These drugs were apparently ineffective, but perhaps other calcium-modulating compounds, specifically targeting endoplasmic reticulum pools of calcium, would

yield a more favorable outcome. In light of the fresh insights from Tu *et al.*, the good news is that we already know a great deal about calcium pharmacology—enough to give us a substantial head start if, indeed, the “calcium hypothesis of Alzheimer’s”¹⁰ is back to stay.

Figure 2 Potential steps leading from familial Alzheimer mutations (APP mutations, PS1 mutations) to neurotoxicity and neurodegeneration, via either Aβ-dependent (left) or Aβ-independent (right) pathways. Proximate mediators of toxicity (Aβ oligomers, calcium) are connected to the cartoon neuron using dashed arrows.

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Alzheimer disease: BACE1 branches out

An enzyme that helps generate clumps of amyloid-β in the brains of people with Alzheimer disease also has a role in myelinating axons, according to a study in *Science* (doi: 10.1126/science.1132341). The findings sound a cautionary note for ongoing efforts to develop drugs to inactivate this enzyme.

The enzyme, BACE1 (beta-site amyloid precursor protein–cleaving enzyme 1), is required to cleave amyloid-β from a larger precursor. (After BACE1-mediated cleavage, the presenilin-containing complex γ-secretase makes the final cleavage, liberating amyloid-β.)

Michael Willem *et al.* found that BACE1 seems to be required for processing a signal, the EGF-like factor neuregulin 1, that activates receptors on Schwann cells. Activation of these receptors is required for myelination.

One observation supporting this hypothesis was that animals deficient in BACE-1 had myelin defects in the peripheral nerves. Shown is a cross-section of the sciatic nerve of an 8-day-old BACE1-deficient mouse; myelin sheath in black. The myelin is thinner than in wild-type mice and some axons lack myelin altogether.

Peripheral nerve myelination occurs early in life, so it is unclear how BACE1 inhibition might affect older animals. Whether BACE1 also has a role in myelination of the central nervous system is also unclear.

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