Exploring Resilience to Alzheimer's Disease through the Lens of Down Syndrome

Peng Jiang[1], Mengmeng Jin[1], Ziyuan Ma[1], Rui Dang[1], Haiwei Zhang[1], Rachael Kim[1], Haipeng Xue[2], Jesse Pascual[3], Ava V. Papetti[1], Steven Finkbeiner[4,5], Elizabeth Head[3], Ying Liu[2],

[1]Department of Cell Biology and Neuroscience, Rutgers University-New Brunswick, Piscataway, NJ 08854, USA
[2]Department of Environmental Health Sciences, Robert Stempel College of Public Health and Social Work, Center for Translational Science, Florida International University, Port St. Lucie, FL 34987, USA
[3]Department of Pathology and Laboratory Medicine, Department of Neurology, University of California, Irvine, CA 92697, USA
[4]Center for Systems and Therapeutics and the Taube/Koret Center for Neurodegenerative Disease, Gladstone Institutes, San Francisco, CA 94158, USA
[5]Departments of Neurology and Physiology, University of California, San Francisco, CA 94158, USA

Down syndrome (DS) is a leading genetic risk factor for Alzheimer's disease (AD), yet some individuals with DS exhibit cognitive resilience despite hallmark AD pathology. Interestingly, DS also confers heightened susceptibility to myeloid leukemia through somatic mutations in hematopoietic cells, mutations that may contribute to neuroprotection. Given that microglia originate from hematopoietic lineages and play central roles in AD pathogenesis, we hypothesize that DS-associated leukemia mutations in microglia may promote resilience to neurodegeneration. To test this, we introduced the DS-linked CSF2RB A455D mutation into human pluripotent stem cells (hPSCs) using CRISPR-Cas9. In human microglia chimeric mouse models, we demonstrate that this mutation mitigates pathological tau-induced neuroinflammation, enhances phagocytosis and autophagy, and reduces senescent and dystrophic microglial phenotypes. Remarkably, these engineered microglia preserve neuronal function and outcompete wild-type microglia in the presence of pathological tau. These findings establish proof-of-concept that genetic engineering of human microglia can confer resistance to tau-driven neurodegeneration, offering a potential strategy for therapeutic microglial replacement in AD.

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Presenter Name and contact information:
Peng Jiang, Ph.D. Associate Professor
Department of Cell Biology and Neuroscience
Rutgers University-New Brunswick
604 Allison Road, Piscataway, NJ 08854
Email: peng.jiang@rutgers.edu
Phone: 848-445-2805