



Evaluating Phagocytosis-Modulating Treatments in iPSC-Derived Microglia Using Disease-Relevant Aggregates

amyl scantox

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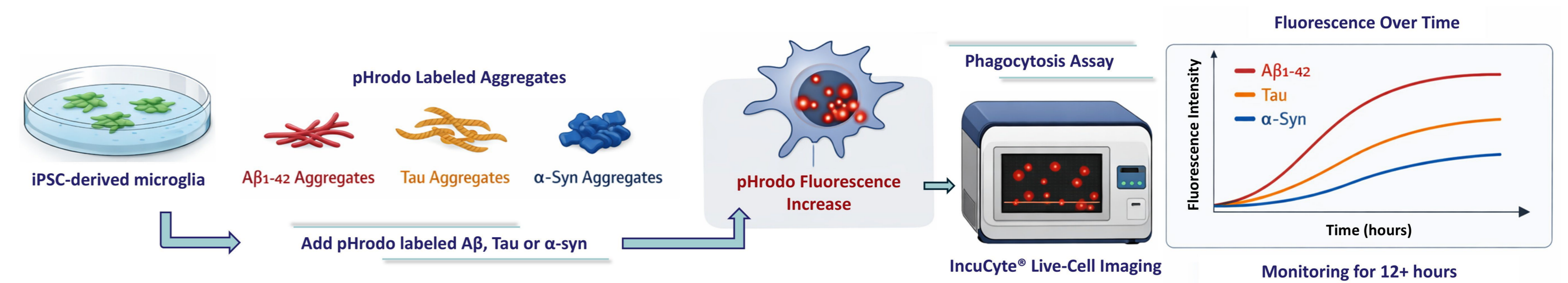


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Objectives

Microglia are key players in the clearance of neurotoxic protein aggregates such as amyloid- β ($A\beta$), tau, and α -synuclein, which are central to the pathology of neurodegenerative diseases including Alzheimer's and Parkinson's. Understanding and modulating microglial phagocytic function is critical for developing effective therapeutic strategies. This study aimed to establish a robust, disease-relevant *in vitro* assay to monitor microglial uptake of pathological protein aggregates and assess the impact of phagocytosis-modulating treatments.

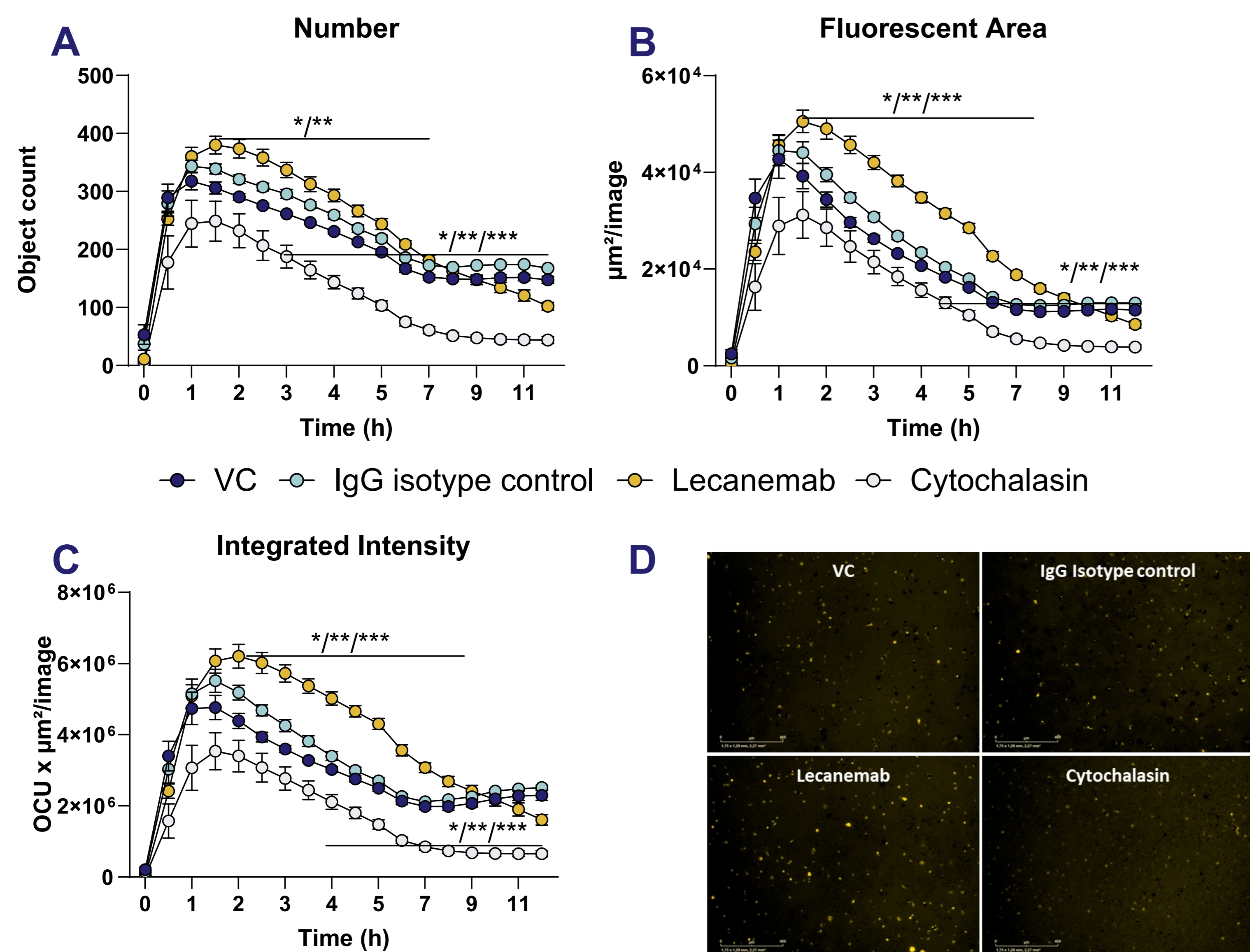
Materials and Methods



Human iPSC-derived microglia were exposed to pre-aggregated proteins labeled with pHrodo™ Red in combination with therapeutic agents, e.g. Lecanemab, microglial uptake was monitored.

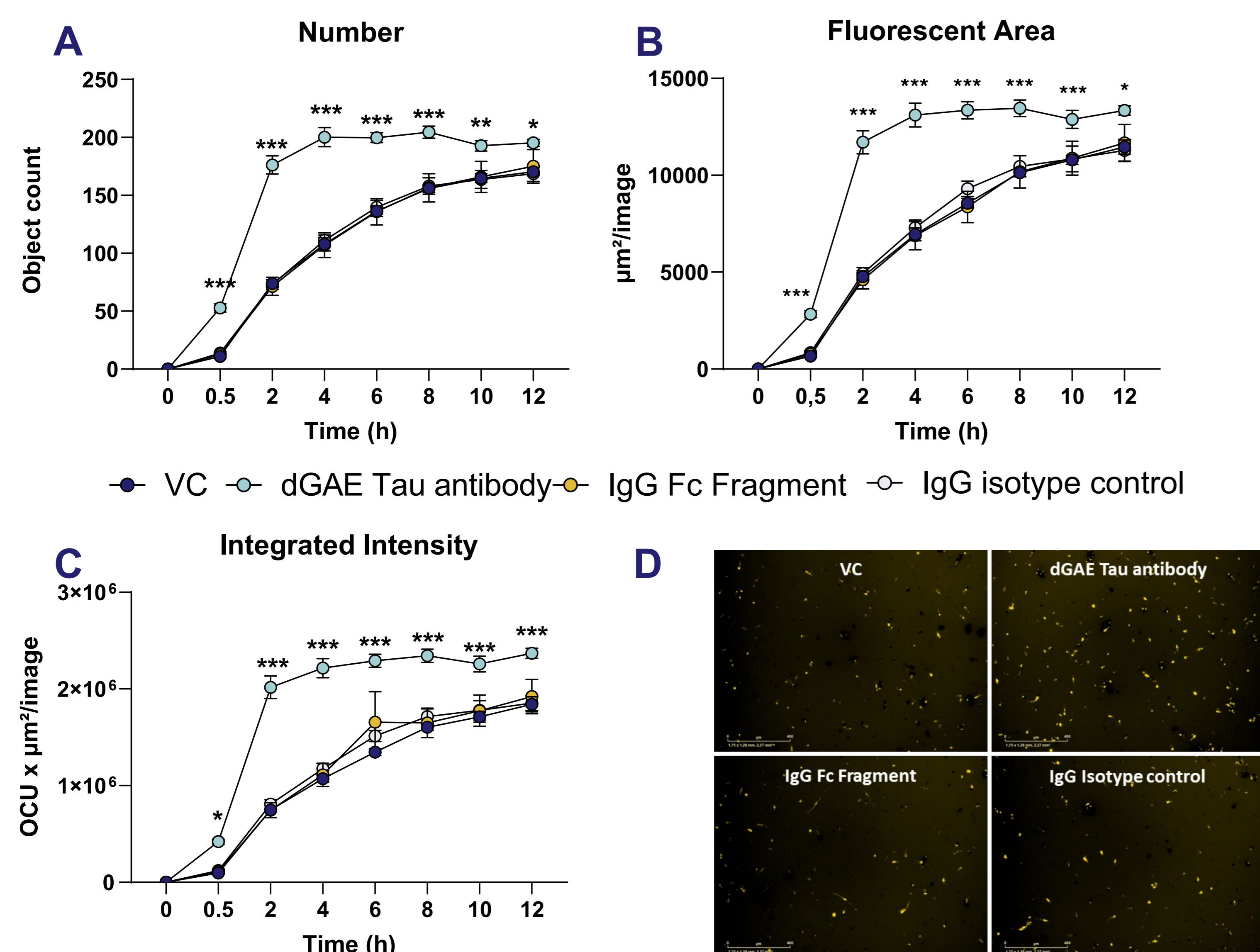
Results

Amyloid- β 1-42



▲ **Figure 1: Microglial phagocytosis of pHrodo $A\beta$ 1-42 over time.** Number of orange objects (A), fluorescent area per image (B) as well as total integrated intensity of the orange signal (C) was monitored over time in cells treated with pHrodo labeled $A\beta$ 1-42 alone (VC) as well as incubated with either IgG isotype control (30 nM), Lecanemab (30 nM) or Cytochalasin (10 μ M). Two-way ANOVA followed by Dunnett's multiple comparisons test. Mean + SEM. n = 4. *p < 0.5; **p < 0.01; ***p < 0.001. D: Representative images of pHrodo $A\beta$ 1-42 phagocytosis after treatment at 5 hours. Scale bar 400 μ m.

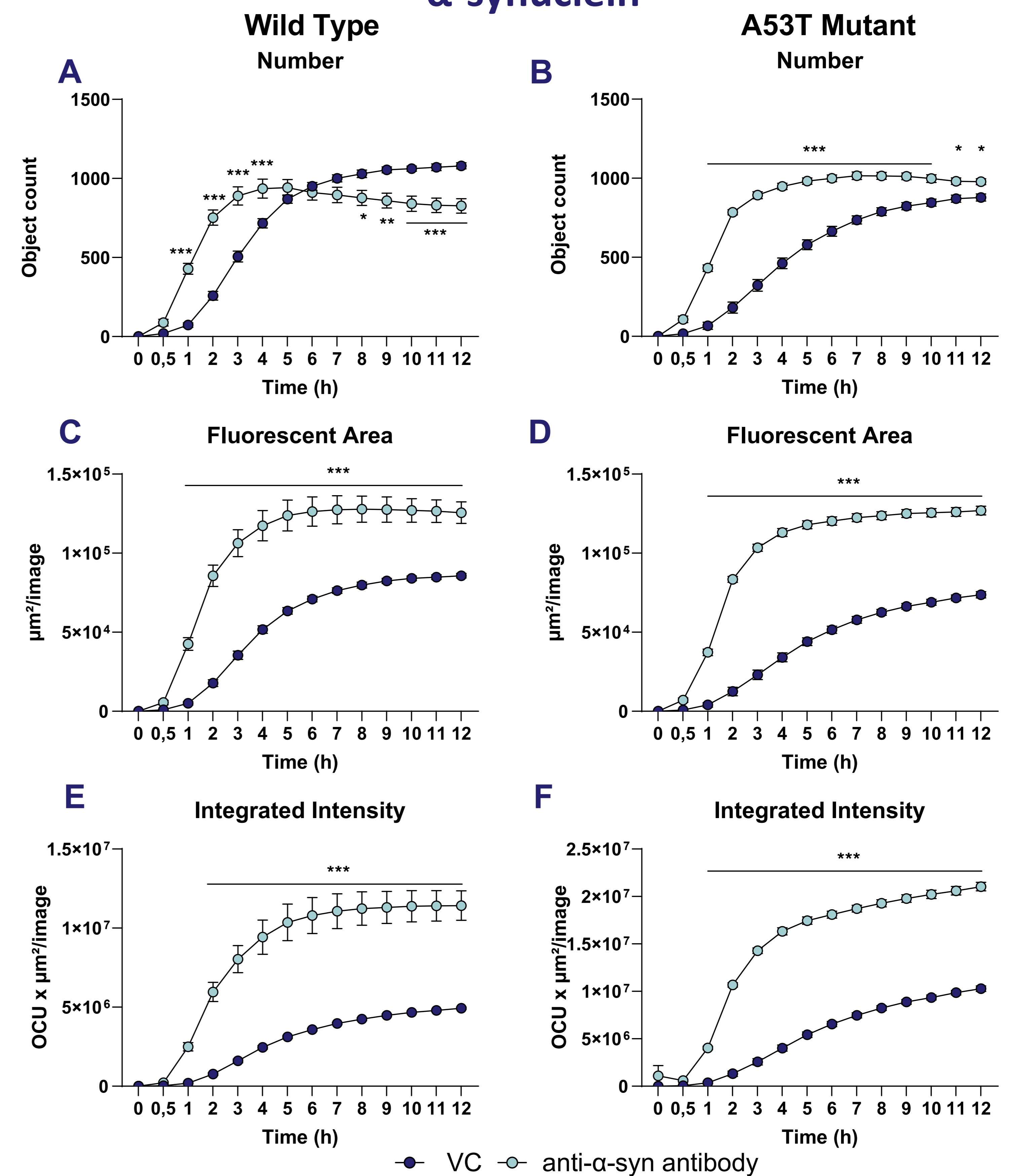
Tau



▲ **Figure 2: Microglial phagocytosis of pHrodo Tau dGAE pre-formed fibrils (PFFs) over time.** Number of orange objects (A), fluorescent area per image (B) as well as total integrated intensity of the orange signal (C) was monitored over time in cells treated with pHrodo labeled Tau dGAE PFFs alone (VC) as well as incubated with either anti-dGAE tau antibody, IgG Fc Fragment antibody or IgG Isotype control. Two-way ANOVA followed by Dunnett's multiple comparisons test. Mean + SEM. n = 6. *p < 0.5; **p < 0.01; ***p < 0.001. D: Representative images of pHrodo tau phagocytosis after treatment at 6 hours. Scale bar 400 μ m.

Results

α -synuclein



▲ **Figure 3: Microglial phagocytosis of pHrodo α -synuclein pre-formed fibrils (PFFs) over time.** Number of orange objects (A, B), fluorescent area per image (C, D) as well as total integrated intensity of the orange signal (E, F) was monitored over time in cells treated with pHrodo labeled wild type or A53T mutant α -synuclein PFFs alone (VC) or in combination with an anti- α -synuclein antibody. Two-way ANOVA followed by Dunnett's multiple comparisons test. Mean + SEM. n = 6. *p < 0.5; **p < 0.01; ***p < 0.001. G, H: Representative images of pHrodo α -synuclein PFF phagocytosis after treatment at 3 hours. Scale bar 400 μ m.

Conclusion

This assay offers a translationally relevant platform for studying microglial phagocytosis in the context of neurodegenerative disease. The combination of standardized iPSC-derived microglia, disease-relevant substrates, and sensitive fluorescence-based detection enables detailed investigation of microglial function and therapeutic modulation. It holds promise for preclinical drug screening and mechanistic studies aimed at restoring microglial clearance capacity in neurodegeneration. **Parts of this project were performed in collaboration with Amyl Therapeutics www.amyltx.com**

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For more information about the models please visit: www.scantox.com
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