Closing Remarks

Meet the Experts – Seoul
14 November 2019

Roelof de Wilde

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Jashvant Undkat, PhD

- Inability to predict tissue concentration levels → causes failure due to safety issues (toxicity) or lack of efficacy
- Unbound Cmax,ss ≠ tissue concentration due to transporters: Asymmetry
- Predicting uptake, biliary and sinusoidal efflux clearance (in addition to metabolic clearance) is of key importance.
- REF can be used to predict tissue drug concentration in vitro: determine Cl_{int},measure abundance of transporter in cell line and tissue of interest.
- Protein abundance measurements should be corrected for plasma membrane associated transporters. Other factors such as age and disease state may affect transporter expresion.
- REF works well for metformin, but not for rosuvastatin. Future needs: multiple transporter substrates and good PET imagining probes that work via multiple transporters.

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Jasminder Sahi, PhD

- Teriflunomide, polymorphisms affect the PK
- 18-20 days T1/2 – entero-hepatic recirculation
- DDI risk at kidney and liver: BCRP, OCT2, OAT3, OATP1B1
- Clinical DDI study done for OAT3, OATP1B1 and BCRP.
- Uric acid used as endogenous marker for BCRP. C_{max} unaffected, but clearance and AUC affected. AUC of 1.5-fold difference indicated minor risk, recommendation for monitoring (i.e. MTX)
- Rosuvastatin done for OATPs (and BCRP). Prediction was 30% AUC change – reality showed 2.5-fold. Recommendation is to do a rosuvastatin dose adjustment to 10 mg. Applicable to US, while less to Asian countries because generally lower concentrations dosed.
- Differences between AUC, based upon POP-PK data:
  - 18% higher AUC in S. Koreans vs. Caucasians, 33% higher AUC in Chinese vs Caucasians
- Smoke, sex, weight, polymorphisms differences exist.
- No polymorphisms affected the AUC based upon internal data, but small number of subjects published study shows polymorphism may play a role. More research is done on this area, because of request of regulators.

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Colin Brown, PhD

- Trend in pharmaceutical drugs showing increase in clearance via kidney, and raised risk of DDIs.
- Proximal tubule cells freshly isolated retain best *in vivo* properties, allowing formation of tight junctions and barrier function *in vitro*.
- Both uptake and efflux transporters are expressed at 30-40% of *in vivo* conditions, while immortalized cell lines retain 0-5% expression.
- Creatinine and Urate behaved as expected, showing net efflux or net (re-) absorption.
- Validation of system demonstrated using clinically relevant drugs cleared by Kidney and inhibition thereof by inhibitors to re-create in vivo observations.
- Species differences happened for drug x, showing net absorption in dog, which could not be inhibited by probenecid, while in rat, NHP and human kidney showed net excretion.
- PTCs show active reabsorption by Megalib-Cubulin (endocytosis), important for large molecules.
- Biologic drug showed toxicity in kidney (in vivo) and could be re-captured in PTCs in vitro via detection of biomarkers NGAL, KIM-1 and Clusterin. In vitro this could have been predicted in PTCs.
- PTCs tested to determine Positve and Negative predictive properties of the model. This is be used to predict nephrotoxicity using biomarkers for 36 compounds.

Tetsuya Terasaki, PhD

- Regulatory mechanism of P-gp function is limited in acute CNS disorder.
- Inflamatory (TNFα) and oxidative stress model was assessed, using vinblastine as probe substrate and PSC833 as inhibitor.
- No differences on expression, but activity reduced by 50%. Phosphorylation of AFAP-1 signal is likely playing a role in this reduction.
- Oxidative stress was causing up to 80% reduction in P-gp function, which is refersible by removing stress factor (hydrogen peroxide).
- Mechanism likely due to internalization of P-gp, and can be observed *In Vitro* too.

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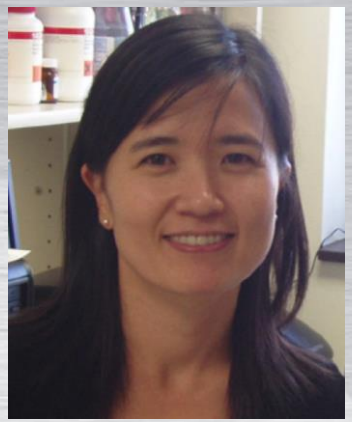
Wooin Lee, PhD



- *In vitro* inhibition data of transporters is used to estimate possible risk for clinical interactions.
- Large variation in *in vitro* inhibition potency is known and the mechanism may be depending on laboratory specific conditions.
- Pre-incubation of cells enhances inhibition potency, as first shown for Cyclosporin A and later many other drugs, showing differences up to 200-fold differences.
- Mechanism 1(?)– could possibly be related to non-specific binding, compounds tend to be lipophilic.
- Mechanism 2 – trans-inhibition = from inside the cell.
- Recent research shows inhibition potency can be rapidly reversed for some compounds, but not for all.

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Takeo Nakanishi, PhD

- OATP2A1 transports prosglandins in exchange for lactate.
- Prostaglandins in the cells are metabolized rapidly.
- OATP2A1 related diseases are PHO and CEAS.
- Oatp2a1 KO mice were developed to show significance role of transporter in fibrosis in lung and it's role in fever.
- In lung, levels of PGE are significantly decreased, but increased in the BAL fluid.

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Ikumi Tamai, PhD

- OATP2B1 is inhibited by flavonoids present in food (fruit juice)
- However, also nano-particles from foods may cause an effect via decreased expression of ASBT and OATP2B1. Possible through microRNA that might act on regulator protein – yet this needs further investigation.
- The finding of nano-particles' possibility to affect expression is novel.
- This research may show that food-derived nano-particles could be used to deliver molecules of interest to intestinal tissue.

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Massimiliano Fonsi, PhD

- *In vitro* and *in vivo* findings were combined to develop Niraparib.
- Bad correlation of clearance in preclinical species using only metabolism data from microsomes.
- Explained by significant extrahepatic metabolism (lung and kidney).
- Knowing the mechanism, using in vitro data the human clearance was determined. Phase II data indeed confirmed extrahepatic metabolism was not observed in human.

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Joan Z Zuo, PhD

- Delivery of drugs to CNS via nasal route of administration.
- *In vitro* model is in Calu-3 cell lines, grown on transwell plates, *in silico* methods, or *in vivo* models.
- Case study on PolyQ (Huntington) disease drug: How to deliver the amino-acid-drug to brain? Intra-nasal delivery by-passes important barriers.
- Nasal route showed higher brain exposure then IV dosed route.
- The formulation was further optimized using for delivery using a gel (trapping of drug).
- Retention time prolonged, resulting in higher delivery to brain.

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A big Thanks for all speakers!

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Thanks to all attendees!

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