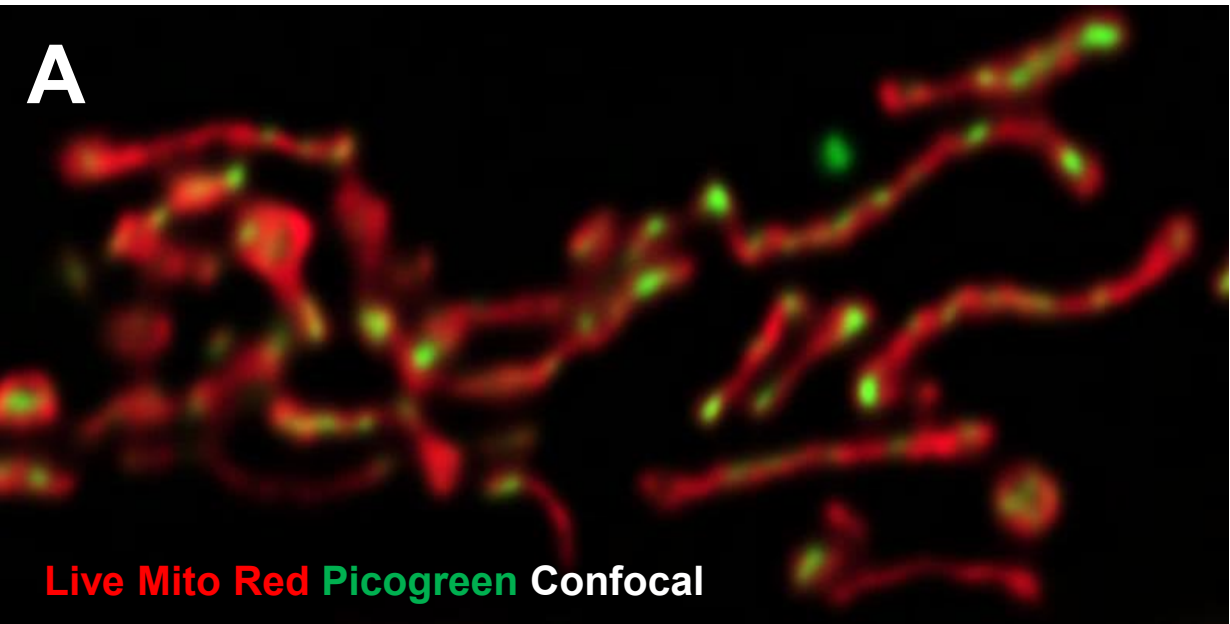
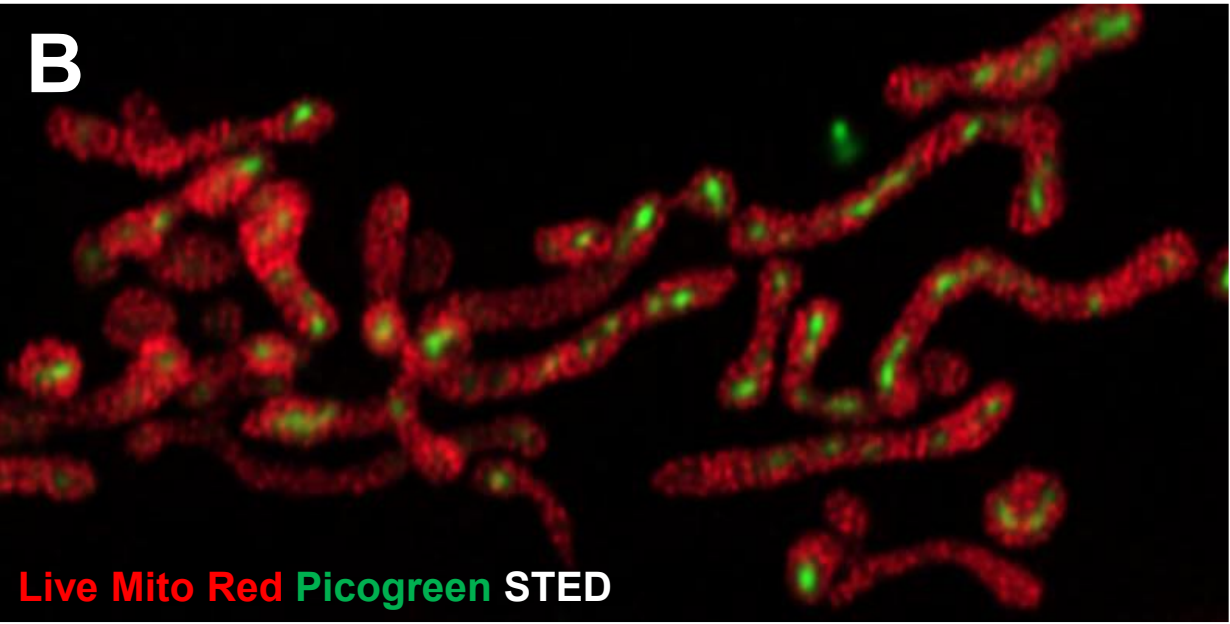
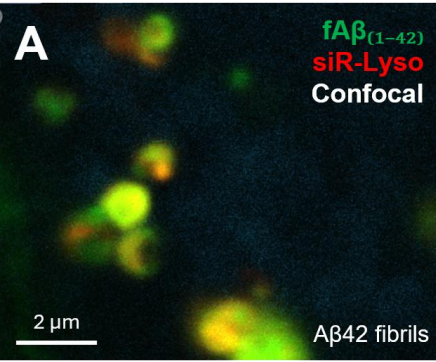
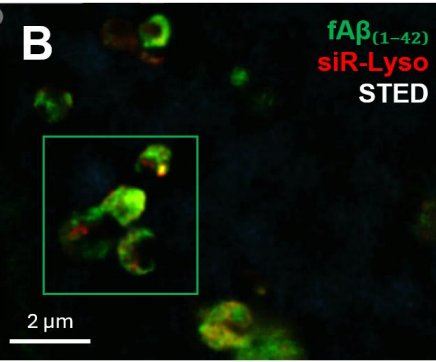
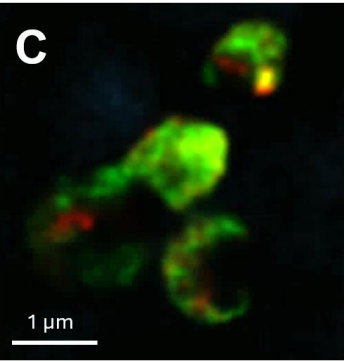
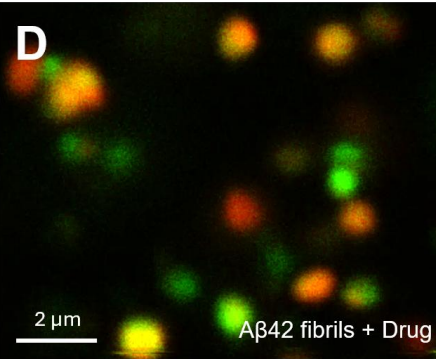
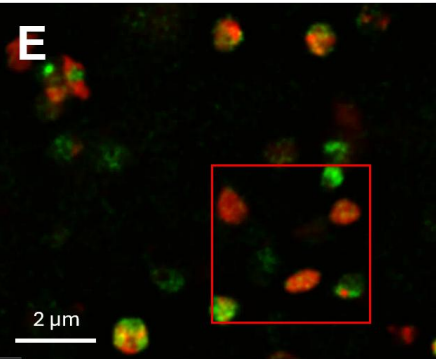
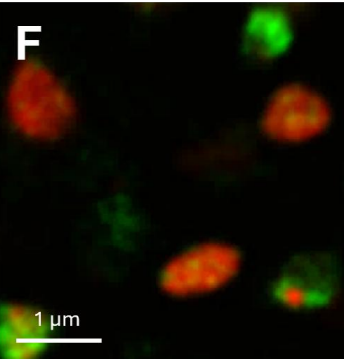
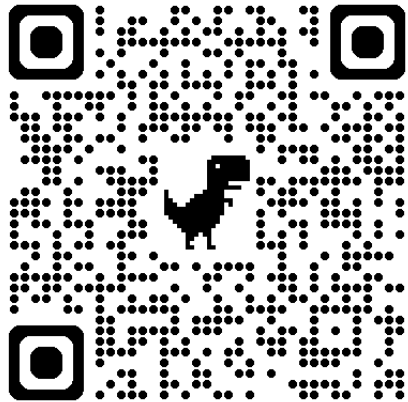


Powerhouses Reimagined: Stem Cells Illuminate Alzheimer's Disease Mysteries

Monday-0005

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STEDYCON super-resolution imaging reveals mitochondrial architecture in APOE4 Alzheimer's disease (AD) patient induced pluripotent stem cells (iPSCs). We also used STEDYCON to identify dramatic autolysosomal and lipid dysregulations after amyloid- β challenge in iPSC-derived microglia (iMGs). Understanding the dynamics of these essential organelle stress responses are critical to our search for metabolic- targeted, personalized therapeutics for APOE4 populations, who have the highest risk of disease as well as adverse side effects to current therapies.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	ACKNOWLEDGEMENTS
Using STEDYCON microscopy, we've captured a digital masterpiece of "mitochondria"—the powerhouses of our cells—in stem cells carrying an APOE4 mutation, the greatest risk factor for Alzheimer's disease (AD). Pathological hallmarks of APOE4 in are the dysregulation of cellular bioenergetics, lipid metabolism and lysosomal functions, particularly in microglia [1]. Understanding how APOE4 disrupts membrane interactions at subcellular organelles, such as lysosomes and mitochondria requires super-resolution imaging. Our integrated approach, spanning from super-resolution mitochondrial phenotyping [2] and human induced pluripotent stem cells (iPSCs) models, holds promise for identifying novel targets and personalized therapeutics that better address the root causes of AD pathology, rather than merely treating their downstream symptoms.	To model AD and screen/identify therapeutics, we utilize patient iPSCs from APOE4/4 AD patients to study the role of organelle stress. In iPSCs labeled with Live Mito Red and Picogreen dye, STEDYCON reveals well-organized mitochondria cristae and mtDNA nucleoids, structures that are not visible with confocal (Fig. 1). A  B  Figure 1: STEDYCON Live Imaging of Mitochondrial Membranes and mtDNA Dynamics in Patient iPSCs.	Microglia are the brain's resident immune cells that play critical roles in amyloid phagocytosis, clearance and neuroinflammation. Therefore, we generated iPSC-derived microglia from APOE4/4 AD and APOE3/3 healthy donors to study their role. A  B  C  D  E  F  Figure 2: STEDYCON Imaging of Fibrillar Aβ Accumulation and Clearance in Lysosomes of APOE4 Patient Microglia. In patient microglia challenged with amyloid-β 42 (fAβ₁₋₄₂) oligomers for 24 hours, STEDYCON imaging resolves the intra-lysosomal (red, siR-Lyso) accumulation pattern of fAβ₁₋₄₂ (green, Fig. 2A-C). This was shown to be reduced by co-treatment with a metabolism-targeted drug (Fig. 2D-F).	Building on our integrated platform, we are conducting high-throughput screening of repurposed FDA-approved compounds that enhance mitochondrial biogenesis, improve oxidative phosphorylation, reduce oxidative stress, and restore lysosomal-autophagy function — nominating new mitochondria-targeted therapeutic strategies for APOE4-associated disease. Resolving the interactions between lipids and cellular membranes including lysosomal demands resolution well below the diffraction limit. By harnessing the potential of these patient-derived stem cell lines combined with advanced super-resolution imaging techniques and functional metabolic assays, we are gaining unprecedented insights into how mitochondrial dysfunction, lysosomal impairment, and cellular senescence converge in APOE4-associated Alzheimer's disease.	UCI iPS core: Induced Pluripotent Stem Cell Lines. UCI ADRC, SCRC, and OBC cores. This work was supported in part by the California for Regenerative Medicine (CIRM) BRIDGES program References: - Sung 2025 et al. Nature npj Aging - Zahedi 2019 et al. iScience
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