

Mivelsiran Therapeutic Hypothesis

Target:

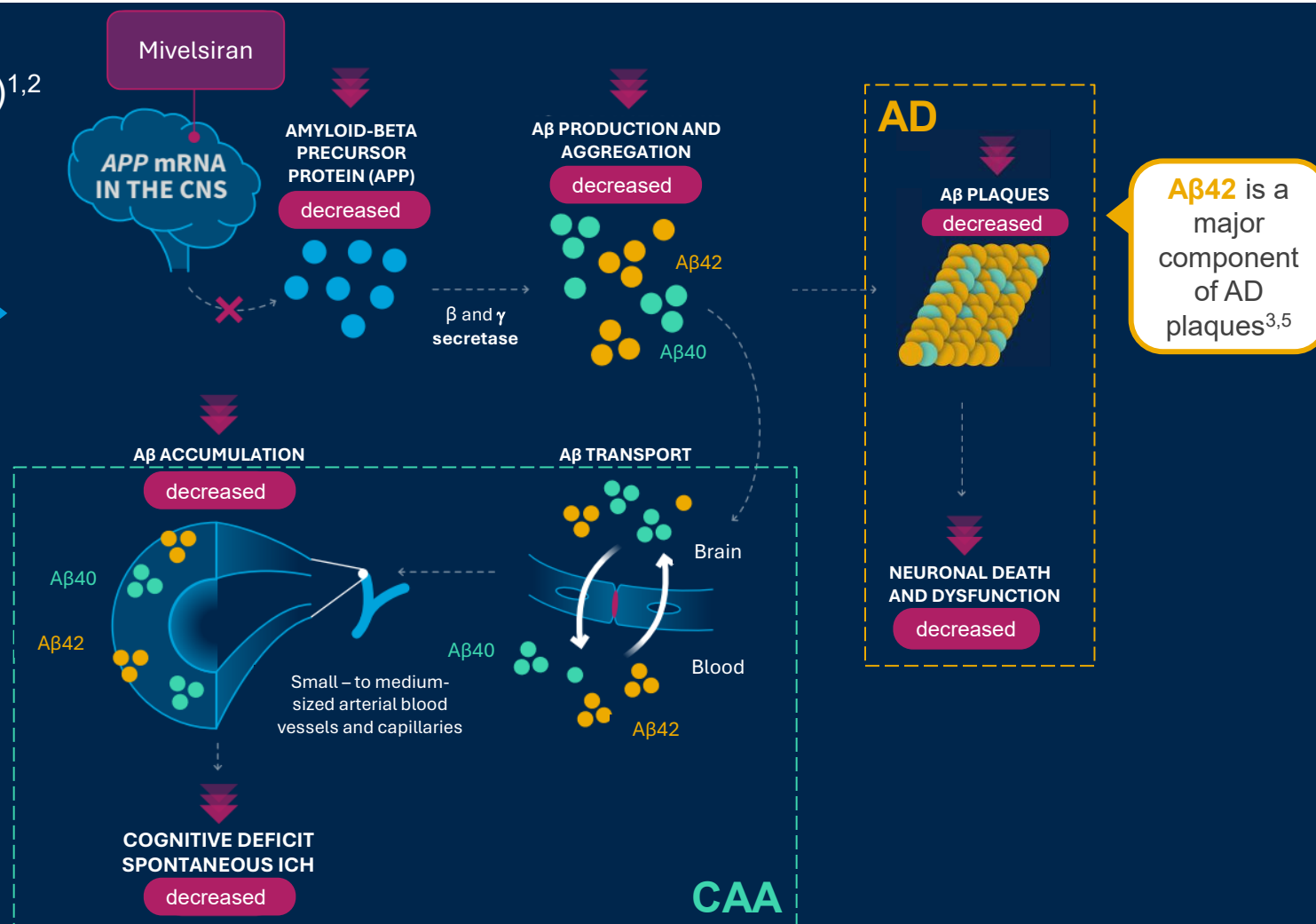
Amyloid-beta precursor protein (APP)^{1,2}

siRNA delivery technology:

C16 conjugation²

APP is the source of intracellular and extracellular cleavage products, including A β -peptides,^{1,2} which can accumulate in brain vessels as two major isoforms—A β 40 and A β 42—in CAA and AD^{2,3}

A β 40 is the predominant form in CAA vascular amyloid deposits^{1,3,4}



Mivelsiran targets APP mRNA in the CNS, reducing production of APP and potentially all downstream APP-derived cleavage products^{2,6}

Figure adapted from Gatti et al. 2020.¹ AD, Alzheimer's disease; APP, A β precursor protein; A β , amyloid-beta; A β 40, amyloid-beta peptide length 40 amino acids; A β 42, amyloid-beta peptide length 42 amino acids; C16, 2'-O-hexadecyl; CAA, cerebral amyloid angiopathy; CNS, central nervous system; ICH, intracerebral hemorrhage; mRNA, messenger RNA; siRNA, small interfering RNA. 1. Gatti L et al. *Int J Mol Sci.* 2020;21(10):3435. 2. Mummery C et al. *Clinical Trials on Alzheimer's Disease (CTAD) Conference*, October 24–27, 2023; Boston, MA, USA. Oral presentation. 3. Greenberg SM et al. *Nat Rev Neurol.* 2020;16(1):30–42. 4. Verbeek MM et al. *Ann Neurol.* 2009;66(2):245–9. 5. Biffi A, Greenberg SM. *J Clin Neurol.* 2011;7:1–9. 6. Brown K et al. *AD/PD 2023 Advances in Science & Therapy International Conference*, March 28–April 1, 2023; Gothenburg, Sweden. Oral presentation.