Biodistribution, pharmacokinetic and toxicity studies on a novel retro-inverso peptide inhibitor of beta-amyloid oligomer formation

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Country

United Kingdom

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Biodistribution, pharmacokinetic and toxicity studies on a novel retro-inverso peptide inhibitor of beta-amyloid oligomer formation

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Alzheimer's Society

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€ 202,237

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01/12/2014

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2

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Research Abstract
Our goal is to develop a new disease-modifying drug for Alzheimer’s disease (AD) that prevents the formation of toxic ?-amyloid oligomers in the brain. We have developed a stable and brain penetrant retro-inverso peptide inhibitor (called RI-OR2-TAT) that binds with high affinity to ?-amyloid monomers and blocks the formation and toxicity of ß-amyloid oligomers in vitro. Encouragingly, this inhibitor also reduces ?-amyloid plaque load and oligomer levels when

injected peripherally (i.p.) into APPswe/PS1E9 (APP/PS1) transgenic mice. We now propose to carry out studies on the distribution, pharmacokinetics (PK) and toxicity of this potential new drug. These studies will include research into the biodistribution of fluorescently-labelled RI-OR2-TAT following its peripheral (i.p.) injection into C57BL/6 wild-type and APP/PS1 transgenic mice. This will determine how much of the inhibitor accumulates in the brain, and in other tissues, in the normal and diseased situation. We will also carry out a pharmacokinetic (PK) study of radiolabelled (tritiated) RI-OR2-TAT in normal mice, to examine the kinetics of drug absorption and elimination, and to establish the route of drug elimination, through collection of faeces and urine. The toxicity of RI-OR2-TAT will be assessed by determining whether it inhibits or activates liver cytochrome P450 enzymes, and by carrying out toxicity studies on cultured hepatocytes, cardiac, stem and neuronal cells. At the end of the project we aim to have a clear idea of whether RI-OR2-TAT has a suitable PK and toxicity profile to justify its further development for human use.

Further information available at:

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