

University of Maryland Baltimore Graduate School

# Announcement of Doctoral Dissertation Defense\*

Candidate: Minori Kinjo

Date, Time, and Place: 04/22/2008, 14:00, PLC 107

Dissertation Title:

Evaluations of a human kidney (HK2 cells) model for drug-induced nephrotoxicity and BK virus infection

Dissertation Abstract\*\*:

Renal transplant patients receive drugs such as tacrolimus (TAC), sirolimus (SRL), cyclosporin (CSA) for immunosuppression, and low-dose cidofovir (CID) for treatment of BK virus associated nephropathy (BKVN). Here, we evaluated the effects of clinically achievable concentrations of drug combination therapy on p-glycoprotein (P-GP) and organic anion (OA) transporters (OAT-1,-3 and MRP2) expression and function in human renal proximal tubule (HK2) cells. HK2 cells were further evaluated as a host for BK virus and a model for drug screening for the treatment of BKVN.

HK2 cells were exposed to drug combinations over 5 days with determination of P-GP and OA transporter expressions and functions in HK2 cells. P-GP function was assessed by rhodamine 123 uptake (R123) and OA transport activity was evaluated by para-aminohippurate transport (PAH) during acute and chronic exposures. Exposure to supraclinical concentrations of TAC, SRL and CSA resulted in significant reductions in cell viability whereas expression of P-GP, and OA transporters remained unchanged. A significant concentration-dependent toxicity was demonstrated by trypan blue exclusion but not by XTT assay, suggesting that membrane-bound cells are required for detection of toxicity. R123 accumulation was significantly increased during TAC, SRL and CSA exposures. PAH transport remained unchanged in the presence of TAC, SRL, and CSA; however a trend towards decreased transport in the presence of CID was observed.

HK2 cells were shown to express Caveolin-1, and were permeable to BK virus. Viral growth was gradual after 20 days post-infection, and stabilized after 55 days. A possible dormant stage of BK viral cycle was observed. The efficacy of CID was tested on the BK virus-infected HK2 cell model, and the quantitative PCR data showed that 24-hour CID exposure suppressed viral replications after 4 days incubation in a concentration-dependent manner.

The key findings in these studies suggest that immunosuppressive agents used in renal patients may impair renal PGP function. Exposure to drug combinations including CID may increase the risk of nephrotoxicity in patients receiving immunosuppressants. A BK virus infected HK2 cell model was developed that could be further utilized to study BK virus infection and new treatments for BKVN.

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*\*The Open Presentation is open to the university community and invitees of the candidate. Any member of the Graduate Faculty may observe the Final Examination. Only committee members may vote. For more information, see **Procedures for Examination of the Doctoral Dissertation.***

*\*\*You must type your abstract on this form in the space provided.*

*Updated: February 24, 2006*