Synthetic Heparins as Safe Disease-modifying Drugs for Early-Stage Treatment of AD via Inhibition of Beta-Secretase: Evaluation in a Transgenic Mouse Model

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Country

United Kingdom

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Synthetic Heparins as Safe Disease-modifying Drugs for Early-Stage Treatment of AD via Inhibition of Beta-Secretase: Evaluation in a Transgenic Mouse Model

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Alzheimer's Society

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€ 354,182

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2

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Research Abstract
We have generated innovative heparin-based drug candidates with a novel allosteric mode of action optimised against the validated target enzyme BACE1 (the key early step creating amyloid brain plaques in AD). The recent Aducanumab antibody phase 1 trial in patients with

pre-symptomatic or mild AD reported encouraging reductions in amyloid levels and significantly improved cognitive functions, indicating that early-stage anti-amyloid treatment is beneficial in patients identified by improved screening methods. Although BACE1 inhibition by an orally delivered drug would be a more preferred strategy, conventional small molecule approaches for active site inhibition of BACE1 have proved notoriously difficult. In contrast, we have developed complex non-anticoagulant heparin-based sugars as partially optimised leads with high potency (low nM IC50s) in vitro and ex vivo, no apparent toxicity in vivo, and a fully synthetic route to single chemical entity druggable compounds. Importantly, our recent data indicates these compounds can be delivered orally with favourable pharmacokinetics, and achieve therapeutic doses in the brain. Preliminary data from late-stage administration in the transgenic mouse models of AD indicate lowering of brain Abeta peptide levels and rescue of cognitive deficits. We now plan to further select and evaluate our best candidates to confirm their safety profile and low toxicity, check their metabolism and pharmacokinetics, and scale up production to test their early-stage administration in the well-established APP/PS1 transgenic mouse model. This would provide a pathway into late preclinical development as promising treatments for AD with excellent safety characteristics suitable for early and long-term administration for disease-modifying outcomes.

Further information available at:

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