

# *The Neuroscience Graduate Program*

*presents:*

**BERKELEY FAHRENTHOLD**

**ADVISOR: RICHARD LIBBY**

*IN A PHD THESIS DEFENSE*

*MONDAY, 20 MARCH 2017*

*1:15 PM IN AUDITORIUM K-307 (3-6408)*

## **ASSESSMENT OF THE INVOLVEMENT OF INTRINSIC AND EXTRINSIC CELL DEATH PATHWAYS IN RETINAL GANGLION CELL DEATH AFTER EXCITOTOXIC INJURY**

Excitotoxicity leads to disruption of the intracellular environment and activation of cytotoxic cascades that exacerbate and/or cause neuronal death. Multiple cell types, including both neurons and glia, are affected by excitotoxic insult. In the mammalian retina, cells that die following this insult are retinal ganglion (RGCs) and amacrine cells. Both intrinsic and extrinsic signals have been hypothesized to activate injury response and cell death pathways that ultimately result in RGC death. Here, I test the importance of a TNF-dependent extrinsic apoptotic pathway and JNK signaling, an intrinsic cell death pathway shown to result in RGC apoptosis after diverse insults, in excitotoxicity induced RGC death. Tumor necrosis factor (TNF), through bid dependent signaling, is known to be a key extrinsic mediator of neuronal degeneration. TNF released by Müller glial cells has also been suggested to be important in RGC death after an excitotoxic injury. To critically test the importance of TNF in RGC death after excitotoxic injury, the excitotoxin N-methyl-D-aspartate (NMDA) was intravitreally injected into mice deficient in TNF. *Tnf* deficiency did not confer short- or long-term protection to RGCs. Further suggesting that TNF mediated extrinsic cell death pathways are not required for excitotoxic RGC death, *Bid* deficiency did not protect RGCs nor did it prevent cytochrome c release. Thus, a key extrinsic pathway that has been implicated in RGC death was found to not be necessary for RGC death after excitotoxic injury. Intrinsic cell signaling pathways have also been implicated in excitotoxic neuronal death. JNK signaling is known to be a critical mediator of NMDA-induced cell death in other neuronal cell types. JNK signaling is also known to be critical for RGC death after a variety injuries and is activated in RGCs after excitotoxic injury. To test the importance of JNK signaling in RGC death after an excitotoxic insult, mice deficient in various JNK isoforms were used. Despite their expression in RGCs, involvement in excitotoxic injury in other neurons, and ability to inhibit RGC death after other insults, attenuating JNK signaling did not prevent RGC death after excitotoxic insult. Collectively, these results indicate that the cell death pathways that orchestrate RGC death after diverse pathological insults are not conserved. Future studies aimed at using a combinatorial approach to target multiple cell death pathways simultaneously will be needed to shed light on the mechanisms that lead to RGC death after an excitotoxic insult.