

Supplementary Information

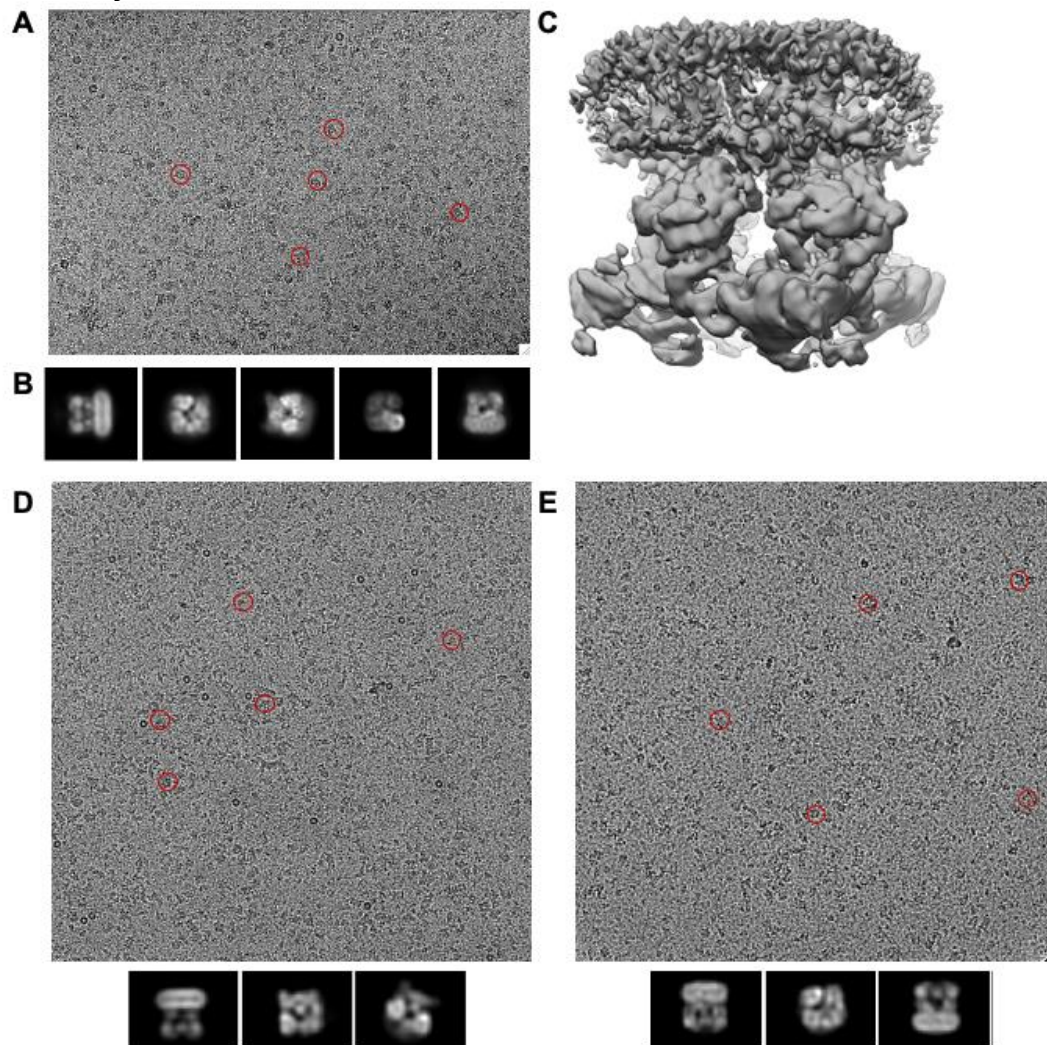


Figure. Progress in TRPM8 study and preprocessing data for proposed cryo-EM samples. **A-C)** Representative micrograph (**A**; 1.07Å/pixel and -2.8µm defocus), 2D classification images (**B**), and 3D reconstruction of TRPM8 in complex with agonist A, resolved to 4 Å resolution (**C**). **D-E)** Based on progress in A), we have prepared more TRPM8 samples and pre-screened the cryo-EM grids, which are ready for high-resolution imaging at NCCAT. Representative micrographs (1.7Å/pixel and -5µm defocus) and preliminary 2D classification images of TRPM8 in complex with agonist A (**D**) and with agonist B (**E**), respectively. Note that we obtained 2D class averages from preprocessing of a small set of screen images. Representative channel particles are marked with red circles. The apparent image contrast for the micrographs is low due to the use of continuous carbon grids.