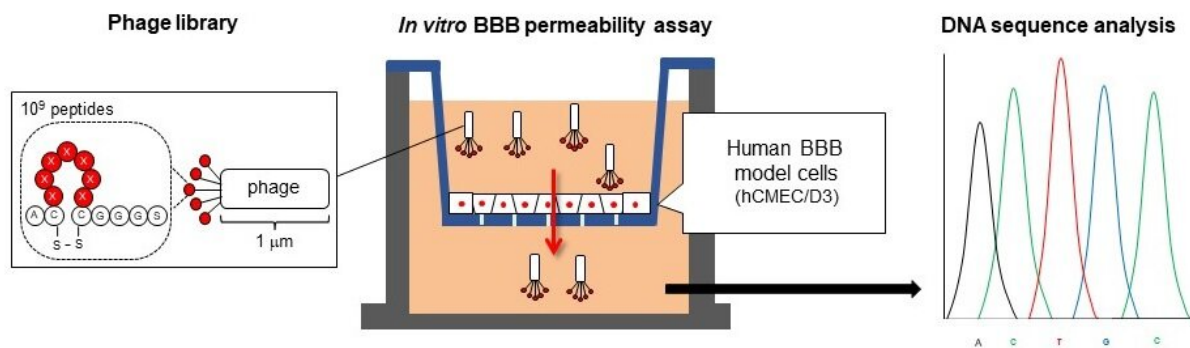


# New nanocarrier drug delivery technology crosses the blood-brain barrier

April 17 2020



A Kumamoto University research group collected phages that penetrate human blood-brain barrier model cells and analyzed the amino acid sequence of the peptides on the permeating phages. Credit: Professor Sumio Ohtsuki

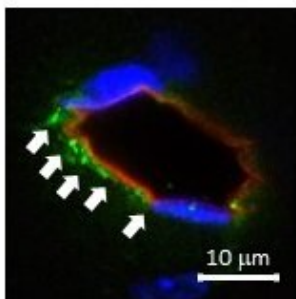
A Japanese research team has developed a cyclic peptide (a chain of amino acids bonded circularly) that enhances blood-brain barrier (BBB) penetration. By attaching the cyclic peptide to the surface of nanoparticles, research and development of new drug nanocarriers for drug delivery to the brain becomes possible.

Unlike [blood circulation](#) to the peripheral organs in the body, the BBB prevents various substances, including many drugs, from moving from the blood into the brain. Biopharmaceuticals and macromolecular drugs are attracting attention as new treatments for previously untreatable

diseases and for improving outcomes. However, these high molecular weight drugs are unable to penetrate the BBB. Technologies that can deliver them to the brain would bring significant progress in the development of medications that act on the brain.

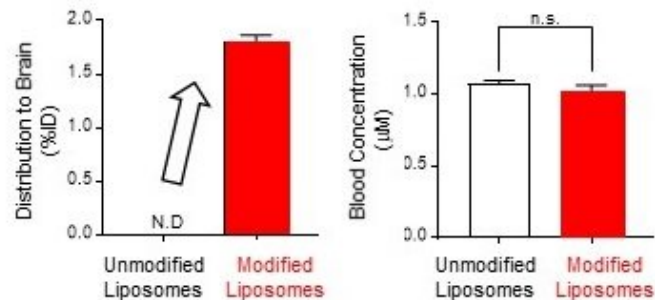
Aiming to develop technologies applicable to various drugs, a research team from Kumamoto University, Japan worked on developing a cyclic peptide able to penetrate the BBB. In their search to find a peptide with the desired function, they turned to viruses called phages. From a phage library listing cyclic peptides with  $10^9$  types of amino acid sequences, the researchers searched for phages able to penetrate human BBB model cells and analyzed their sequences. Since the size of a phage (about 1,000 nanometers) is larger than macromolecular drugs, the scientists expected that these cyclic peptides would also allow [drug](#) penetration into the BBB.

Penetration of phages modified with the identified (new) cyclic peptides



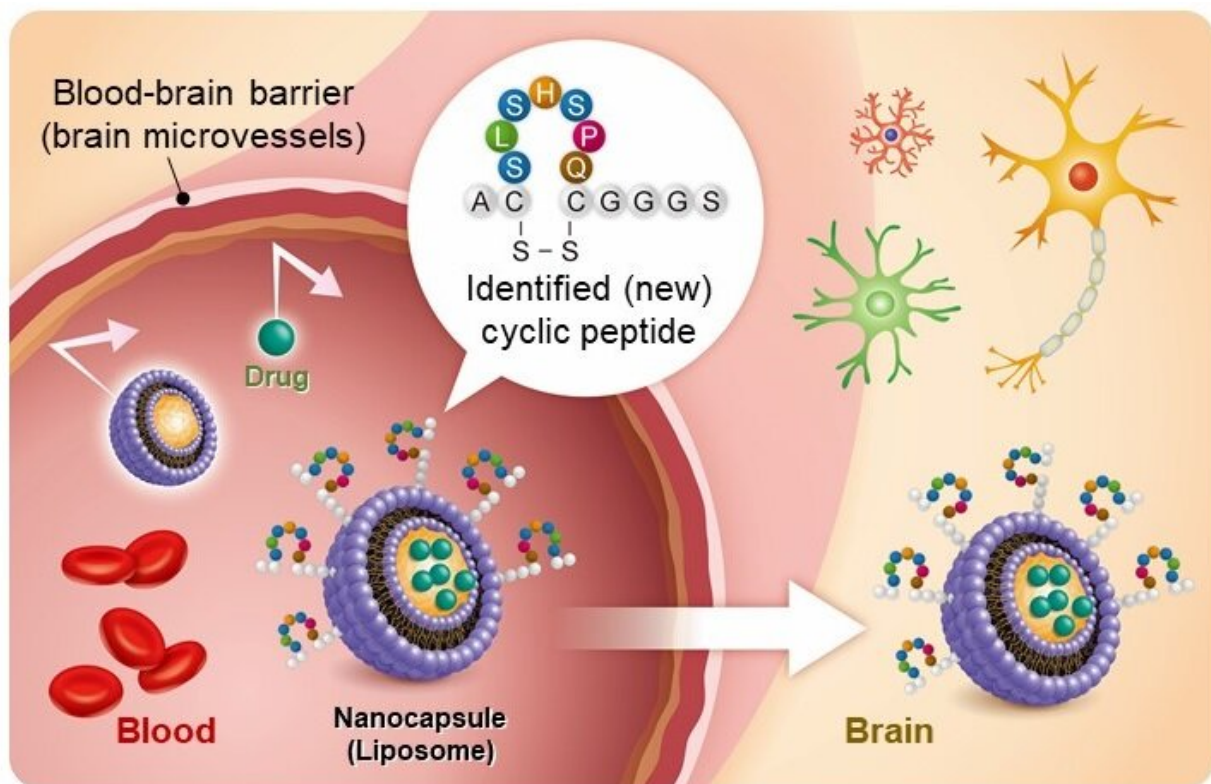
Phages (green) are distributed outside cerebral microvessels (red) 60 min after intravenous injection

Brain distribution and blood concentration of liposomes modified with identified (new) cyclic peptide 60 min after intravenous injection



(Left) The phages with the new cyclic peptide were intravenously injected into a mouse. Sixty minutes later the brain was analyzed and phages were detected in the brain. Credit: Professor Sumio Ohtsuki

Of the two new cyclic [peptides](#) they discovered, one promoted phage penetration not only in human BBB model cells but also in monkey and rat BBB model cells. Furthermore, this phage could be found in the brain of a mouse 60 minutes after intravenous injection. In additional experiments, the researchers modified liposomes by adding the cyclic peptide to the surface of liposomes thereby creating 150 nanometer-sized artificial nanoparticles. When this modified liposome was injected intravenously into a mouse, it was also detected in the brain 60 minutes later showing that the new cyclic peptide facilitates penetration of [phage](#) and liposome nanoparticles through the BBB allowing for delivery into the brain.



Delivery of pharmaceuticals by nanocarrier through the blood-brain barrier can be done using the newly discovered cyclic peptide. Credit: Professor Sumio Ohtsuki

"Liposomes are a nanocarrier that can encapsulate various substances. The liposome whose surface has been modified with this new cyclic peptide can be used as a nanocarrier to bypass the BBB. A way to deliver macromolecular drugs to the [brain](#) has been opened," said Professor Ohtsuki. "We expect this research to contribute significantly toward the development of drugs for central nervous system diseases, including Alzheimer's disease."

**More information:** Shunsuke Yamaguchi et al, Novel cyclic peptides facilitating transcellular blood-brain barrier transport of macromolecules in vitro and in vivo, *Journal of Controlled Release* (2020). [DOI: 10.1016/j.jconrel.2020.03.001](#)

Provided by Kumamoto University

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