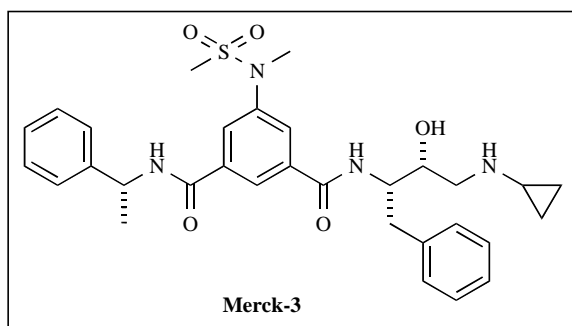


Molecule of the Month

In vivo inhibition of BACE-1 leads to A β lowering and increased APP α processing without effect on Neuregulin-1. Alzheimer's disease (AD), the most common neurodegenerative disorder amongst the elderly, afflicts over 8 million people worldwide and leads to progressive memory loss and severe cognitive dysfunction [1]. The pathological hallmarks of AD include the deposition of amyloid plaques (A β , amyloid- β peptide) and the formation of neurofibrillary tangles (Tau protein). A β is generated by the proteolysis of amyloid precursor protein (APP) which can be processed through either an amyloidogenic or non-amyloidogenic pathway (Figure 1)[1-3]. In the amyloidogenic pathway, APP is sequentially cleaved by β -secretase and then γ -secretase which leads to A β formation. In the non-amyloidogenic pathway, APP is cleaved by α -secretase to form APP $_{s\alpha}$ and precluding the generation of A β [1-3].



Despite almost a decade of research by multiple pharmaceutical companies, there have been no reports of centrally active BACE-1 inhibitors. In a recent report (*J. Pharmacol. Exp. Ther.* **2008**, *324*, 957-969), Sankaranarayanan and co-workers at Merck reported that *in vivo* BACE-1 inhibition leads to A β lowering and increased α -secretase processing of amyloid precursor protein without effects on Neuregulin-1 (NRG-1) [4]. In this study, the potent (IC₅₀ = 30 nM), selective and cell permeable BACE-1 inhibitor, coined **Merck-3** (originally reported in Stachel *et al.*, *J. Med. Chem.* **2004**, *47*, 6447-6450), was administered directly into the lateral ventricles of mice expressing wild-type APP, to determine the effects of BACE-1 inhibition brain A β , APP and NRG-1 [4,5]. The effect on NRG-1 is critically important to determine, as recent studies have shown that BACE-1 knockdown can lead to hypomyelination, resulting from a decline in NRG-1 processing.

The Merck team found that inhibition of BACE-1 *in vivo* with **Merck-3** led to significant dose- and time-dependent lowering of brain A β ₄₀ and A β ₄₂. These studies also demonstrated that *in vivo* BACE-1 inhibition also led to a robust decrease in secreted sAPP β which was accompanied by a concomitant increase in brain sAPP α levels [4]. These data support the long-held hypothesis that BACE-1 inhibition represents a disease-modifying approach for the treatment of AD; however, would NRG-1 be a show stopper?

The Merck team also examined NRG-1 processing in both homozygous (-/-) and heterozygous (+/-) BACE-1 knockout (KO) mice. An increase in full-length NRG-1 was observed in both 15-day-old BACE-1 homozygous KO (-/-) mice and heterozygous (+/-) BACE-1 knockout (KO) mice; importantly, this increase in NRG-1 processing was not detected in either 30-day-old or 2-year-old BACE-1 (-/-) KO mice [4]. Thus, these data indicated that BACE-1 knockdown only leads to a transient decrease in NRG-1 processing in mice. Similarly, pharmacological inhibition of BACE-1 in adult mice with Merck-3 had no significant effect on NRG-1 processing.

The final conclusions from this important study indicate that BACE-1 is the major β -site cleavage enzyme for APP and that selective BACE-1 inhibition lowers brain A β and redirects APP processing toward the non-amyloidogenic α -secretase pathway, without significant effect on NRG-1 processing. While **Merck-3** had to be administered i.c.v. to acquire this data, its importance in achieving *in vivo* target validation for BACE-1 inhibition, without impact on NRG-1, can not be understated. The development of centrally active BACE-1 inhibitors are eagerly awaited to combat AD, the cruelest of neurodegenerative disorders and a major unmet medical need.

REFERENCES

- [1] Sorbera, L.A.; Bozzo, J.; Serradell, N. Alzheimer's disease one century later: the search for effective therapeutic targets continues. *Drugs of the Future* **2007**, *32*, 625-641.
- [2] Selkoe, D.J. Alzheimer's disease: genes, proteins, and therapy. *Physiol. Rev.* **2001**, *81*, 741-766.
- [3] Hardy, J.; Selkoe, D.J. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* **2002**, *297*, 353-356.
- [4] Sankaranarayanan, S.; Price, E.A.; Wu, G.; Crouthamel, M-C.; Shi, X-P.; Tugusheva, K.; Tyler, K.A.; Kahana, J.; Ellis, J.; Jin, L.; Steele, T.; Stachel, S.; Coburn, C.; Simon, A.J. *In vivo* β -secretase inhibition leads to A β -lowering and increased α -secretase processing of amyloid precursor protein without effect on neuregulin-1. *J. Pharmacol. Exp. Ther.* **2008**, *324*, 957-969.
- [5] Stachel, S.J.; Coburn, C.A.; Steele, T.G.; Jones, K.G.; Loutzenhiser, E.F.; Gregro, A.R.; Rajapakse, H.A.; Lai, M-T.; Crouthamel, M-C.; Xu, M.; Tugusheva, K.; Lineberger, J.E.; Pietrak, B.L.; Espeseth, A.S.; Shi, X-P.; Chen-Dodson, E.; Holloway, M.K.; Munshi, S.; Simon, A.J.; Kuo, L.; Vacca, J.P. Structure-based design of potent and selective cell-permeable inhibitors of human β -secretase (BACE-1). *J. Med. Chem.* **2004**, *47*, 6447-6450.

Craig W. Lindsley

Vanderbilt University,
Vanderbilt University Medical Center
Departments of Pharmacology and Chemistry
Robinson Research Building 804
Nashville, TN 37232-6600,
USA