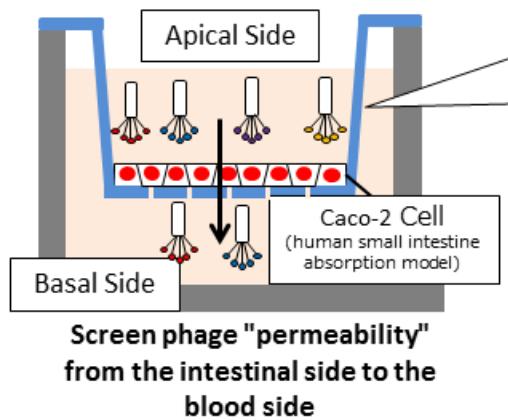


Small intestine permeable peptides facilitate digestive tract absorption

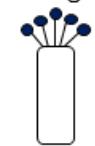
September 21 2017

Screening of phage group by human small intestine absorption model



A cyclic peptide presenting phage was captured as a model macromolecule.

Phage



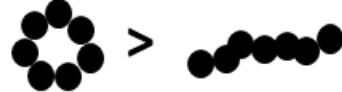
Molecular weight
≈ 610,000 (g/mol)



Biopharmaceuticals
E.g., Insulin

Molecular weight
≈ several thousand to tens of thousands (g/mol)

Stability in intestinal tract



Orally administered biopharmaceuticals must permeate human small intestinal epithelial cells. This may be done by identifying innovative cyclic peptides that facilitate small intestinal absorption of phage macromolecules that are larger than biopharmaceuticals. (Reprinted from the Journal of Controlled Release, 262, Shunsuke Yamaguchi, Shingo Ito, Mio Kurogi-Hirayama, Sumio Ohtsuki, Identification of cyclic peptides for facilitation of transcellular transport of phages across intestinal epithelium in vitro and in vivo, 232-238, 2017 with permission from Elsevier.)

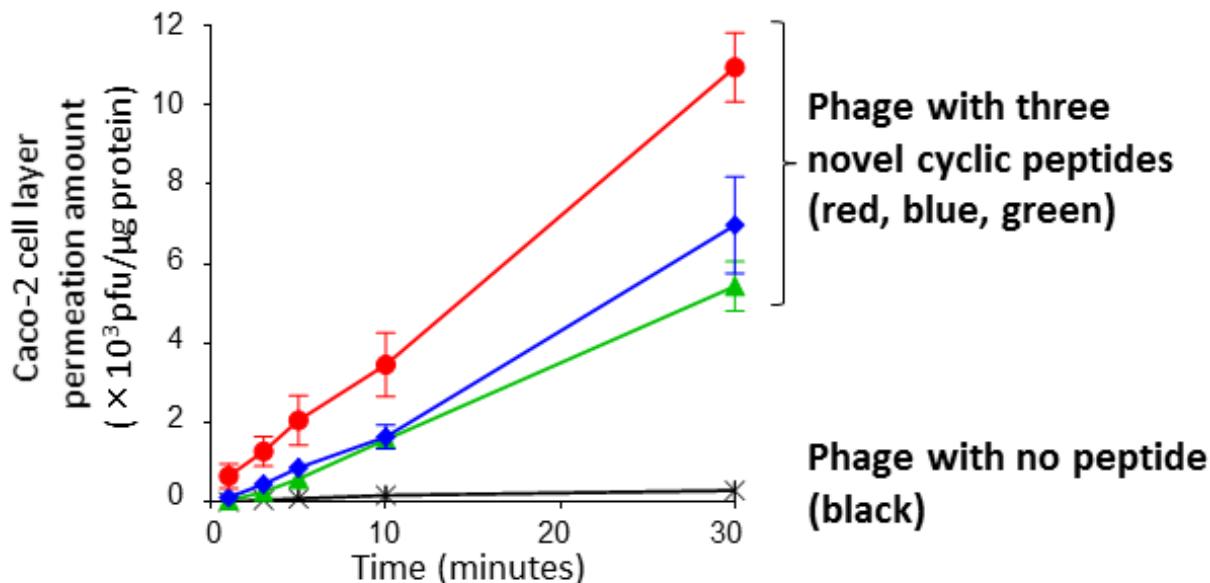
Because biopharmaceuticals are medium- and high-molecular-weight, biologically active macromolecules, they are not easily absorbed by the

small intestine, resulting in a bottleneck for oral administration. Now, researchers from Kumamoto University in Japan have found a new, small-intestine-permeable peptide that can facilitate digestive tract absorption of biopharmaceutical products. The discovery is expected to contribute greatly to the development of orally administered drugs for medications that are currently only available by injection, including widely used biopharmaceuticals such as insulin.

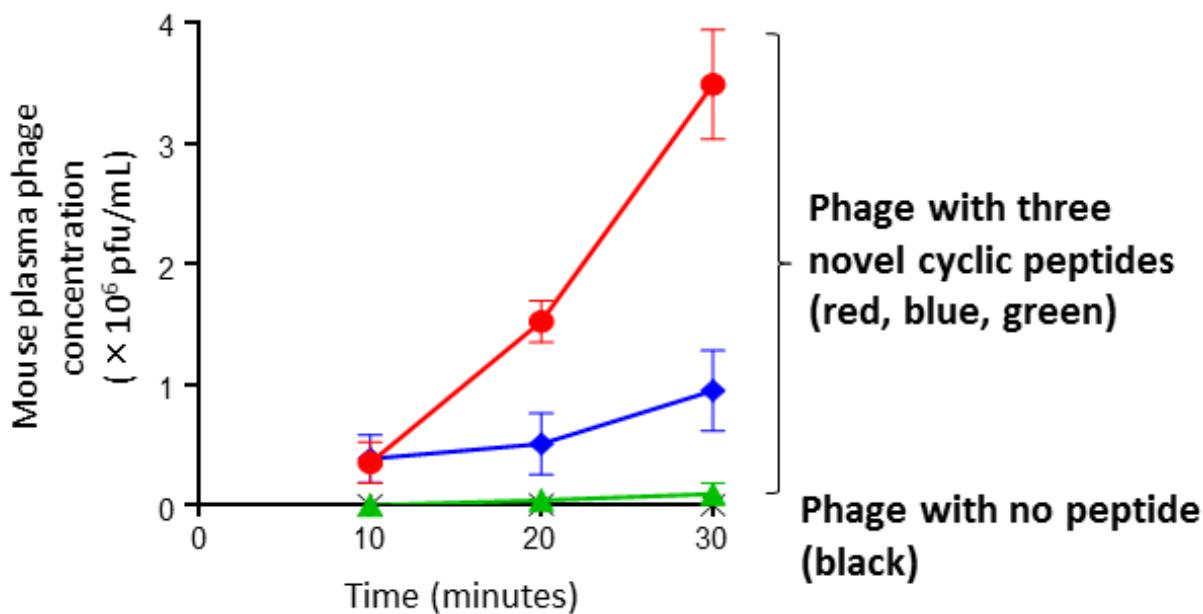
Orally administered medicines are among the most convenient and safest types of medications. Many drugs currently on the market are low molecular weight compounds that can be absorbed by the small [intestine](#). Bio-medicines such as insulin, antibodies and nucleic acids are almost completely unabsorbed in the small intestine because they are macromolecular compounds with large constituent molecular weights. Therefore, there are currently no oral formulations for these biopharmaceuticals, so they are administered through injections, which are physically and mentally burdensome to the patient.

Cell-penetrating [peptides](#) (CPPs) are peptides that facilitate the delivery of molecules with low cell membrane permeability, including proteins and nucleic acids, through the cell membrane. It is therefore a promising method to facilitate small intestine [absorption](#) (penetration) of polymer drugs. However, when using existing CPPs to bind to biopharmaceuticals, the effect on intestinal absorption improvement is small.

Caco-2 cell permeability experiment



Mouse small intestine absorption experiment



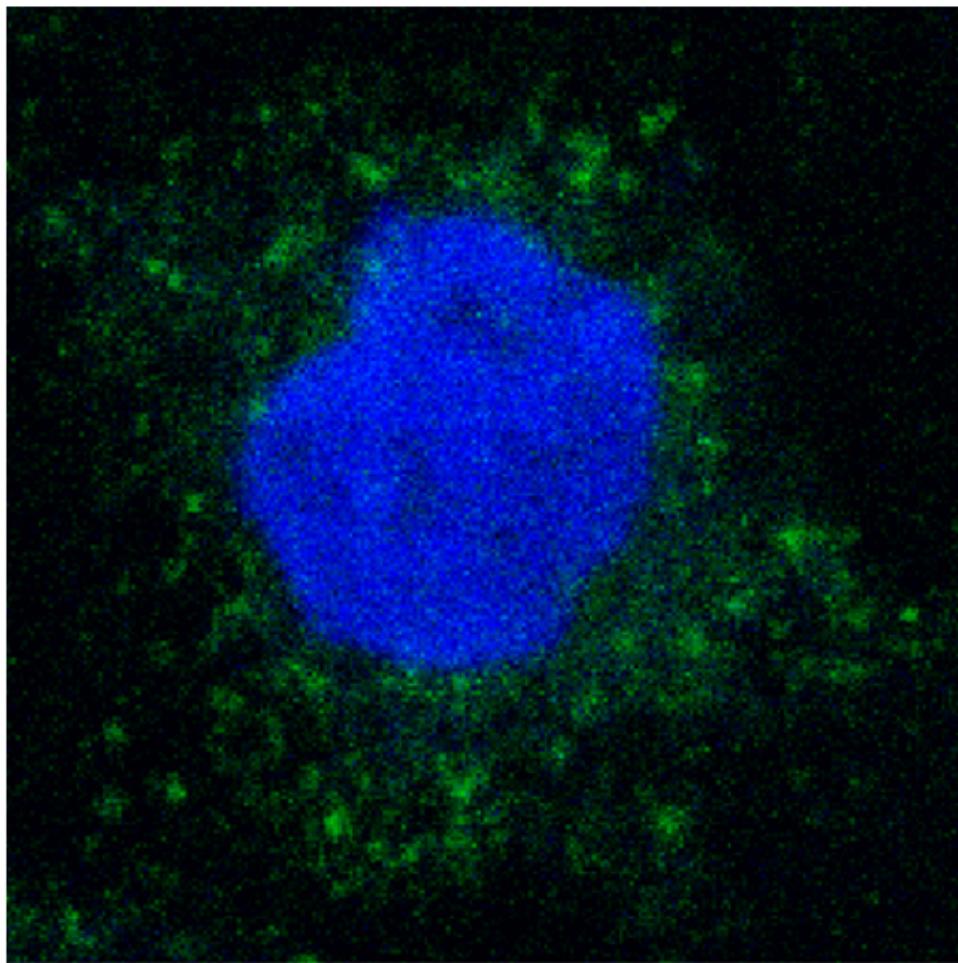
Phage permeability facilitation by identified cyclic peptides across human intestinal model cells and mouse small intestine. [Top] Caco-2 cell permeability experiment, [Bottom] Mouse small intestine absorption experiment. (Reprinted from the *Journal of Controlled Release*, 262, Shunsuke Yamaguchi, Shingo Ito, Mio Kurogi-Hirayama, Sumio Ohtsuki, Identification of cyclic peptides for

facilitation of transcellular transport of phages across intestinal epithelium in vitro and in vivo, 232-238, 2017 with permission from Elsevier.)

Kumamoto University researchers thought that even though existing CPPs facilitate the transport from the gastrointestinal tract into small intestinal epithelial cells, transportation from inside the cells to the blood is not well facilitated. Therefore, they searched for "small intestinal permeable peptides" to improve biopharmaceuticals absorption in the digestive tract.

Viruses called phages are widely used to search for peptides with specific functions. From a phage library presenting cyclic peptides of amino acid sequences, researchers gathered phages that permeated across the Caco-2 cell layer. They then analyzed the phage peptides that permeated the cell since Caco-2 cells are widely used as a human small intestine absorption model. Since phages are typically larger than biopharmaceuticals, around 1 micrometer in size, cyclic peptides promoting small intestinal absorption of phages should have the ability to facilitate absorption of biopharmaceuticals.

Three new cyclic peptides were identified as a result of the analysis. These cyclic peptides facilitated the absorption of phages in Caco-2 cells and in mouse small intestines. An analysis of this cyclic peptide found that it is transferred into the cell through macropinocytosis, a mechanism utilized for incorporating large, extracellular substances into the cell.



[Blue] Core of Caco-2 cells, [Green] Novel cyclic peptide incorporated into Caco-2 cells.(Reprinted from the *Journal of Controlled Release*, 262, Shunsuke Yamaguchi, Shingo Ito, Mio Kurogi-Hirayama, Sumio Ohtsuki, Identification of cyclic peptides for facilitation of transcellular transport of phages across intestinal epithelium in vitro and in vivo, 232-238, 2017 with permission from Elsevier.)

"The goal of our research was to enable the oral administration of medicines with large molecular weights. These medications are not readily absorbed by the small intestine and are typically administered through injection. We have cleared this hurdle by binding new intestine-permeable [cyclic peptides](#) to [biopharmaceuticals](#)," said Professor Sumio

Ohtsuki of Kumamoto University's [Department of Pharmaceutical Microbiology](#). "We expect that our developments will lead to improved patient QOL."

This finding was posted online in the *Journal of Controlled Release* on 27 July 2017.

More information: Shunsuke Yamaguchi et al, Identification of cyclic peptides for facilitation of transcellular transport of phages across intestinal epithelium in vitro and in vivo, *Journal of Controlled Release* (2017). [DOI: 10.1016/j.jconrel.2017.07.037](https://doi.org/10.1016/j.jconrel.2017.07.037)

Provided by Kumamoto University

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