Using Click Chemistry to Modulate the Aggregation of the Parkinson's Disease Protein

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the presence of protein aggregates called Lewy bodies. These plaques are primarily composed of oligomers of the protein α-synuclein (αS), which is a small protein of 140 amino acids that is natively unfolded, however the folding of this protein has been found to be accelerated in the presence of metal ions, particularly copper. One ideology that has been used for therapeutic removal of endogenous metal ions is chelation therapy. Click chemistry, or the Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC), involves the reaction of an alkyne and an azide, resulting in the formation of a 1,2,3-substituted triazole. This reaction is well known for being extremely versatile, accommodating a wide variety of functionalized alkynes and azides. Recently,

click chemistry was used to successfully generate a copper chelator in situ where copper ions within protein deposits acted as both the catalyst and target of the reaction. We are looking to extend this ideology to PD therapy, by preparing a small library of click reagents that will be selectively activated in the Cu-containing aggregates of αS. Following the click reaction, the newly formed products will act as a Cu-chelator, removing the Cu from the protein thus aiding in the degradation of the Lewy bodies.