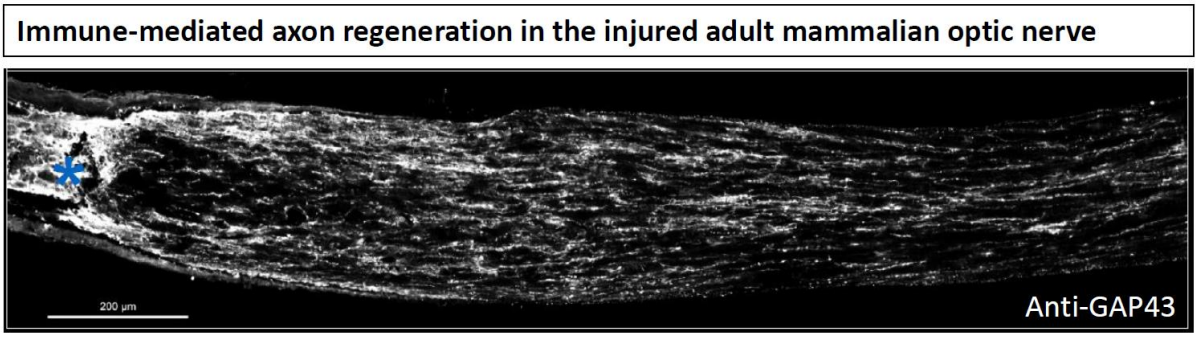
Weekly Colloquium
Tuesday, 6/20/2017, 12:30pm, Billings Building – Rosedale Conference Room

"Immune-Mediated Neural Repair Mechanisms in the Injured Adult Mammalian Central Nervous System"

Roman J. Giger, Ph.D.
George Linius Streeter Collegiate Professor
Department of Cell & Developmental Biology and Neurology
University of Michigan School of Medicine
Ann Arbor, MI

Abstract
Innate immunity can facilitate nervous system regeneration, yet the underlying cellular and molecular mechanisms are not well understood. We recently found that intraocular injection of lipopolysaccharide (LPS), a bacterial cell wall component, or the fungal cell wall extract zymosan both lead to rapid and comparable intravitreal accumulation of blood-derived myeloid cells. However, when combined with retro-orbital optic nerve crush injury, lengthy growth of severed retinal ganglion cell (RGC) axons occurs only in zymosan-injected mice, and not in LPS-injected mice. In mice deficient for the pattern recognition receptor dectin-1 but not Toll-like receptor-2 (TLR2), zymosan-mediated RGC regeneration is greatly reduced. The combined loss of dectin-1 and TLR2 completely blocks the proregenerative effects of zymosan. In the retina, dectin-1 is expressed by microglia and dendritic cells, but not by RGCs. Dectin-1 is also present on blood-derived myeloid cells that accumulate in the vitreous. Intraocular injection of the dectin-1 ligand curdlan [a particulate form of β(1, 3)-glucan] promotes optic nerve regeneration comparable to zymosan in WT mice, but not in dectin-1(-/-) mice. Particulate β(1, 3)-glucan leads to increased Erk1/2 MAP-kinase signaling and cAMP response element-binding protein (CREB) activation in myeloid cells in vivo. Loss of the dectin-1 downstream effector caspase recruitment domain 9 (CARD9) blocks CREB activation and attenuates the axon-regenerative effects of β(1, 3)-glucan. Studies with dectin-1(-/-)/WT reciprocal bone marrow chimeric mice revealed a requirement for dectin-1 in both retina-resident immune cells and bone marrow-derived cells for β(1, 3)-glucan-elicited optic nerve regeneration.

Collectively, these studies identify a molecular framework of how innate immunity enables repair of injured central nervous system neurons.



Publications:

Baldwin, K.T., Carbajal, K.S., Segal, B.M., and Giger, R.J. (2015) Neuroinflammation triggered by β-glucan/dectin-1 signaling enables CNS axon regeneration. *Proc Natl Acad Sci U S A* 112(8):2581-6

Mironova. Y. and Giger, R.J. (2013) Where no synapses go: Gatekeepers of circuit remodeling and synaptic strength. *Trends in Neurosci*. S0166-2236: 64-77

Mironova, Y.A., Lenk, G.M., Lin, J.P., Lee, S.J., Twiss, J.L., Vaccari, I., Bolino, A., Havton, L.A., Min, S.H., Abrams, C.S., Shrager, P., Meisler, M.H., Giger, R.J. (2016). PI(3,5)P_2 biosynthesis regulates oligodendrocyte differentiation by intrinsic and extrinsic mechanism. *Elife*. 2016 Mar 23;5. pii: e13023. doi: 10.7554/eLife.13023

For more information contact: dwhite@burke.org

Burke Medical Research Institute
Academic Affiliate of Weill Cornell Medicine
785 Mamaroneck Avenue, White Plains, NY 10605 | T. 914.597.2551 | www.burke.org