SFB 35 Colloquia in Membrane Transport

Venue: Medical University Vienna, Center for Physiology and Pharmacology,

Institute of Pharmacology, Waehringerstrasse 13a, 1090 Vienna,

"**Leseraum**".

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Friday 15.04.2016 14:00 s.t. **Bert Poolman** (host: H. Sitte)

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"Ligand-binding mechanisms and substrate delivery in ATP-binding cassette transporters at the single-molecule level"

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Abstract.

Type-I ABC importers play a pivotal role in the physiology of microorganisms, incl. amino acid supply for nutrition, pathogenicity and cell volume regulation. We focus on the homodimeric GlnPQ with two different substrate-binding domains (SBDs) per membrane domain, which offers a unique model system to decipher how conformational changes drive membrane transport (1). We demonstrate that the two SBDs have evolved to capture different amino acids by a previously undocumented type of induced-fit mechanism. We show that, following amino acid capture, the closed conformation of each SBD interacts autonomously with the TMDs, and SBD1 and SBD2 compete with each other for substrate delivery. Remarkably, SBD2 competes more strongly with SBD1 in the open-unliganded than in the closed-liganded state, which impacts the rate of transport at low amino acid concentrations. We find that the rate-determining step(s) depend on the SBD and the amino acid transported. We conclude that the lifetime of the closed conformation controls both SBD docking to the translocator and substrate release. Our findings have widespread implications for the workings of substrate-binding protein-dependent ABC importers, and recent progress from single-molecule FRET studies will be presented.

1. Gouridis G, Schuurman-Wolters GK, Plotz E, Husada F, Vietrov R, de Boer, M, Cordes T and Poolman (2015) Conformational dynamics in substrate-binding domains influence transport in the ABC importer GlnPQ. *Nature Struct Molec Biol,* 22:57-64