TOOLBOX

# Cell's own machinery can deliver therapies to the brain

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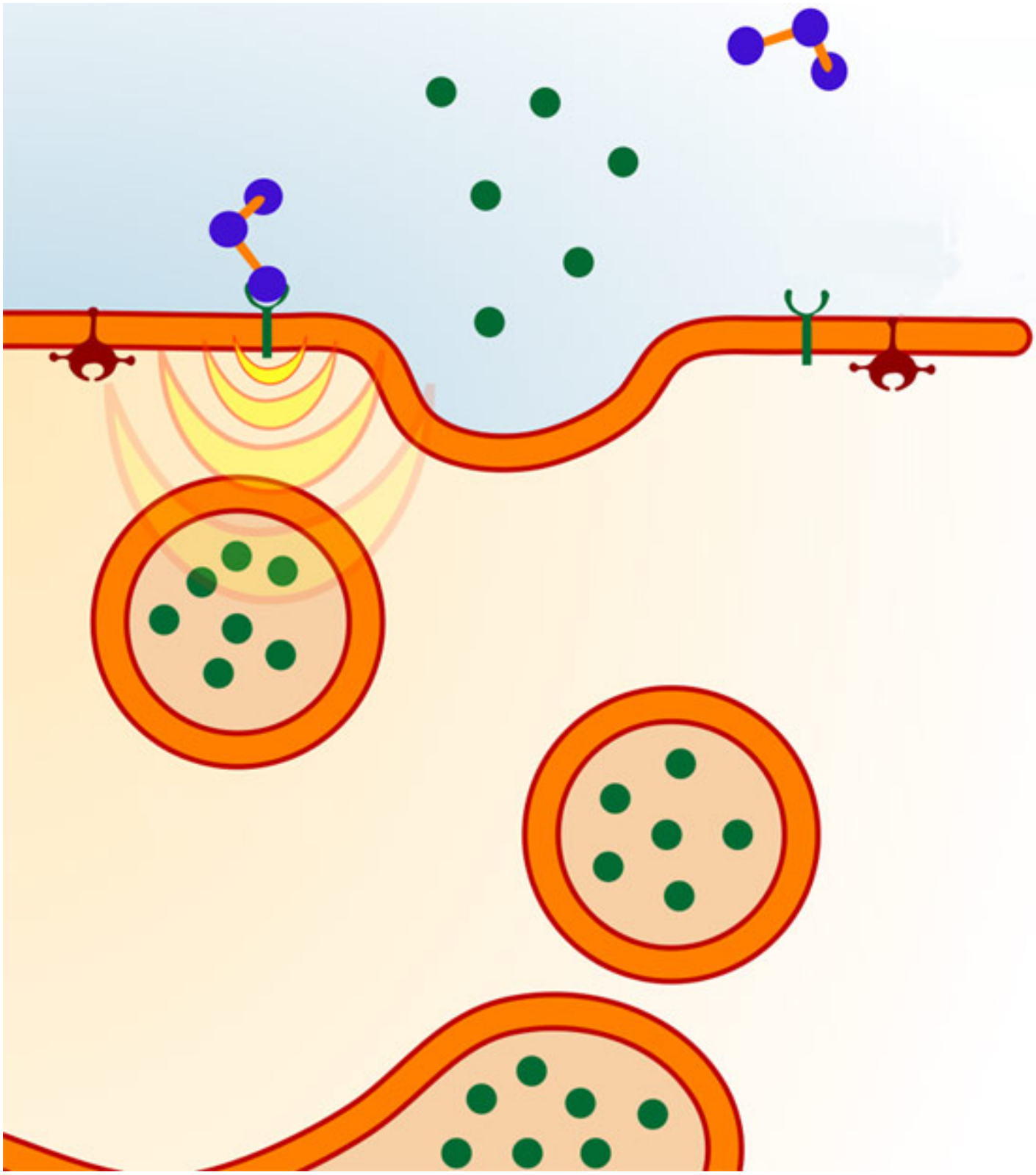

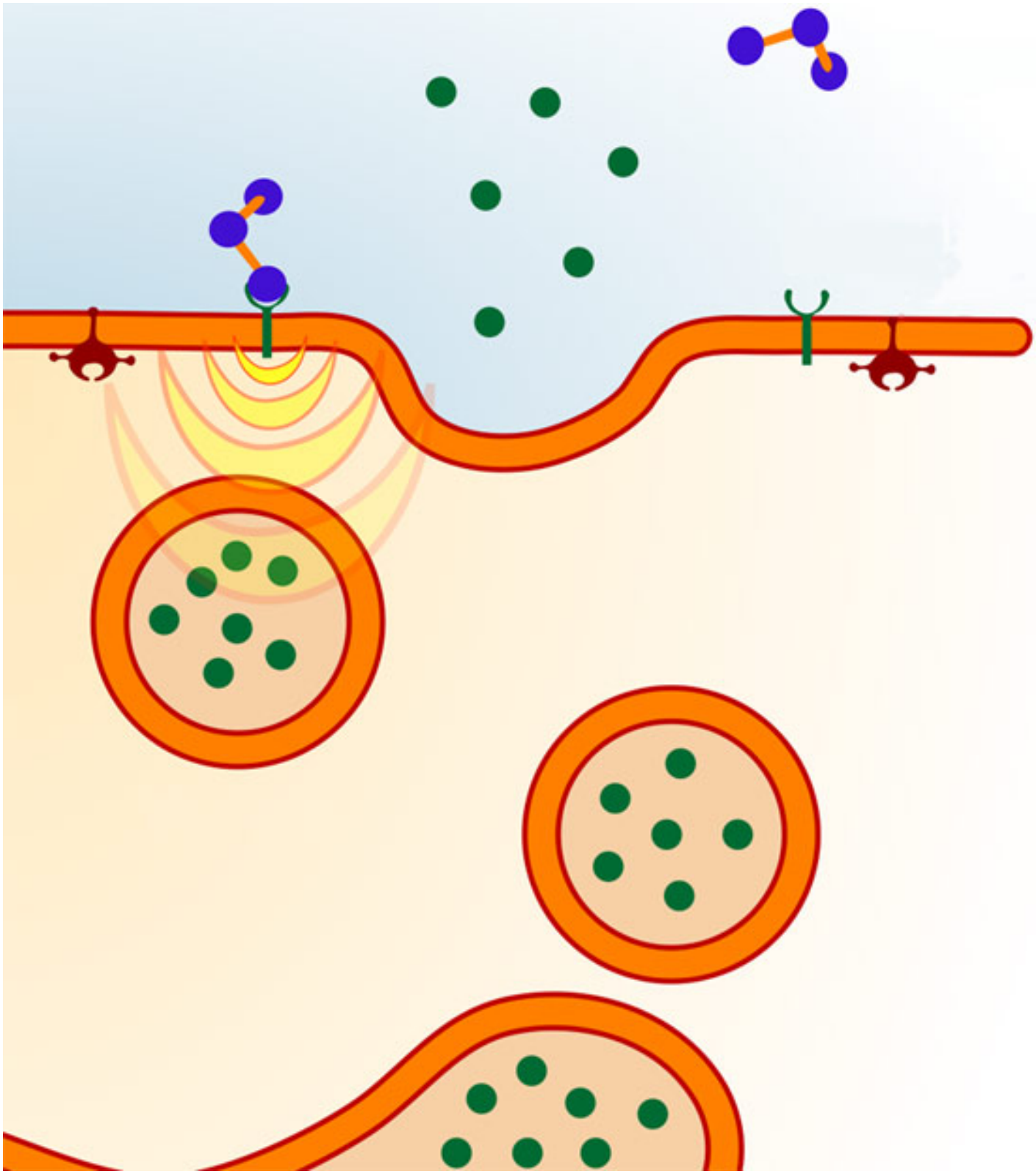

Express delivery: Researchers can use bubbles of cellular membrane, called exosomes, to carry therapies into the brain.

Exosomes, the brain's system for delivering and recycling molecules, can be manipulated to **carry therapeutic fragments of RNA or DNA** across the blood-brain barrier and into neurons. The ingenious new technique was published 20 March in *Nature Biotechnology*.

As studies uncover the genetic and molecular causes of autism, gene therapy — silencing the expression or boosting levels of a particular gene product — could emerge as a therapeutic option.

Targeting these genes to brain cells is complicated, however. Injecting constructs into the blood delivers them indiscriminately to all tissues, and the blood-brain barrier prevents most molecules from crossing into the brain at all.

In the new study, researchers solved both problems by coating mouse exosomes — bubbles of membrane that pinch off and merge their contents when they fuse with another membrane — with a brain-targeting protein.

The exosomes are engineered from mouse bone marrow, and purified and filled with short genetic fragments called siRNA, or short interfering RNA. These fragments bind to and silence specific messages that code for protein. When injected into mice, exosomes containing siRNA for BACE1, a protein associated with Alzheimer's disease, lower BACE1 protein levels by 62 percent in brain tissue.

Injecting siRNA for GAPDH — a protein present in all tissues — into blood silences the protein in the liver, spleen and kidney, but not the brain. By contrast, when GAPDH siRNA is delivered in brain-specific exosomes, it has no effect on these tissues and targets only neurons and other brain cells, including microglia.

Although the genetic causes of autism are not yet well enough understood to suggest a clear target for gene therapy, the ability to target molecules specifically to the brain has potentially wide applications for research into all neurodevelopmental disorders.