Title of Dissertation: BIOENGINEERED MODELS OF ALZHEIMER'S DISEASE: STUDYING AMYLOID BETA (Aβ) PROTEIN AGGREGATION WITHIN 3D SCAFFOLDS

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Bagels and coffee will be provided

Abstract:

Alzheimer's disease (AD) is the most common form of dementia and is associated with the accumulation of amyloid-β (Aβ), a peptide that can aggregate into larger species with presumed neurotoxicity. Drugs targeting Aβ have shown great promise in 2D *in vitro* cultures and mouse models, yet human clinical trials for AD have yielded highly disappointing results.

In developing this project, I proposed that 2D *in vitro* culture systems that have been used for discovering and developing AD drugs have significant limitations. Specifically, I hypothesized that Aβ aggregation is vastly different in 2D cultures vs 3D environments, such as brain tissue. In 2D cultures, Aβ can freely diffuse and aggregate. In 3D environments, however, Aβ rearrangements are spatially restricted or "confined". Such confinement acts to exclude solvent from Aβ, resulting in Aβ having an increased local concentration and decreased entropy. The net outcome of these effects is the destabilization of disordered Aβ structures, shifting equilibrium towards larger aggregate species. It is striking that only a few 3D *in vitro* AD models have been reported, all of which ignore potential changes to Aβ structure and function that may occur within 3D systems.

This dissertation reports my investigation of Aβ aggregation and toxicity in 3D hydrogels compared to 2D culture using biophysical tools including transmission electron microscopy, fluorescence correlation spectroscopy, and thioflavin T assays. In 3D hydrogels, I found that Aβ rapidly transitions from unstructured and likely toxic oligomeric species to stable β-sheet aggregates. In 2D cultures, however, the oligomeric species has prolonged persistence. Despite quantitative differences in aggregation kinetics between hydrogels of various mesh size and bioactivity, all of the 3D hydrogels tested had attenuated Aβ cytotoxicity vs 2D culture. Therefore, this work suggests that efforts to develop AD drugs using 2D *in vitro* models may overestimate the potential toxicity of Aβ, and thus offers an explanation for the decades of failed AD drug clinical trials. These findings imply that drug discovery and development for AD, and potentially other diseases, will more rapidly identify therapeutics with greater efficacy if 3D cultures are included in early testing stages.