

University of Maryland Baltimore Graduate School

Announcement of Doctoral Dissertation Defense*

Candidate: Samantha Q. Wales

Date, Time, and Place: April 11, 2008, 11 a.m. HSFII Auditorium

Dissertation Title: Molecular mechanisms of neuroprotection by the herpes simplex virus type 2 gene ICP10PK

Dissertation Abstract**:

Recent progress in molecular biology has focused interest on gene therapy as a strategy for the control of chronic and acute neurodegenerative disorders. However, the selection of the appropriate gene and delivery vector is a clinical challenge. Herpes simplex virus type 2 (HSV-2) is a promising gene delivery vector, as it is neurotropic, has a large genome that is amenable to genetic manipulation, and unlike HSV-1, it does not cause encephalitis in adult humans. HSV-2 contains an anti-apoptotic serine/threonine protein kinase (known as ICP10PK), that acts as a constitutively activated growth factor receptor. It activates Ras and its downstream MEK/ERK survival pathway and inhibits apoptosis caused by virus infection of primary hippocampal cultures (Perkins *et al.* 2003b, Perkins *et al.* 2002a). The studies described in this report were designed to examine the molecular mechanisms of ICP10PK-mediated neuroprotection, and ensure that it can act independently of other viral proteins. Rat pheochromocytoma (PC12) cells stably transfected with ICP10PK (PC47 and PC70 cells) or its kinase-negative mutant p139TM (PC139 cells), were neuronally differentiated by culture with nerve growth factor (NGF) and examined for cell survival after NGF withdrawal. Apoptosis was seen in PC12 and PC139, but not PC47 and PC70 cells. In PC47 cells, neuroprotection was MEK- and PKA-dependent, associated with stabilization/activation of the transcription factor cAMP-responsive element binding protein (CREB), inhibition (phosphorylation) of the pro-apoptotic protein Bad and stabilization of the anti-apoptotic proteins Bcl-2 and Bag-1. In PC70 cells, neuroprotection occurred downstream of caspase activation, and involved MEK-dependent up-regulation of the anti-apoptotic protein XIAP and down-regulation of the XIAP inhibitor Smac/DIABLO. To examine whether ICP10PK is also neuroprotective in other paradigms, we examined its effect in an *in vitro* model of Parkinson's Disease, using the neurotoxin MPP⁺. ICP10PK, but not p139TM, inhibited MPP⁺-induced programmed cell death through inhibition of calpain-dependent Bax translocation to the mitochondria, AIF nuclear translocation, and caspase activation, indicating that the actions of ICP10PK are kinase-dependent. Collectively, the data indicate that ICP10PK has broad-spectrum neuroprotective activity that extends beyond apoptotic cellular programs. Further study of its use as a gene therapy strategy is warranted.

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Dissertation Committee Members (names and titles):

Dr. Cindy Smith, Assistant Professor
Dr. Jessica Mong, Assistant Professor
Dr. William Randall, Associate Professor
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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.**

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