In Silico Modeling Can Predict the Unforeseen Renal Failure Caused by SGX523, a c-MET Kinase Inhibitor

Abstract Number 753

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Introduction

- SGX523 is a quinoline containing, c-MET kinase inhibitor with an IC_{50} of 4 nM (Buchanan SG et al., 2009)
  - Inhibited the growth of human glioblastoma lung and gastric cancer xenografts in mice
- In a Phase 1 clinical trial, all six patients that received an 80 mg dose developed renal failure (Infante JR et al., 2013)
- Follow-up studies revealed that the cause of renal toxicity was drug-induced nephropathy due to a metabolite of SGX523 that was not detected in preclinical studies (Diamond S et al., 2010)
  - Aldehyde oxidase (AOX) transforms the quinoline ring into a quinolinone
  - Generation of the quinolinone metabolite (M11) is species-dependent
    - Formed in human and monkey liver S-9 but not in dog S-9 incubations
- We used predicted properties as inputs to PBPK simulations in order to predict the toxicokinetics of SGX523 and M11

Methodology

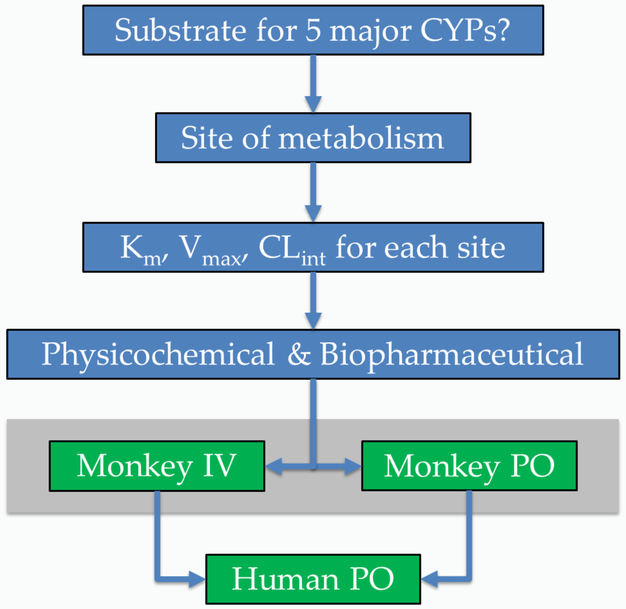


Figure 1 – Blue boxes represent predictions from artificial neural network ensemble (ANNE) models (ADMET Predictor™). Green boxes represent PBPK simulations (GastroPlus™). PBPK simulations for cynomolgus monkey were used to validate the model by comparison to sparse PK data.

SGX523 Metabolism

SGX523 Metabolites in Monkey (Diamond S et al., 2010)

- Primary metabolites
  - N-desmethyl (M5)
  - Monooxygenation (M6 and M9)
  - 2-quinolinone-SGX523 (M11)
- Secondary metabolites
  - N-desmethyl monooxygenation (M3)
  - Dioxygenation (M4)
  - N-desmethyl 2-quinolinone-SGX523 (M8)

Color code
Red – NADPH-dependent
Green – NADPH-independent
Blue - Both

Predicted Metabolites

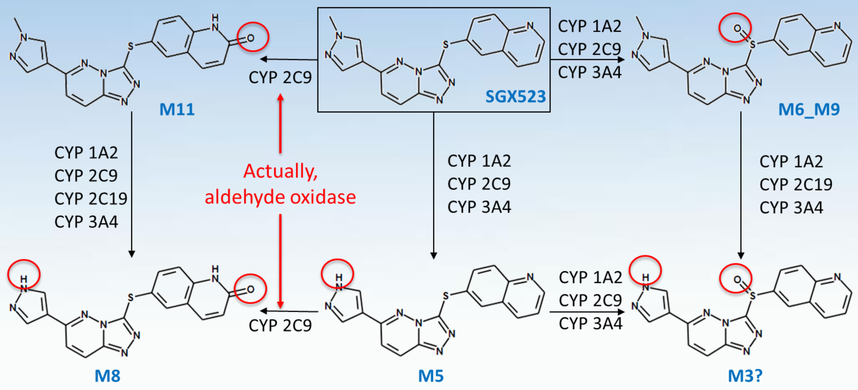


Figure 2 – SGX523 is predicted to be a substrate for CYP 1A2, 2C9, and 3A4 but not a substrate for CYP 2A6, 2B6, 2C8, 2C19, 2D6, and 2E1. The sulfoxide labeled M6_M9, above, could be either one of the reported monooxygenase products M6 or M9. The desmethyl product, M5 above, is formed from hydroxylation of the methyl group and creates an unstable intermediate that decomposes to M5 and formaldehyde. We predict that CYP 2C9 hydroxylates the C-2 carbon of the quinoline ring and tautomerizes to the lactam, M11. However, the predicted CL_{int} is very low as shown in Figure 3.

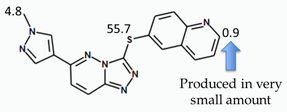
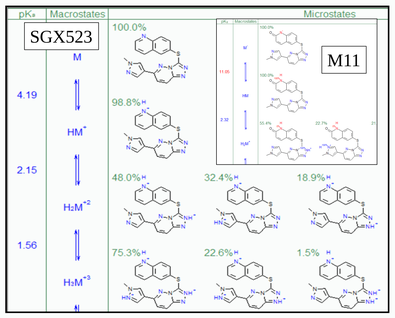


Figure 3 – Predicted CL_{int} [µL/min/mg microsomal protein] values for the 3 sites of metabolism.

Physicochemical & Biopharmaceutical Predictions

Model	Description	SGX523	M3	M5	M6_M9	M8	M11
S+logP	logP	3.0	1.6	3.1	1.4	2.8	2.7
S+Basic_pKa	quinoline nitrogen	4.2	3.8	4.1	3.8	-	-
S+Sw [µg/mL]	solubility in pure water	2.5	184	0.62	629	0.16	0.56
S+Peff [x10^4 cm/s]	human jejunal permeability	4.6	1.8	3.1	2.8	2.7	3.8
S+PrUnbnd	% unbound in plasma	3.9%	7.9%	3.9%	8.8%	3.6%	3.7%
S+RBP	blood to plasma concentration ratio	0.9	1.0	0.9	1.0	0.7	0.7



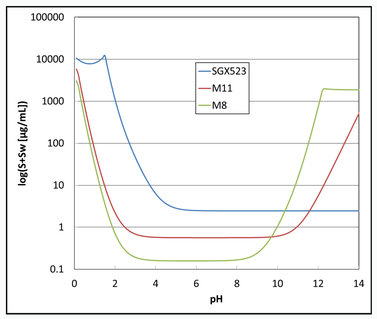


Figure 4 – Left image: predicted microstates and pK_a's of SGX523 and M11 (inset). Right image: predicted aqueous solubility (log scale) versus pH for SGX523, M8, and M11.

Cynomolgus Monkey PBPK Simulations

- Assumed parent is only cleared by AO enzyme in the liver
- AO enzyme level in liver from experimental data (Fu C et al., 2013)
- V_{max} = 140 nmol/min/mg protein for AO enzyme (Diamond S et al., 2010); assumed unbound
- Predicted K_m for CYP 2C9 was used for the AO enzyme
- Used Fup*GFR to calculate amount in urine for parent

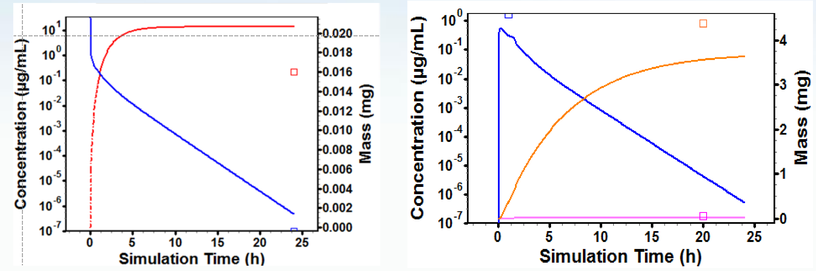


Figure 5 – Left image: IV bolus (1.6 mg/kg). Blue line is plasma concentration of SGX523. Red line is amount of SGX523 in urine versus time. Red square corresponds to experimental amount of dose excreted intact (0.2%) in urine. Predicted V_d = 6.24 L versus observed value of 3.25 L. **Graph on right** is PO (6.2 mg/kg). Blue line is plasma concentration versus time for SGX523. Orange line is amount of M11 in urine versus time. Orange square is experimental amount of M11. The renal filtration clearance was adjusted to match the experimental point.

Human PBPK Simulation

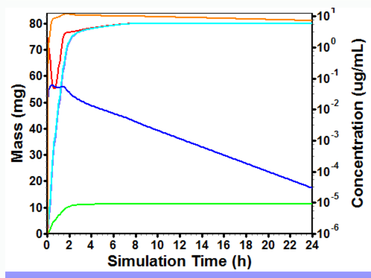


Figure 6 – Absorption and dissolution plots for an 80 mg PO dose of SGX523. Orange line is concentration (axis on right) of M11 in kidney tubule.

Conclusions

Oxidative metabolism results in conversion of the basic quinoline (predicted pK_a of 4.2) in SGX523 to an acidic lactam with a predicted pK_a of 11.0. This also results in decreased aqueous solubility; the predicted solubility drops from 2.5 µg/mL in SGX523 (obs. = 5.4) to 0.56 µg/mL in M11 (obs. = 0.13). Our PBPK simulations show high concentrations of M11 in the lumen of the kidney, beyond its solubility, creating the probability of precipitation. Thus, our in silico analysis predicts the observed renal toxicity in humans and monkeys due to crystallization of the metabolite in the kidney.

References

ADMET Predictor 7.2, Simulations Plus, Inc. Lancaster CA
Buchanan SG et al. (**2009**) *Mol Cancer Ther* 8:3181-3190.
Diamond S et al. (**2010**) *Drug Metab. Dispos.* **38**:1277-1285.
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