

Supplementary Information

We have prepared TRPM8 samples in complex with various agonists and inhibitors: TRPM8 in complex with icilin/ Ca^{2+} with shorter incubation time, with a novel agonist, and with an inhibitor, respectively (Fig. B-D).

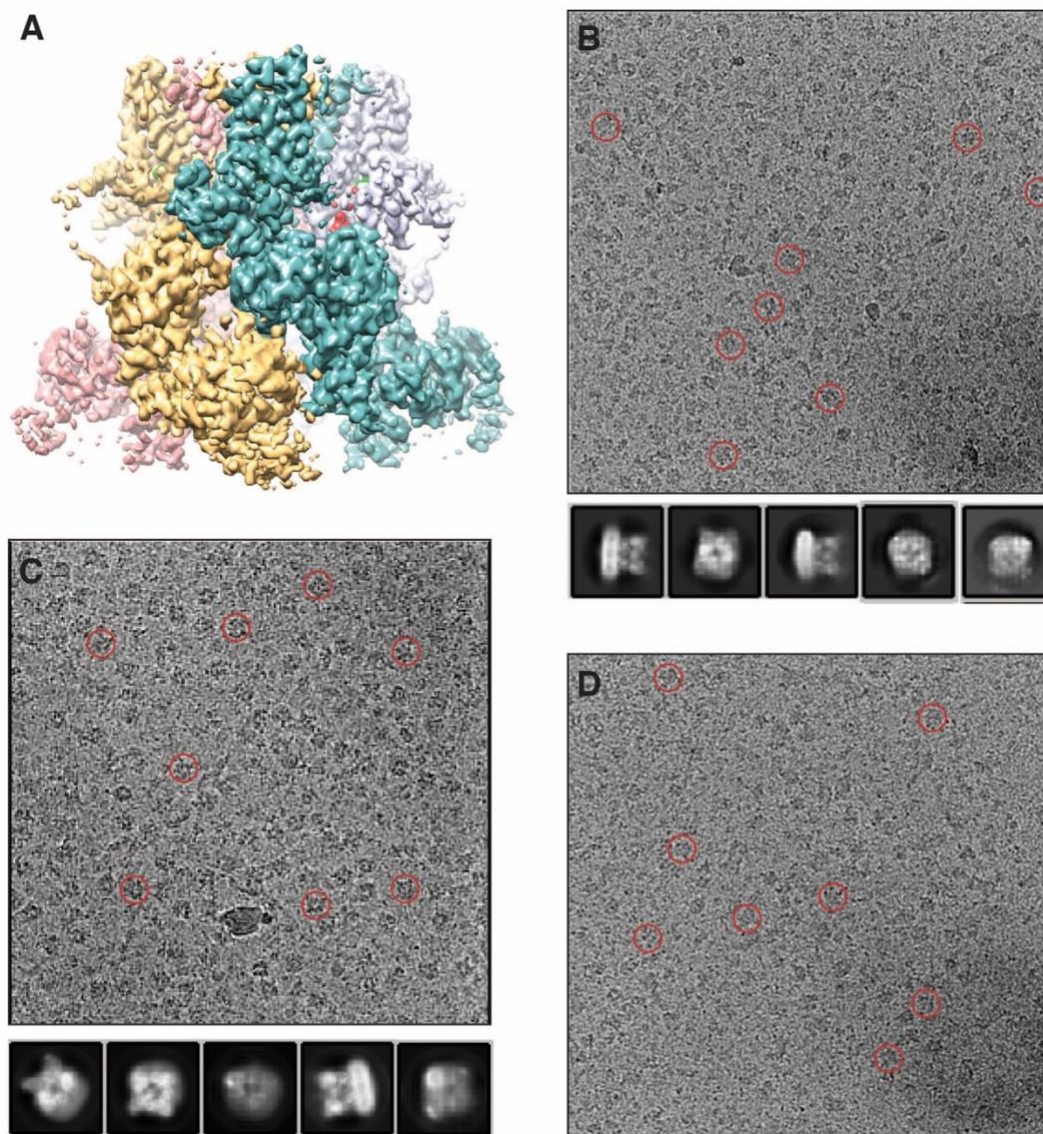


Figure. Preliminary cryo-EM sample screening and reconstruction for TRPM8 samples.

A) 3D reconstruction of TRPM8 with the agonist WS-12 and PIP_2 -bound, resolved to ~ 4 Å resolution (published result (Yin et al, Science 2019)).

B) Representative micrograph (top; defocus $-3 \mu\text{m}$ and 1.08 Å/pixel) and 2D classification images (bottom) of TRPM8 in complex with icilin/ Ca^{2+} with shorter incubation time. Red circles indicate examples of individual protein particles.

C) Representative micrograph (top; defocus $-1.8 \mu\text{m}$ and 0.932 Å/pixel) and 2D classification images (bottom) of TRPM8 in complex with a novel agonist. Red circles indicate examples of individual protein particles.

D) Representative micrograph (defocus $-2.5 \mu\text{m}$ and 1.08 Å/pixel) of TRPM8 in complex with an inhibitor. Red circles indicate examples of individual protein particles.

Please note that because we use continuous carbon grids, the apparent contrast for all micrographs is low.