Structural studies of aquaporin inhibition

Raminta Venskutonytė [1, *], Peng Huang[1], Hannah Åbacka[1,] Carter J. Wilson[4,] Malene Lykke Wind[2,] Michael Rűtzler[5], Anna Hagström-Andersson,[3] Pontus Gourdon[1,2], Bert L. de Groot[4], Karin Lindkvist- Petersson[1,*]

[1] Department of Experimental Medical Science, Lund University, Lund 22184, Sweden.

[2] Department of Biomedical Sciences, Copenhagen University, DK-2200 Copenhagen N, Denmark.

[3] Department of Laboratory Medicine, Division of Clinical Genetics, Lund University, Lund 22184, Sweden.

[4] Computational Biomolecular Dynamics Group, Department of Theoretical and Computational Biophysics, Max Planck Institute for Multidisciplinary Sciences, 37077 Gottingen, Germany.

[5] ApoGlyx, Lund 22381, Sweden.

* LINXS Institute of Advanced Neutron and X-Ray Science, Lund 22370, Sweden.

Aquaporins (AQPs) are membrane proteins, involved in the transport of water, glycerol and other solutes across the cell membrane. They have an important role in metabolism and have been implicated in cancer development. Particularly, aquaglyceroporins AQP7 and AQP3 have been shown to be expressed in breast cancer and are therefore possible drug targets. Several inhibitors binding to AQPs have been reported and shown to block the movement of the solutes through the channel pore. To understand the molecular determinants of the inhibitor-protein interactions in the AQPs we have solved the cryo-EM structures of AQP7 in complex with one inhibitor and two structures of AQP3 with two different promising inhibitor compounds. Moreover, we support the structural data with MD simulations and functional assays. These results provide a good basis for further drug development targeting AQPs.