

Extended Abstract

# Design, Synthesis, and Biological Evaluation of Bimodal Glycopeptides as Inhibitors of Neurotoxic Protein Aggregation <sup>†</sup>

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Post-translational modifications (PTM) of proteins are becoming the focus of a growing base of research due to their implications in a broad spectrum of neurodegenerative diseases. Various PTMs have been identified to alter their subjects' toxic profiles, playing critical roles in disease aetiology. Regarding Alzheimer's disease (AD), dysregulated phosphorylation is reported to promote pathogenic processing of the microtubule-associated tau protein. Among PTMs, the enzymatic addition of *N*-acetyl-D-glucosamine (GlcNAc) residues to Ser/Thr residues is reported to deliver protective effects against the pathogenic processing of both of amyloid precursor protein (APP) and tau. Modification of tau with as few as one single O-GlcNAc residue inhibits its toxic self-assembly. The modification has the same effect on the assembly of the Parkinson's-associated  $\alpha$ -synuclein protein also [1]. A trend is beginning to form, as O-GlcNAcylation (O-linked GlcNAc modification) affects the processing of the proteins implicated in AD, PD, amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) in a similar manner. As such, manipulation of numerous proteins' O-GlcNAcylation statuses has been proposed to offer therapeutic routes toward addressing dementia's varied underlying pathologies [2].

Targeting upstream cellular processes sometimes yields mechanism-based toxicity, however, and the enzymes governing O-GlcNAc cycling modify thousands of acceptor substrates. We propose that synthetic [3], O-GlcNAc-modified peptidomimetics may qualify as useful chemical tools that probe exclusively the effects of GlcNAc-mediated inhibition of protein self-assembly. Moreover, their strong, reversible binding qualifies peptides as model *ex vivo* imaging agents. Here we have designed, synthesised, and are in the process of evaluating novel bimodal glycopeptides derived from the native  $\alpha$ -synuclein sequence for their ability to inhibit wild-type  $\alpha$ -synuclein aggregation.

## References

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