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# Structure and Function of Aqua(glycero)porins
## A Path to Drug Design

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Akademisk avhandling för filosofie doktorsexamen i Naturvetenskap, som med tillstånd från Naturvetenskapliga fakulteten kommer att offentligt försvaras fredag den 29:e april 2011 kl. 9:00 i föreläsningssalen KA, Institutionen för Kemi, Kemigården 4, Göteborg.

ISBN: 978-91-628-8267-9
Online: http://hdl.handle.net/2077/24754

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**Abstract**

Membrane proteins are a major class of the drug targets. Rational design of drugs requires knowledge about the structure and function of these proteins. Working with membrane proteins, however, is experimentally challenging as the required technology is still emerging.

Water being the medium of life, Nature has evolved specialized water channels called aquaporins. These transporters are found in all kingdoms of life – from simple microorganisms to humans – and function to maintain water homeostasis. These water channels are surprisingly similar in structure and are divided into two major groups: While orthodox aquaporins transport water only, the closely related aquaglyceroporins also transport small solutes like glycerol or other sugar alcohols. Aquaporins have been suggested to be involved in a wide variety of human disorders, but also as a means to combat malicious parasites.

During the course of this work, we discovered the only aquaporin from the yeast *Pichia pastoris*. We determined its atomic structure using X-ray crystallography to 0.90 Å resolution, the highest resolution for any membrane protein to date. Surprisingly, this structure showed the water pore being closed by its elongated N-terminus and provided in detail information on the water transport mechanism through this pore. Further functional characterization by a combination of size-based water conduction assays and temperature-dependent crystallography revealed that the channel can be opened. We suggested a gating mechanism *via* phosphorylation and mechanosensing, which was found to be beneficial to the survival of the organism.

Medically, protein structures like these can also be used for rational drug design. For aqua(glycero)porins, however, the discovery of inhibitors is hampered by the lack of a medium- to high-throughput assay to test potential channel blockers. Using novel technology based on surface plasmon resonance (Biacore™), we established a fully automated drug screening assay with the capability to test up to 50 compounds/day. Application of this method in combination with virtual screening yielded a drug lead with an $IC_{50}$-value of 1-10 μM against the aquaglyceroporin from the malaria parasite *Plasmodium falciparum*.