Findings by UChicago researchers about a key enzyme in the development of Alzheimer’s disease point to a new way of targeting an important protein for therapies.

In a study published in *Cell Reports*, Gopal Thinakaran, PhD, professor of neurobiology, neurology, and pathology, and his team described how the enzyme beta-secretase 1 (BACE1) utilizes a unique, previously unknown transportation system in the brain.

A hallmark of Alzheimer’s disease, amyloid plaques are formed from protein fragments known as beta-amyloid, which is toxic to neurons. BACE1 plays a key role in this process. The enzyme is known to travel along nerve projections and accumulate in the junctions between neurons, where it initiates the production of beta-amyloid.

Led by postdoctoral fellow Virginie Buggia-Prévot, PhD, and neuroscience graduate student Celia Fernandez, Thinakaran and his team devised a way to track BACE1 movement. They labelled BACE1 with a jellyfish-derived yellow fluorescence protein, allowing them to visualize and record in real time the dynamic movement of BACE1 through neurons with a microscope.

Through a series of remarkable videos, the team found that BACE1 was transported in a manner never before seen. The enzyme traveled back and forth from the cell body of the neuron down the axon, a long projection that sends electrical signals to other neurons. But BACE1 moved in only one direction along dendrites, the multibranched neuronal projections that receive electrical impulses from other neurons.

Searching for the underlying mechanism of this unique transportation system, the researchers found that BACE1 resides and travels in small bubbles known as endosomes and that a group of proteins known as EHD regulates this movement. When EHD was blocked, BACE1 transport was reduced. Importantly, this reduced the levels of beta-amyloid as well.

The team hopes to develop a comprehensive understanding of this transport system, what role it plays in Alzheimer’s disease, and how it might some day be controlled in order to reduce amyloid burden in the brain.

“Understanding the details regarding the cellular and molecular mechanisms involved in beta-amyloid production is a topic of central importance in Alzheimer’s disease research,” Thinakaran said.