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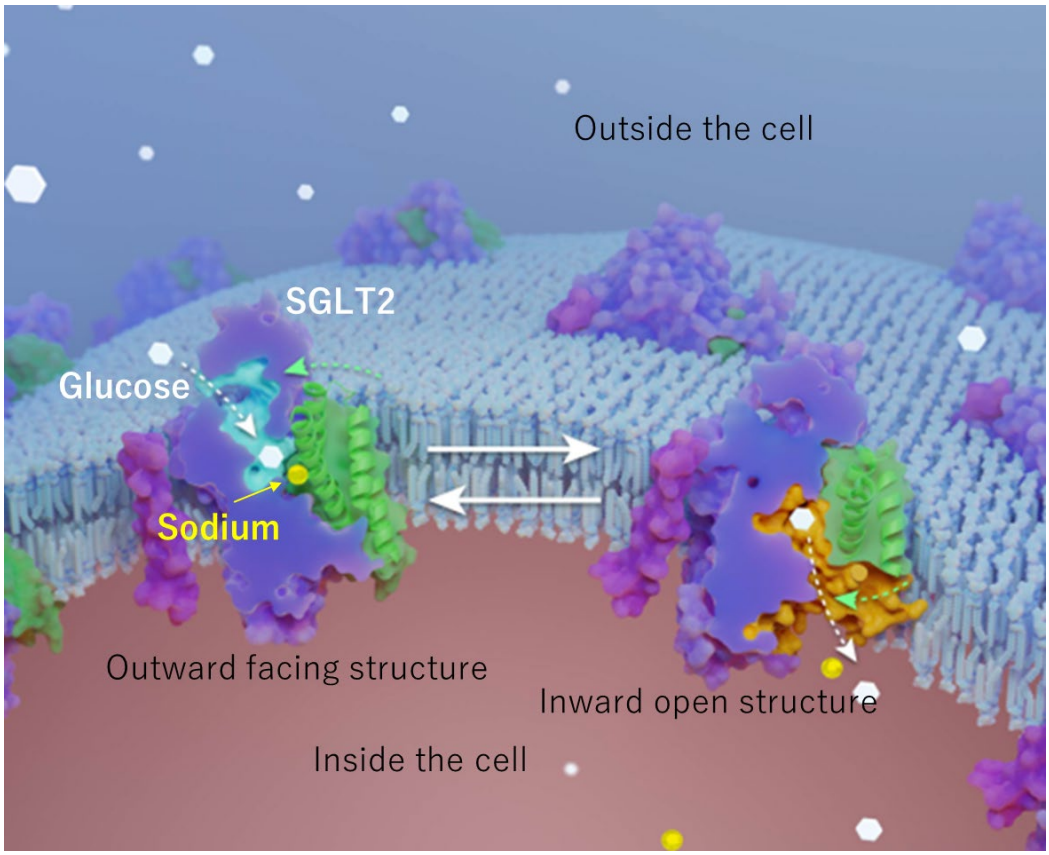
The mechanism of intracellular glucose uptake of SGLT2 was elucidated by Cryo-electron Microscopy analysis in a joint study with the University of Tokyo Published in Nature Structural & Molecular Biology

Mitsubishi Tanabe Pharma Corporation (Head Office: Chuo-ku, Osaka; Representative Director: Akihiro Tsujimura; hereinafter, "MTPC"), a member of the Mitsubishi Chemical Group, succeeded in Cryo-electron Microscopy analysis of SGLT2*-inhibitor complexes at high resolution in joint research with Professor Osamu Nureki at the Graduate School of Science, The University of Tokyo, and successfully elucidated the mechanism of glucose uptake. The results of this research were published in Nature Structural & Molecular Biology in December 2023**.

SGLT2 inhibitor is a type 2 diabetes drug that lowers blood glucose levels by inhibiting SGLT2, a transporter involved in glucose reabsorption in the renal tubules. In the present joint research, we analyzed the complex structure of different types of SGLT2 inhibitors with the target SGLT2 using cryo-electron microscopy. As a result, we have found that four gliflozin compounds, including the in-house product canagliflozin, bind to the glucose-binding site in the outward open structure along with sodium bound, while phlorizin, a natural product that initiated drug discovery, binds to the site on the cytoplasmic side of the inward open structure where sodium does not bind.
Based on the knowledge obtained from these structures, we examined them with our own experimental data based on in-house transporter functional analysis technology and found that sodium is the starting point for structural changes when SGLT2 transports glucose, and sodium release leads to glucose uptake. (Figure below)



The results were achieved through MTPC's advanced protein analysis technology and the University of Tokyo's Cryo-electron Microscopy analysis technology. In the future, we will advance our understanding of the mechanisms of not only SGLT2 but also other transporters with similar mechanisms, leading to new drug discovery for diseases that involve them.

MTPC will continue taking on the challenge of drug discovery for diseases where unmet medical needs remain by advancing open innovation with a variety of internal and external partners, including academia.

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* Sodium glucose co-transporter

**Title: Transport and inhibition mechanism of the human SGLT2–MAP17 glucose transporter
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