

# Lysosome Dysfunction—A Primary Catalyst and Driver of Alzheimer’s Disease

**April 21**

**Tuesday, 12:30 pm**

**Billings Building—Rosedale Room**

**SPEAKER:**



**Ralph A. Nixon, M.D., Ph.D.**

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**Host: Gary E. Gibson, Ph.D.**

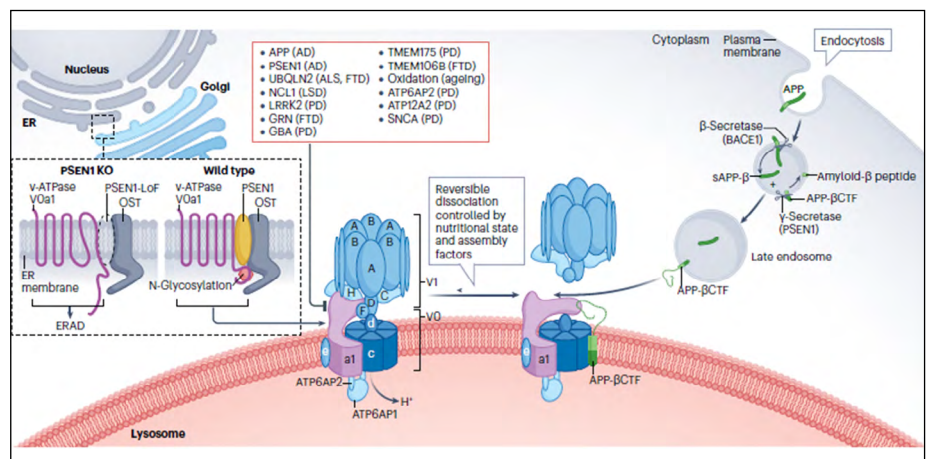
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## Abstract

The genetics underlying early-onset AD have long been viewed as uniquely supporting the sole primary role of abeta in AD pathogenesis. Evidence will be presented that the endosomal-lysosomal-autophagy network (ELA) is an equally compelling primary target of causative and risk AD genes. I will discuss the molecular and cellular underpinnings of this role that make ELA disruption an essential partner with APP metabolites in instigating and driving disease pathogenesis.



## Publications

1. Im E, Jiang Y, Stavrides PH, Darji S, Erdjument-Bromage H, Neubert TA, Choi JY, Wegiel J, Lee JH, Nixon RA. *Lysosomal dysfunction in Down syndrome and Alzheimer mouse models is caused by v-ATPase inhibition by Tyr(682)-phosphorylated APP βCTF*. *Sci Adv*. 2023 Jul 28;9(30):eadg1925. PubMed Central PMCID: PMC10371027.
2. Lee JH, Yang DS, Goulbourne CN, Im E, Stavrides P, Pensalfini A, Chan H, Bouchet-Marquis C, Bleiwas C, Berg MJ, Huo C, Peddy J, Pawlik M, Levy E, Rao M, Staufenbiel M, Nixon RA. *Faulty autolysosome acidification in Alzheimer’s disease mouse models induces autophagic build-up of Aβ in neurons, yielding senile plaques*. *Nat Neurosci*. 2022 Jun;25(6):688-701. PubMed Central PMCID: PMC9174056.
3. Jiang Y, Sachdeva K, Goulbourne CN, Berg MJ, Peddy J, Stavrides PH, Pensalfini A, Pawlik M, Malampati S, Whyte L, Basavarajappa BS, Subbanna S, Bleiwas C, Smiley JF, Mathews PM, Nixon RA. *Increased Neuronal Expression of the Early Endosomal Adaptor APPL1 Replicates Alzheimer’s Disease-Related Endosomal and Synaptic Dysfunction with Cholinergic Neurodegeneration*. *J Neurosci*. 2025 Jul 16;45(29) PubMed Central PMCID: PMC12268982.