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This proposal is representative of the projects currently on offer in our group. For more details of active research projects, please visit the Research section of our webpage at: http://www.chem.leeds.ac.uk/People/Foster.html

Development of a small molecule inhibitor of Chst for restoration of cognition in Alzheimer's disease

It is estimated that as many as 850k people in the UK have Alzheimer's disease (AD*)*. The incidence of the disease is rising in line with the aging population bringing it with escalating healthcare costs of £35 billion by 2025. There are currently no good preventative treatments or new therapeutic interventions for AD that may modify disease progression or the long-term outlook of patients with this condition.

The project aims to restore cognition in AD through regenerative biology based on the central nervous system extracellular matrix. We have shown that chondroitin sulphate, the product of chondroitin sulphate sulfotransferase (Chst), limits plasticity in the brain. In late ageing changes in the sulphation state turn off compensatory plasticity, triggering cognitive decline. The ratio between different chondroitin sulphates increases in the aged brain and transgenic mice with high specific chondroitin sulphates ratios demonstrated early memory loss as young as 3-months old.

The objective of the project will be to design and optimise small-molecule inhibitors of chondroitin sulfotransferase to restore cognitive decline. We have recently identified two classes of small molecule inhibitors of Chst with low uM potency which have the potential for further optimisation. No competitor small molecule inhibitors of Chst have been described to date.

This studentship aims to achieve the following objectives:

1. To demonstrate the ability to design drug-like and potent inhibitors of Chst
2. To demonstrate the potential for incorporation of structural hypothesis to optimisation based on *in silico* design and aim to support this work through mutation studies and collaboration with others in the Astbury Centre at Leeds for co-ligand structure determination
3. To optimise the inhibitors for drug-likeness and pharmaceutical and pharmacokinetic properties consistent with a bioavailable agent
4. To identify new hits by fragment screening (NMR or crystallography)
5. To validate the use of inhibitors in supporting the understanding of the link between AD and Chst biology

A key focus of this project will be to optimise the inhibitors for Chst potency, selectivity and physiochemical properties consistent with the properties of an orally bioavailable therapeutic. This will be achieved by strategic modification of the compounds by consideration of SAR and rationalisation of a structure-based component through use of protein structural models and a pharmacophore model for Chst modulation, as well as optimisation of physicochemical properties directed by computational prediction and *in vitro* assay. All synthesised compounds will be tested for Chst inhibition using appropriate biochemical and cellular *in vitro* assays and for selectivity using a panel of Chst enzyme homologues. The overall aim of the project will be to identify a novel strategy to target Alzheimer's disease.

The project would suit a student with general interests in medicinal chemistry and drug design. The student will receive training in medicinal chemistry, molecular modelling and general drug design as well as assay design and general biology of the target class.