

University of Maryland Baltimore Graduate School

# Announcement of Doctoral Dissertation Defense\*

Candidate: Aakanksha Khandelwal

Date, Time, and Place: Friday, November 30, 11:00 am, HSF-II Room 600

Dissertation Title: Retinoids and retinoic acid metabolism blocking agents in combination with histone deacetylase inhibitors for prostate cancer therapy

## Dissertation Abstract\*\*:

All-trans-retinoic acid (ATRA), a metabolite of vitamin A, is 5 to 8 times lower in prostate carcinoma tissue when compared to a normal prostate and benign prostatic hyperplasia. ATRA plays a major role in a number of biological processes and is metabolized by cytochrome P450 enzymes into inactive polar metabolites. The anti-cancer effects of a novel class of agents called atypical retinoic acid metabolism blocking agents (RAMBAs) was examined in a hormone refractory prostate cancer model. We hypothesized that certain RAMBAs in combination with low doses of HDACIs would result in a synergistic inhibition of prostate cancer cell and tumor growth.

One particular RAMBA, VN/66-1 which displays favorable pharmacokinetics and minimal toxicity was found to be highly potent in inhibiting PC-3 cell growth. Two HDACIs, SAHA and MS-275 were also found to be potent in inhibiting PC-3 cell viability. The combinations of VN/66-1 + MS-275 and VN/66-1 + SAHA were synergistic in inhibiting PC-3 cell growth, caused cell cytostaticity/ cytotoxicity and induced a marked G2/M phase arrest and apoptosis. Mechanistic studies indicated the combinations caused DNA damage, increased acetylation of histones H3 and H4 and up-regulation of RAR $\beta$  and p21<sup>WAF1/CIP1</sup>.

Treatment of PC-3 xenografts with VN/66-1 (10 mg/kg/day) + MS-275 (2.5 mg/kg/day) for 18 days, resulted in an 85% reduction in final mean tumor volume compared with control. The combination of VN/66-1 + SAHA, however, did not reduce tumor growth as effectively as the two agents individually.

The data collected suggest that the mechanism of action of the combination of VN/66-1 + MS-275 is through apoptosis and DNA damage-induced p21 activation. Active p21 is involved in the inhibition of the cdc2-cyclin B1 complex resulting in eventual G2/M phase arrest. This induction of p21 is also in part due to the enhancement of acetylation of histones H3 and H4 which is also responsible for the activation of tumor suppressor gene RAR $\beta$  which is also plays a role in mediating cell death. These results suggest that VN/66-1 or its combination with MS-275 may be a novel therapy for the treatment of hormone refractory prostate carcinoma.

Dissertation Committee Chair (name and title):

Vincent C. O. Njar, Associate Professor

Dissertation Committee Members (names and titles):

Angela Brodie, Professor

Renty Franklin, Professor

Amy Fulton, Professor

Yun Qiu, Associate Professor

*\*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