PROTEASES

Novel route to protease targeting

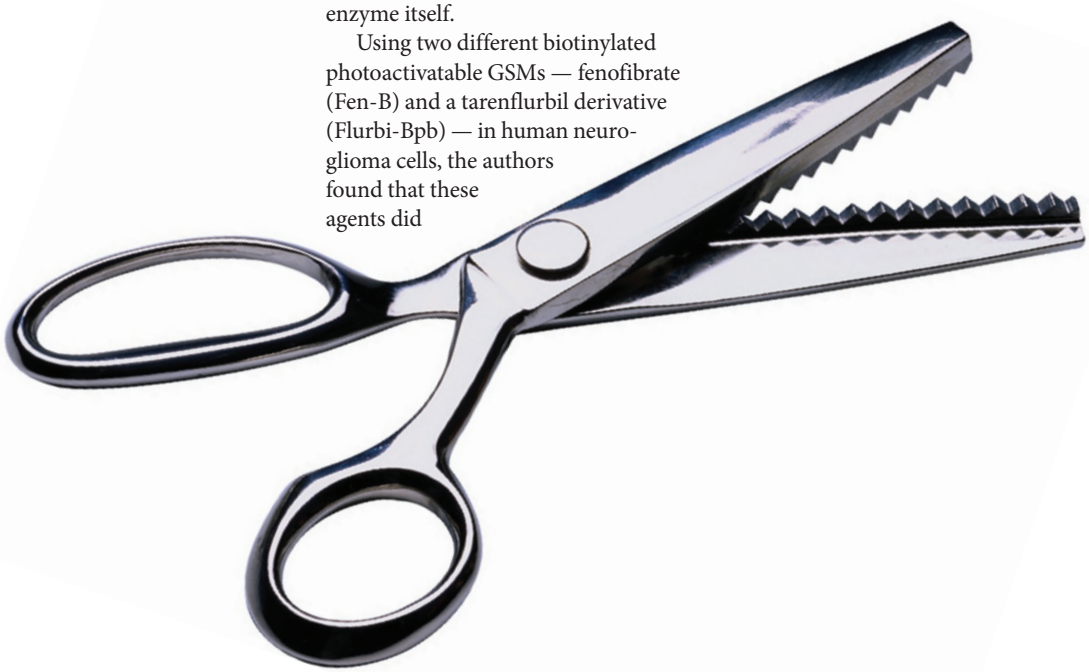
The membrane protease γ-secretase, which processes the amyloid precursor protein (APP) to produce Aβ42, the 42-residue isoform of the amyloid-β peptide, has been a popular therapeutic target for Alzheimer's disease. Many efforts have focused on developing direct protease inhibitors, but intriguingly, a subset of non-steroidal anti-inflammatory drugs (NSAIDs) have been found to act as γ-secretase modulators (GSMs) that can selectively lower Aβ42 levels. Now, writing in *Nature*, Kukar *et al.* shed new light on the underlying mechanism, showing that GSMs target APP, the enzyme's substrate, rather than the enzyme itself.

Using two different biotinylated photoactivatable GSMs — fenofibrate (Fen-B) and a tarenflurbil derivative (Flurbi-Bpb) — in human neuroglioma cells, the authors found that these agents did not label any of the core components of the γ-secretase complex, but instead bound to APP. Although the GSM photoprobes could also bind to Notch (another γ-secretase substrate) *in vitro*, the binding affinity was considerably lower than that for APP. Targeting APP is likely to be a common mechanism of action for GSMs, as both Aβ42-lowering and Aβ42-raising GSMs competed with Fen-B for APP labelling.

Interestingly, the binding site of GSMs resides in a region of APP that has previously been shown to be crucial for amyloid-β aggregation. Furthermore, the authors show that several structurally unrelated compounds that bind to this region can also act as GSMs (altering the levels of Aβ42 and decreasing amyloid-β aggregation *in vivo*), and that mutation of this region alters the sensitivity of APP to GSMs.

Disappointingly, it has recently been announced that tarenflurbil failed in a late-stage clinical trial in Alzheimer's disease (http://www.myriad.com/news/release/1170283). Nevertheless, the findings from Kukar *et al.* suggest that it might be possible to develop optimized small molecules that can decrease Aβ42 production and prevent amyloid-β aggregation by selectively binding to APP. Furthermore, the study also raises the exciting possibility that substrate targeting might represent a novel general therapeutic strategy for modulating proteolytic enzymes.

Monica Hoyos Flight



ORIGINAL RESEARCH PAPER Kukar, T. L. *et al.* Substrate-targeting γ-secretase modulators. *Nature* **453**, 925–929 (2008)
FURTHER READING Kodadek, T. Molecular cloaking devices. Substrate-targeting γ-secretase modulators. *Nature* **453**, 861–862 (2008) | Melnikova, I. Therapies for Alzheimer's disease. *Nature Rev. Drug Discov.* **6**, 341–342 (2007)