

## PROGRESS IN NEUROSCIENCE PINS

Seminar Series of the Brain & Mind Research Institute Weill Cornell Medical College (WCMC)



The Graduate Program in Neuroscience of WCMC and Sloan Kettering Institute

Thursday, 3/5/15, 4 PM, coffee at 3:45 PM Weill Auditorium

## "Lysosomal Function and Two Neurodegenerative Diseases: Alzheimer's and Niemann Pick type C"

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## Abstract:

I will discuss two ongoing projects in the laboratory that illustrate the transition from basic research to understanding and potentially treating diseases. Niemann-Pick C disease is a rare, recessive, inherited lysosomal storage disease that leads to progressive neurological defects and frequently death before age 20. At the cellular level, the disease is caused by failure to properly transport cholesterol out of late endosomes and lysosomes (LE/Ly). We conducted a high throughput screen to identify molecules that might correct the defect. Among the hits were histone deacetylase inhibitors, including two that have now been approved as cancer therapies by the FDA. We have taken one of these, SAHA or Vorinostat, into a phase 1 clinical trial.

The second project studies Alzheimer's disease. We had observed previously that microglia internalize fibrillar forms of Alzheimer's amyloid  $\beta$  peptide (fA $\beta$ ) and deliver them to LE/Ly, but they fail to degrade the fibrils. We found that in primary microglia, a chloride transporter, CIC-7, is not delivered efficiently to lysosomes, causing incomplete lysosomal acidification. CIC-7 protein appears to be degraded by an endoplasmic reticulum-associated degradation pathway. Activation of microglia with macrophage colony-stimulating factor induces trafficking of CIC-7 to lysosomes, leading to lysosomal acidification and increased fA $\beta$  degradation. These findings suggest a novel mechanism of lysosomal pH regulation in activated microglia that is required for fA $\beta$  degradation. We also found that boosting the levels of certain proteases in microglia can facilitate degradation of fA $\beta$ .

## **Recent relevant publications:**

1) Pipalia, N.H., Cosner C.C., Huang, A, Chatterjee A., Bourbon, P., Farley, N., Helquist, P., Wiest, O., and Maxfield, F.R. (2011) Histone deacetylase inhibitor treatment dramatically reduces cholesterol accumulation in Niemann-Pick Type C1 mutant human fibroblasts. Proc. Natl. Acad. Sci., USA, **108**: 5620-5625. PMCID: PMC3078401

2) Majumdar, A., Capetillo-Zarate, E., Cruz, D., Gouras, G.K., and Maxfield, F.R. (2011) Degradation of Alzheimer's amyloid fibrils by microglia requires delivery of CIC-7 to lysosomes. Mol Biol Cell, **22**: 1664-1676. PMCID: PMC3093319

3) Helquist, P., Maxfield, F.R., Wiech, N.L., and Wiest, O. (2013) Treatment of Niemann-Pick Type C Disease by Histone Deacetylase Inhibitors. Neurotherapeutics **10**:688-697. PMCID: PMC3805865



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