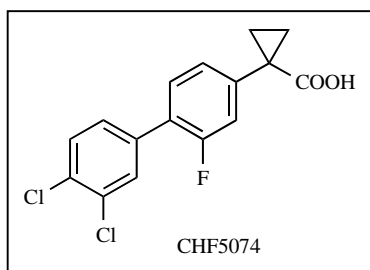


## Molecule of the Month

**CHF5074 - A novel NSAID-derived  $\gamma$ -secretase modulator that reduces brain  $\beta$ -amyloid pathology without peripheral toxicity.** Some nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to decrease A $\beta$ 42 production, and upon long-term use, may delay or prevent the onset of Alzheimer's disease (AD) in both transgenic mice and humans [1-3]. The mechanism proposed to account for this effect on A $\beta$ 42 is allosteric modulation of presenilin-1, the major component of the  $\gamma$ -secretase complex responsible for the formation of A $\beta$  [4,5]. Importantly, the inhibition of A $\beta$ 42 is independent of the anti-COX activity, and the  $\gamma$ -secretase modulator activity depends on the NSAID chemotype, with some NSAIDs (ibuprofen, indomethacin, flurbiprofen and sulindac) displaying activity and other not (naproxen, aspirin and celecoxib)[1,4,6]. Moreover, the A $\beta$ 42-lowering effects of NSAIDs differ from classical  $\gamma$ -secretase inhibitors as they do not inhibit  $\gamma$ -secretase-mediate cleavage of APP at the  $\epsilon$  site or Notch-1; however, the application of NSAIDs for the treatment of AD has been hindered by the gastrointestinal toxicity of COX inhibition [1,7].



A recent manuscript from Imbimido, *et.al.* (*J. Pharm Exp. Ther.* **2007**, 323, 822-830) presented the first demonstration that chronic administration of an NSAID-derived  $\gamma$ -secretase modulator (CHF 5074), devoid of both anticyclooxygenase (COX) and Notch-inter-fereing activities, can significantly reduce the deposition of A $\beta$  in the brain [8]. CHF5074 in human neuroglioma cells preferentially lowers A $\beta$ 42 (IC<sub>50</sub> = 40  $\mu$ M) without effect on COX-1 or COX-2 enzymes up to 300  $\mu$ M, and also had no effect on the expression profile of several Notch intracellular domain-responsive genes when dosed at 100  $\mu$ M. In addition, CHF5074 possessed good oral bioavailability in rats (%F = 50) and a long half-life ( $t_{1/2}$  = 20.7 h). In the study, aged Tg2576 mice were chronically dosed with CHF5074 (in diet 61 mg/kg/day) for 4 months, a well tolerated and safe dose [8]. Compared with controls, the area occupied by plaques and the number of plaques in

cortex (-52% and -48%, respectively) and hippocampus (-76% and -66%, respectively) were significantly reduced in CHF5074 treated animals. Furthermore, biochemical analysis demonstrated that CHF5074-treated animals displayed reduced total brain A $\beta$ 40 (-49%) and A $\beta$ 42 (-43%) levels. In a human neuroglioma cell line expressing the Swedish mutated form of APP (H4swe), CHF5074 reduced A $\beta$ 40 and A $\beta$ 42 secretion with IC<sub>50</sub> values of 3.6  $\mu$ M and 18.4  $\mu$ M, respectively [8]. Histopathological examination of the GI-tract of the chronically treated Tg2567 mice produced no abnormal findings, further indicating the lack of COX-related toxicity [8]. Based on these data, CHF5074 represents a promising new lead for the development of a potential therapeutic agent for the treatment of Alzheimer's disease.

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**Craig W. Lindsley**

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