An Integrated Approach to Evaluate the Risk of pH-Dependent Drug-Drug Interactions of Molecular Targeted Agents

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Oncology Drug Development Challenges

• Despite significant progress in the understanding of genetic determinants of cancer, only 1 in 10 oncology molecules that entered phase III drug trials from 2004-2009 were approved by the FDA.

• The therapeutic index for many molecular-targeted agents is quite narrow.
  – MTD approach to determine dose and schedule versus exposure-driven cancer biological response.
  – A “personalized” approach is needed to define optimal dose and schedule to achieve maximal efficacy with an acceptable safety profile.

• Each Cancer patient represents a ‘special population’.
  – Cancer patients may take up to 12-20 concomitant medications + multiple complimentary alternative medicines.
  – Some cancer patients develop liver metastasis or have had significant gastric surgery.
Sources of PK Variability

Intrinsic (Host Dependent)
- Disease
- Age, Gender, Ethnicity
- Special populations and PGx
- Ethnic differences in hypochlorhydria (Japanese ~ 60%, European ~ 10%; H.pylori is known to cause hypochlorhydria)
- DME and Transporter polymorphisms

Physicochemical and CMC Properties
Biopharmaceutical
- Solubility, permeability, pKa
- Tablet compression, coating and matrix
- Excipients
- Particle size

Extrinsic Factors
Environment
- Drug-Drug Interaction (DDI)
  - pH-dependent absorption
  - Drug Metabolism and Drug Transport
- Food-effect
- Patient Compliance

Lapatinib Food-Effect: Value of an Egg McMuffin

<table>
<thead>
<tr>
<th>Breakfast</th>
<th>AUC0-inf GMR 90% CI</th>
<th>Cmax GMR 90% CI</th>
</tr>
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<tbody>
<tr>
<td>Low Fat</td>
<td>2.67 (2.16-3.16)</td>
<td>2.42 (2.02-2.90)</td>
</tr>
<tr>
<td>High Fat</td>
<td>4.25 (3.60-5.02)</td>
<td>3.03 (2.53-3.63)</td>
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JCO March 10, 2009
Influence of pH-dependent Solubility on Maximum Absorbable Dose (MAD) of a Weakly Basic Drug or NME

Many Molecular Targeted Agents Display pH-dependent Solubility

- Approximately 50-70% of recently approved orally administered targeted cancer therapies display pH-dependent solubility.

- We hypothesize that a decrease in the overall exposure of an orally administered cancer therapy may occur due to concomitant ARA use and this could lead to compromised efficacy and overall patient outcomes.

Budha et al., CPT Aug, 2012
### Impact on Labeling of Molecular Targeted Agents

- **Dasatinib (Sprycel®):** Avoid PPIs and H2RAs
- **Erlotinib (Tarceva®):** Avoid PPIs and time stagger H2RAs
- **Idelalisib (CAL101, Zydelig®):** nothing Stated about PK interaction in label, however, more diarrhea and rash were observed in patients taking idelalisib with PPIs (FDA Office Director Summary Review NDA 206545)

### High Prevalence of Acid-Reducing Agent (ARA) Use in Patients with Cancer: Potential Impact of PPIs on PK of Orally Administered Drugs

- Altered gastric pH is known to impair drug absorption of many weakly basic drugs
- To alleviate symptoms of GERD, dyspepsia, and gastritis, cancer patients frequently use ARAs such as PPIs, H2RAs, and antacids, of which PPIs are the most effective
  - ~15-60% of Cancer Patients report using acid-reducing agents during their cancer treatment

FDA Decision Tree for Weak Base Drugs

Points to Consider for Timing of a Clinical ARA Assessment

- Is solubility poor?
- Is solubility pH-dependent?
- Is dose high?
- Is therapeutic index narrow?
- Does PBPK modeling suggest an impact of PPI?
- Can PopPK modeling describe PK in HV and Cancer pts?

Example ARA Assessment Strategy

Example ARA Assessment Decision Tree

Period 1
Period 2
Period 3

A
B
C
B
A
C
B

Positive
Negative

No additional studies; worst case has been evaluated

Further evaluate ARA impact:
- H2RAs or antacids
- Time-staggered dosing

Conduct a clinical PPI-DDI assessment early

Evaluate need for a study during development or post-approval
Proton Pump Inhibitor (PPI) Pharmacology (aka “Nexium Nation”)

- All PPI’s are substituted benzimidazoles.
  - Undergo chemical activation within parietal cell.
  - Only active parietal cells are inhibited (approximately 70-80% following meal).
  - Maximum inhibition at 3-4 days.

- Activated molecule irreversibly inhibits Proton Pump (H⁺/K⁺ ATPase).
  - Long off rate (up to 1 week to wash out).
  - Rebound acid hypersecretion when PPI’s are discontinued.

- H₂-receptor antagonists (H₂RA) competitively inhibit and wash out quickly.

- Altered intestinal pH is known to impair drug absorption and has been reported in multiple therapeutic areas (CV, anti-viral, and oncology).

Omeprazole

GDC-0941 Physicochemical Properties

BCS: Class 2 (Low Solubility/High Permeability)

MDCK permeability (A to B): 10 x 10⁻⁶ cm/s

Log P: 3.22 ± 0.22

pKa: 1.54 (basic), 4.24 (basic)

Solid form: Crystalline salt

pH-solubility:
- pH 1: 0.75 mg/mL
- pH 4.4: < 0.001 mg/mL
- Simulated gastric fluid (SGF, pH 1.2): 0.25 mg/mL
- Fasted state simulated intestinal fluid (FaSSIF, pH 6.8): < 0.001 mg/mL

D:S ratio = 100L

Gena Dalziel, Jack Pellet, and Laurent Salphati Mol Pharmaceutics 2013
The phosphoinositide 3-kinase (PI3K) signaling pathway is deregulated in a wide variety of cancers. GDC-0941 is a potent and selective pan-inhibitor of class I PI3K. It demonstrates excellent in vivo activity in tumor xenograft models and is currently in clinical drug development.

- GDC-0941 is in multiple clinical trials for various cancers (e.g. BC, mBC, NSCLC).
- GDC-0941 displays linear PK from 15-450 mg. Based on its physicochemical properties – high permeability and poor solubility at physiologically relevant pH values (4 – 7.5), GDC-0941 classifies as BCS class II drug.

### Rabeprazole Significantly Reduces GDC-0941 AUC and Cmax in Fasted or Fed State

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cmax GMR (90% CI)</th>
<th>AUC0-∞ GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High fat meal</td>
<td>0.87 (0.70, 1.06)</td>
<td>1.28 (1.08, 1.51)</td>
</tr>
<tr>
<td>PPI fasting</td>
<td>0.31 (0.21, 0.46)</td>
<td>0.46 (0.35, 0.61)</td>
</tr>
<tr>
<td>PPI + high fat meal</td>
<td>0.43 (0.37, 0.50)</td>
<td>0.57 (0.50, 0.65)</td>
</tr>
</tbody>
</table>
PBPK approach to evaluate the impact of food and gastric pH on the pharmacokinetics of GDC-0941

Stomach emptying does not occur until its contents reach pH around 2~4

- The PK of fasted group could be well-predicted using default fasted physiology, with longer stomach transit time and precipitation time, indicating that GDC-0941 forms supersaturated solution in the stomach and small intestine. Increased STT and Long Tprecip (90000s) needed to account for the supersaturation tendency of GDC-0941.

Population PK (PopPK) of GDC-0941
Healthy Volunteer Data

- PopPK analysis suggested a decrease of absorption rate constant and an increase of relative bioavailability with food, regardless of PPI, and also suggested a decreased relative bioavailability by PPI, regardless of food.
PopPK Model Describes Impact of Gastric pH and Food on GDC-0941 Absorption Variability: Relative Bioavailability (F) and Absorption Rate Constant (Ka)

- Impact of pH and Food on F and Ka for each period
  - pH is major driver of GDC-0941 absorption variability
  - Food ('Standard FDA meal' High Fat/Protein)

Summary of PBPK and PopPK

**PBPK**
- PBPK modeling was conducted for group mean and individuals using GastroPlus v. 8.5 with the goal to understand the impact of pH and food on the PK of GDC-0941.
- As a weak base with pKa values of 4.2 and 1.5, GDC-0941 belongs to the group of compounds with solubility-limited absorption and supersaturation tendency
- The PK of fasted group could be well-predicted using default fasted physiology parameters with Longer Tprecip (90000s) to account for the supersaturation tendency of GDC-0941
- The PBPK approach provided mechanistic explanation for different absorption rate and bioavailability under different physiological conditions

**PopPK**
- Two-compartment model with first-order absorption with lag time (Tlag) and first-order elimination from the central compartment.
- PopPK analysis suggested a decrease of absorption rate constant and a increase of relative bioavailability with food, regardless of PPI; and also suggested a decreased relative bioavailability by PPI, regardless of food.
- Model translation from healthy volunteer to oncology setting is currently underway.
  - Dose
  - Formulation
  - Conmeds as covariates
Mitigation Strategies
PPI and H2RA pH-dependent Interactions with Erlotinib: ‘Time-Staggering Approach’

- Omeprazole 40 mg QD reduces erlotinib AUC (46%) and Cmax (61%).
- Co-administration with ranitidine decreases erlotinib bioavailability. However, the effect can be minimized by time-staggered dosing of ranitidine 150 mg BID (10 hrs before/2hrs after).

Re-acidification as a Mitigation Strategy to overcome pharmacological-induced hypochlorhydria

- Acidic Beverages
  - Coke
  - Sprite
  - Ginger ale
  - Crystal Lite

- “Digestive aids”
  - Glutamic Acid (Acidulin®)
  - Betaine HCl (BHCl)
  - Betaine Citrate

Coke pH 2.5, H+ =0.79 mmol
BHCl pH 1.71, H+ =9.7 mmol (2 × 750 mg tablets)
pH-modulation in Canine Model: Influence of Pentagastrin and Famotidine Pretreatment on GDC-0941 Exposure

T=0, GDC-0941 administration

<table>
<thead>
<tr>
<th>Compound</th>
<th>Treatment</th>
<th>AUC_{last} (µM•hr)</th>
<th>C_{max} (µM)</th>
<th>T_{max} (hr)</th>
<th>\text{FF}</th>
<th>C_{max} (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDC-0941</td>
<td>2x20 mg tab</td>
<td>11.8</td>
<td>1.83</td>
<td>2.00</td>
<td>6 -fold</td>
<td>9.1</td>
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<tr>
<td>Dasatinib</td>
<td>50 mg tab</td>
<td>1.56</td>
<td>0.226</td>
<td>&lt;LLOQ</td>
<td>&lt;LLOQ</td>
<td>*~30-fold</td>
</tr>
<tr>
<td>GDC-0980</td>
<td>10 mg tab</td>
<td>5.02</td>
<td>0.768</td>
<td>1.50</td>
<td>2-fold</td>
<td>4.0</td>
</tr>
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</table>

*calculated based on measurable concentration

Betaine HCl Improves GDC-0941 Exposure in Dog Model: Famotidine-Induced Achlorhydria

- Betaine HCl improves GDC-0941 exposure in the presence of famotidine
- Preclinical PoC of ‘re-acidification’ hypothesis

Re-acidification as Mitigation Strategy of Pharmacological-induced Hypochlorhydria

**Hypothesis**

- With the objective of allowing patients to continue taking the most effective and common ARA therapy, PPIs, and thereby maintain an elevated pH and the associated palliative relief, **we hypothesize that temporarily re-acidifying the gastric environment at the time of molecular targeted cancer treatment may allow for maximum absorption, exposure, and efficacy of the cancer therapy...while patients are still benefiting from continuous PPI therapy**

**The Clinical Study (LZ Benet Lab Collaboration, UCSF)**

- **Part 1** – Pilot study evaluating gastric re-acidification with betaineHCl in healthy volunteers with pharmacologically-induced hypochlorhydria.
- **Part 2** – Evaluate the effect of re-acidifying agent, betaine HCl, on dasatinib pharmacokinetics in healthy volunteers with and without pharmacologically-induced hypochlorhydria.

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**Gastric pH Method Development: Heidelberg Capsule pH Monitoring**

- **Gastric pH assessment**
  - N/G suction or placement of probe
    - Expertise to obtain gastric suction or place N/G lead
    - Uncomfortable (X3)
  - Heidelberg Capsule
    - Wireless pH sensing capsule
    - pH telemetry transmitted for ‘real time’ measurement
    - Must tether capsule to measure gastric pH for more than 20 min

http://www.phcapsule.com/nutinfo.htm
Part 1: Betaine-HCl Re-acidification of Rabeprazole-induced Achlorhydria in Healthy Volunteers

- Days 1-4: 20mg Rabeprazole PO, BID
- Day 5: 20mg Rabeprazole PO
- 2 hours later: 1500mg BHCl PO

Gastric pH Measurements

Heidelberg Capsule to HV, 20 mg rabeprazole administered BID, Heidelberg capsule with tether swallow T=0

Part 2: Dasatinib PK (control, plus PPI, plus PPI/betaine-HCl re-acidification)

- N = 10 Subjects (9 male, 1 female)
- Treatment A: Day 1: 100mg Dasatinib PO
- Treatment B: Days 1-3: 20mg Rabeprazole PO, BID
- Treatment C: Days 1-3: 20mg Rabeprazole PO, BID
- Treatment B: Day 4: 20mg Rabeprazole PO 2hrs prior to 100mg Dasatinib PO
- Treatment C: Day 4: 20mg Rabeprazole PO 2hrs prior to 100mg Dasatinib + 1500mg BHCl

Marc Yago, PhD Candidate UCSF
Rabeprazole Significantly Decreases Dasatinib Exposure in Healthy Volunteers

Yago et al., The AAPS Journal, Vol. 16, No. 6, November 2014

Betaine-HCl Increases Dasatinib Exposure in Subjects with Pharmacologically-induced Hypochlorydria

Yago et al., The AAPS Journal, Vol. 16, No. 6, November 2014
Dasatinib-Rabeprazole-BHCl provides Clinical PoC: Translation of Single dose HV to Chronic Administration is Needed

- Long term tolerability of BHCl in Cancer patients with GERDs is unknown

- Regimen adherence may be challenging
  - Combo formulation limited by tablet size and dose adjustment options
  - BHCl w/out PPI may significantly enhance dasatinib exposure
    - Many patients take BHCl as digestive aid

- Additional research needed to determine whether low dasatinib exposure results in the development of drug resistance and loss of dasatinib efficacy

Conclusions and Future Directions

- How (and when) should pH-dependent solubility and PPI-DDI risks be addressed?
  - Target Candidate Profile, IND, EoP2, NDA, or PMC
    - Can pH-dependent DDI be predicted with PBPK (GastroPlus/Simcyp)?
  - Substitute H2-blocker for PPI and try to time-stagger treatments to avoid a clinically significant DDI
    - Limited potential given 1) the extent of the interaction for certain drugs (ex. dasatinib and erlotinib) and 2) unlikely patient compliance given the frequent and chronic use for palliative relief and complexity of dosing strategy.
  - Temporary gastric re-acidification at time of dosing may serve as a potential strategy to avoid a clinically significant DDI.

- The FDA recognizes the potential significance of this PPI-DDI and is more frequently requesting additional studies to explore the extent of this interaction on small molecule orally-administered molecular targeted agents with pH-dependent solubility (e.g., PMC for many of the recently approved molecular targeted agents).
  - Lei Zhang and CDER Collaborators have recently published white paper in CPT: *pH-Dependent Drug–Drug Interactions for Weak Base Drugs: Potential Implications for New Drug Development* Clinical Pharmacology & Therapeutics (2014); 96 2, 266–277. doi:10.1038/clpt.2014.87
## pH-Dependent Collaborators

<table>
<thead>
<tr>
<th>UCSF Collaborators</th>
<th>GNE Collaborators</th>
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<tr>
<td>• Les Benet</td>
<td>• Tong Lu</td>
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<tr>
<td>• Adam Frymoyer (Stanford)</td>
<td>• Gena Dalziel</td>
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<td>• Marc Anthony Yago</td>
<td>• Laurent Salphati</td>
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<td>• Kari Morrissey</td>
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<td>• Gillian Smelick</td>
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<td>• Nag Budha</td>
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<td>• Jin Jin</td>
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<td>• Jodie Pang</td>
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<td>• Marie Borin</td>
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<td>• David Stirling</td>
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<td>• Jackson Pellet</td>
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<td>• Rick Graham</td>
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<td>• Mark Dresser</td>
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<td>• Amita Joshi</td>
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<td></td>
<td>• Sara Kenkare-Mitra</td>
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<table>
<thead>
<tr>
<th>GDC-0941 and GDC-0980 teams</th>
<th>Simulations Plus</th>
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<tbody>
<tr>
<td>• Scott Holden</td>
<td>• Grazyna Fraczkiewicz</td>
</tr>
<tr>
<td>• Kathryn Mazina</td>
<td></td>
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<tr>
<td>• Gallia Levy</td>
<td></td>
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<td>• Jennifer Lauchle</td>
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<td>• Mika Derynck</td>
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<td>• Glenn Morrison</td>
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**THANK YOU!!**
November 4, 2013: Vol. 10

- Impaired Drug Absorption Due to High Stomach pH: A Review of Strategies for Mitigation of Such Effect To Enable Pharmaceutical Product Development
- Ion Pairing with Bile Salts Modulates Intestinal Permeability and Contributes to Food–Drug Interaction of BCS Class III Compound Trospium Chloride
- Mechanistic Understanding of the Effect of PPIs and Acidic Carbonated Beverages on the Oral Absorption of Itraconazole Based on Absorption Modeling with Appropriate in Vitro Data

Special Thanks to Theme Contributors & Gena Dalziel, Kimberly Barrett, and Gordon Amidon

Extensive Inter-subject Variability in Orally Administered Anti-Cancer Drug PK

- Many of the advanced therapeutics shown above are orally administered tyrosine kinase inhibitors
- Common to observe 30-80% variability in PK following oral administration in humans
- PK variability may impact clinical outcomes in cancer therapy with respect to both toxicity and efficacy