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 16.10.2015 14:00 s.t. **Leonid Sazanov** (host: T. Stockner)

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"Structure and mechanism of respiratory complex I, a giant molecular proton pump"

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Abstract. NADH-ubiquinone oxidoreductase (complex I) is the first and largest enzyme in the respiratory chain of mitochondria and many bacteria. It couples electron transfer between NADH and ubiquinone to the translocation of four protons across the membrane. It is a major contributor to the proton flux used for ATP generation in mitochondria, being one of the key enzymes essential for life as we know it. Mutations in complex I lead to the most common human genetic disorders. It is an L-shaped assembly formed by membrane and hydrophilic arms. Mitochondrial complex I consists of 44 subunits of about 1 MDa in total, whilst the prokaryotic enzyme is simpler and generally consists of 14 conserved "core" subunits. We use the bacterial enzyme as a "minimal" model to understand the mechanism of complex I. We have determined first atomic structures of complex I, starting with the hydrophilic domain, followed by the membrane domain and, finally, the recent structure of the entire *Thermus thermophilus* complex (536 kDa, 16 subunits, 9 Fe-S clusters, 64 TM helices). Structures suggest a unique mechanism of coupling between electron transfer in the hydrophilic domain and proton translocation in the membrane domain, via long-range (up to ~200 Å) conformational changes. It resembles a steam engine, with coupling elements (akin to coupling rods) linking parts of this molecular machine, including several antiporter-like subunits. I will discuss our current work, which is aimed at elucidating the molecular details of the coupling mechanism through determination of structures of the complex in different redox states with various bound substrates/inhibitors, using both X-ray crystallography and new cryo-EM methods.