**Supplementary file 1: Cryo-EM data collection, refinement, and validation statistics**

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| ‍ | **Human PAC with diC8-PI(4,5)P2 at pH 4.0** |
| **Full PAC map** | **Focused map on PAC ECD and the extracellular region of TMD** |
| **Data collection and processing** |  |  |
| Magnification  | 105,000 | 105,000 |
| Voltage (kV) | 300 | 300 |
| Electron exposure (e–/Å2) | 50 | 50 |
| Defocus range (μm) | –0.6 to –2.4 | –0.6 to –2.4 |
| Pixel size (Å) | 0.826 | 0.826 |
| Symmetry imposed | C3 | C3 |
| Initial particle images (no.) | 5,859,347 | 5,859,347 |
| Final particle images (no.) | 84,149 | 84,149 |
| Map resolution (Å) FSC threshold | 2.710.143 | 2.700.143 |
| Map resolution range (Å) | 2.2 – 8.9 | 2.2 – 6.9 |
|  |  |  |
| **Refinement** |  |  |
| Initial model used (PDB code) | *7SQH* | *7SQH* |
| Model resolution (Å) FSC threshold | 3.040.5 | 3.050.5 |
| Map sharpening *B* factor (Å2) | –95 | –96.3 |
| Model composition Non-hydrogen atoms Protein residues Ligands | 690384915 | 682283415 |
| R.m.s. deviations Bond lengths (Å) Bond angles (°) | 0.0030.518 | 0.0030.521 |
|  Validation MolProbity score Clashscore Poor rotamers (%)  | 1.407.240.00 | 1.407.230.00 |
|  Ramachandran plot Favored (%) Allowed (%) Disallowed (%) | 98.931.070.00 | 98.911.090.00 |