotherapy
- Population approach with NONMEM 7.2
- All model parameters associated to inter-patient variability
- No covariate effects were explored
- PD model used to describe response vs exposure
- Steady-state conditions were assumed

$$E = E_0 \times \left( 1 - I_{w,e} \times \frac{C^m}{C + IC_{50}} \right)$$

- Select a set of effect magnitudes
  - 20, 40, 60, 80% decrease in malignant cells with respect to baseline
  - Identify for each subject the corresponding concentration pair
  - Non-modelling step using raw data from drug combination

- For each drug get access to the variance-covariance matrix for each individual set of PD parameters obtained from the popPD analysis in monotherapy
- Create (simulate) for each patient 1000 sets of PD parameters
- Calculate the concentration (C) that elicits a response equal to the response to the combination for each set of simulated parameters & pre-defined effect magnitude & studied drug
- Calculate the 95% PI of CA and CB
- Generate the isologogram
- Calculate the combination index
- Using the 2.5th percentile of each C
  - Allows characterization of the interaction
  - Additional descriptor to correlate with clinical response

- Summarize the isologogram using color maps to better interpret results and decision making about the choice of the drug combination

Studied Population & Methodology

- Seventy adult patients diagnosed with de novo AML
- Marrow samples were collected at diagnosis, sent to the laboratory, and incubated for 48 hours in well plates containing single drugs [Cytarabine (cyt), Idarubicin (ida)] or combinations of the two drugs
- Cyt (μM) = 0, 0.039, 0.156, 0.625, 2.5 & 10
- Idia (μM) = 0.0039, 0.0156, 0.0625, 0.25 & 1
- Cyt & Idia = 0.039/0.0039, 0.156/0.0156, 0.625/0.0625
  - 2.5/0.25, 10/1
- Annexin V-FITC was used to quantify the drug-induced apoptosis
- Response measured was number of malignant cells alive

![Graph showing predicted response vs concentration for different drug combinations]

Conclusions

- We present an efficient methodology to characterize the type of drug interaction for individualize treatments
- Modelling is limited to data obtained from monotherapy avoiding the use of PD models for drug interactions and estimating interaction parameters