BACE1 INHIBITORS FOR THE TREATMENT OF ALZHEIMER’S DISEASE

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Introduction: Beta-site amyloid precursor protein cleaving enzyme1 (BACE1) is a type I transmembrane aspartic acid protease. Based on the key role of BACE1 in the amyloid cascade, inhibition of BACE1 is a tractable target for slowing down or halting Alzheimer’s disease progression.

Aims: Small molecule BACE1 inhibitors would be expected to prevent the generation of Aβ peptides and consequently reduce the detrimental effects of Aβ toxicity and the formation of amyloid plaques in the brain.

Methods: Potent and selective inhibitors of human BACE1 were identified using rational drug design and X-ray technology. The inhibitors were characterized in vitro in cell lines and primary mouse cortical neurons, and pharmacokinetic and pharmacodynamic (PK/PD) properties were evaluated in vivo in C57BL/6 mice and guinea pigs.

Results: In human SH-SY5Y cells and primary mouse cortical neurons our novel small molecule BACE1 inhibitors display a concentration dependent inhibition of Aβ release. Furthermore, we find that our BACE1 inhibitors exhibit dose- and time-dependent lowering of plasma, brain and CSF Aβ levels in both mice and guinea pigs. There is a good correlation between the concentrations required to inhibit Aβ release in primary neurons and effective free brain concentrations.

Conclusions: These results demonstrate that AZ’s oral small molecule BACE1 inhibitors reduce the levels of Aβ in brain, CSF and plasma, thereby supporting BACE1 inhibition as a feasible approach for disease modification in AD.