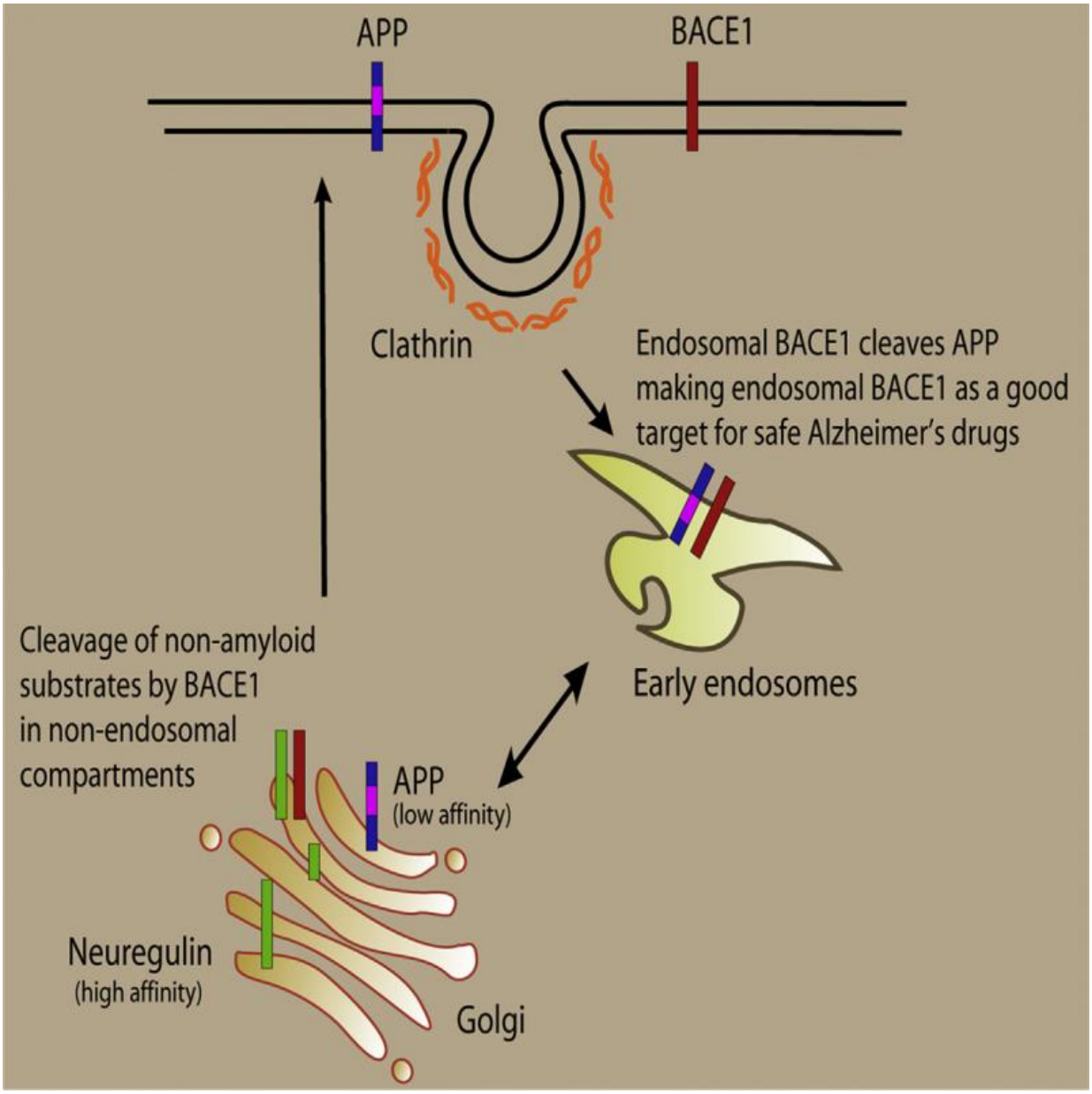
Researchers work to block harmful behavior of key Alzheimer's enzyme

February 25 2016



This visual abstract depicts how Ben Halima et al. demonstrate the feasibility of designing drugs targeting the Alzheimer-related enzyme BACE1 without affecting its physiological function. Using structural, biochemical, and cellular approaches, they show that BACE1 inhibitors can be designed to specifically inhibit its disease-causing activity, enhancing their potential as therapeutics without undesired side effects. Credit: Ben Halima et al./*Cell Reports* 2016

Enzymes rarely have one job. So, attempts to shut down the enzyme that causes the hallmarks of Alzheimer's disease often mean side effects, because these therapies prevent the enzyme from carrying out many other functions. A study appearing February 25 in *Cell Reports* presents a new therapeutic strategy: blocking the most harmful behavior enzyme while allowing it to work normally otherwise. This potential approach now needs to be further developed and tested in pre-clinical trials.

In the brains of patients with Alzheimer's disease (AD), amyloid precursor protein is broken apart, and the resulting fragments—β-amyloid peptides, or Aβ peptides—aggregate to form plaques. Aβ peptides are produced by the action of two enzymes called beta- and gamma-secretases. Inhibiting either of these enzymes would block the production of toxic Aβ peptides; however, attempts to inhibit gamma-secretase caused problems in clinical trials because the enzyme also cleaves more than 20 other proteins important for normal physiology. β-secretase is now considered an alternative therapeutic target for AD, and a wide variety of inhibitors have been developed; however, β-secretase also cleaves several other proteins with normal functions in the body.

In their latest research, Lawrence Rajendran, of the University of Zurich in Switzerland, and his colleagues discovered that, unlike non-amyloid proteins, the Alzheimer's-associated amyloid precursor protein is cleaved by β-secretase in membrane-bound compartments inside cells, called

endosomes. Exploiting this compartmentalization, the team developed an endosomally-targeted β-secretase inhibitor that specifically blocked cleavage of amyloid precursor protein but not non-amyloid proteins. This is the first time such specificity has been achieved, and it thus provides a potentially promising way to treat AD without causing major side effects.

"The current β-secretase inhibitors inhibit both the Alzheimer's disease process and physiologically relevant processes, and this would be a major problem, similar to the gamma-secretase inhibitors that failed in the clinic; however, with our strategy, we now can specifically inhibit the Alzheimer's process thereby avoiding any side effects," says Rajendran. He and his team plan to develop this inhibitor further and test it in clinical trials.

More information: *Cell Reports*, Ben Halima et al.: "Specific Inhibition of β -Secretase Processing of the Alzheimer Disease Amyloid Precursor Protein" dx.doi.org/10.1016/j.celrep.2016.01.076

Provided by Cell Press