POLYMER-ENGINEERED AB-DEGRADING PROTEASES VIA PHOTO-ATRP FOR ALZHEIMER'S DISEASE THERAPEUTICS

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Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by the accumulation of toxic β-amyloid (Aβ) peptides in the brain[1]. Current treatments, particularly monoclonal antibody (mAb) therapies, are limited by high production costs, poor catalytic efficiency (1:1 stoichiometry with Aβ), and the need for frequent injections[2]. In contrast, Aβ- degrading proteases (AβDPs), such as neprilysin and insulin-degrading enzyme, offer catalytic degradation of Aβ with greater therapeutic potential[3,4]. However, native AβDPs suffer from instability, immunogenicity, and short *in vivo* half-lives, limiting their clinical application.

Materials and methods: To enhance AβDP stability and function, we employed visible-light- mediated, oxygen-tolerant photo-ATRP (Atom Transfer Radical Polymerization) to graft polymers directly from protein surfaces under mild, aqueous conditions. Initial method development used bovine serum albumin (BSA) as a model protein. BSA was functionalized with NHS-activated ATRP initiators to produce BSA-Br macroinitiators. Subsequently, photo-ATRP was used to grow polymers from the BSA surface oligo(ethylene glycol) methacrylate (OEGMA) and carboxybetaine methacrylate (CBMA). Conjugates were characterized via GPC, fluorescence assays. Next, we will synthesize and characterize AβDP-polymer conjugates using the same photo- ATRP method.

Results: BSA-polymer conjugates displayed enhanced resistance to proteolytic degradation. Successful polymer growth confirmed by molecular weight shifts. These results validated the protein-compatibility and shielding effect of the polymer grafts under biologically relevant conditions.

Conclusion: This study positions as the first application of photo-ATRP «grafting-from» polymerization to engineer Aβ-degrading enzymes. The polymer conjugation significantly improves protein stability and immune evasion while retaining catalytic potential. This platform presents a promising strategy for next-generation enzyme-based therapeutics in AD, addressing critical limitations of current antibody-based approaches. The integration of polymer chemistry and neurobiology opens new pathways for creating catalytically active, long-circulating, and biocompatible therapeutic enzymes.

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Keywords: Alzheimer's disease, Aβ-degrading enzymes, beta amyloid, polymers, atom-transfer radical polymerization (ATRP), enhanced stability.

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