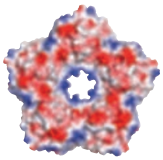
ALZHEIMER DISEASE

Could SAP depletion stabilize Alzheimer disease?



Serum amyloid P component (SAP; Figure 1) is normally present in plasma and cerebrospinal fluid, and also occurs in the amyloid plaques and neurofibrillary tangles that form the main brain lesions of Alzheimer disease (AD). Simon Kolstoe and colleagues from the University College London Medical School (London, UK) have published the results of a small, pilot, proof-of-concept human trial showing that an experimental drug, CPHPC, can almost completely deplete SAP from the circulation of patients with AD and, most notably, also results in the virtual obliteration of SAP from the cerebrospinal fluid.

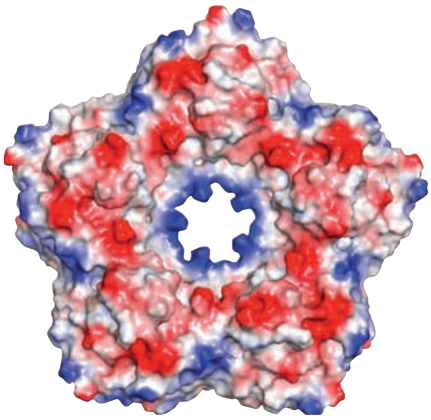
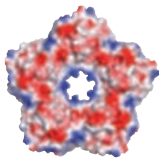


Figure 1 | Three-dimensional structure of serum amyloid P component. The coloring shows the surface charge distribution.

"Targeting SAP for the treatment or prevention of AD is a valid strategy—intracerebral amyloid plaques and neurofibrillary tangles always contain SAP and several studies have demonstrated that SAP itself is neurocytotoxic for neuronal cells both *in vitro* and *in vivo*," explains senior author Mark Pepys. Despite the efforts of many researchers, both in universities and pharmaceutical companies, effective treatments for AD remain out of our grasp. "Obviously amyloid-β, its precursor and its metabolism are at the heart of AD pathogenesis but they are exceptionally difficult targets for pharmacological intervention," Pepys explained. These biological obstacles have so far hindered progress, even though many large and small pharmaceutical companies have already spent millions trying to overcome them.



CPHPC is a novel palindromic bis-D-proline drug, (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid. The current study confirms the remarkable effect of CPHPC and reports the mechanism by which the drug causes almost complete depletion of SAP from the circulation and from the cerebrospinal fluid. "We also show for the first time the three-dimensional structure of SAP bound to a potential pathophysiologically relevant ligand, which is likely to be the structure recognized by SAP on the hyperphosphorylated tau protein found in neurofibrillary tangles," says Pepys.

CPHPC was safe and well tolerated. Although the trial duration of 12 weeks was too short to reveal any clinical benefit, encouragingly none of the five patients showed any deterioration in function as measured either by cognitive testing or MRI scanning. "An essential next step is to conduct a longer and larger scale, placebo-controlled, double-blinded phase IIa trial to pursue CPHPC as a candidate drug that could help meet the major unmet medical need in AD," says Pepys.

Kathryn Senior

Original article Kolstoe S. E. *et al.* Molecular dissection of Alzheimer's disease neuropathology by depletion of serum amyloid P component. *PNAS* doi:10.1073_pnas.0902640106