MS8-O5 The crystal structure of the Na^+-translocating NADH ubiquinone oxidoreductase from *Vibrio cholerae*

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The human pathogen *Vibrio cholerae* maintains a Na^+ gradient across the cytoplasmic membrane. The generated sodium motive force is essential for substrate uptake, motility, pathogenicity, or efflux of antibiotics. This gradient is generated by an integral membrane protein complex, the NADH:ubiquinone oxidoreductase (NQR). It catalyzes the same reaction like mitochondrial complex I but both respiratory enzymes exhibit a completely different architecture. NQR is closely related to the so-called RNF complex that is very common in bacteria and occurs as well as in archaea. The NQR complex consists of six different subunits, NqrA-NqrF. In order to get insights into the mechanism of redox driven Na^+-transport we have isolated and crystallized the NQR of *Vibrio cholerae* . The crystals of the entire membrane complex diffract to 3.5 Å [1]. Moreover, we determined independently the structures of the major soluble domains of subunits NqrA, C and F at 1.9 Å, 1.6 Å and 1.7 Å, respectively, completing large parts of the structure of the respiratory complex at high resolution [1]. Altogether, the structural information gives a detailed picture of the NQR and allows also a close view on the core subunits of homologous RNF complex. The structural information available now allows for the first time the detailed analysis of the ion translocation pathway across the membrane and of the coupling between redox and translocation reactions. Moreover, recent structural information indicates that the pumping mechanism involves a large confromational change of the entire membrane protein complex.

References

[1] Steuber, J., Vohl, G., Casutt, M.S., Vorburger, T., Diederichs, K., and Fritz, G. (2014) Structure of the *V. cholerae* Na+-pumping NADH:quinone oxidoreductase. Nature 516: 62-67

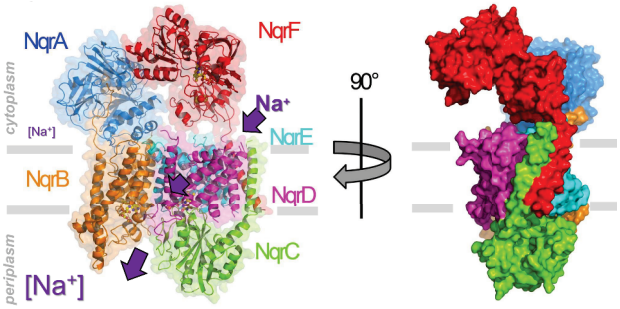

Figure 1. Structure of Na^+-pumping NQR of *Vibrio cholerae*. The six subunits are shown in different colours, respectively. The membrane plane is indicated by grey bars.

Keywords: Membrane protein, Na+-pump, Vibrio cholerae,

MS9. Pharmaceutical crystallography and drug design

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MS9-O1 Current perspectives in fragment-based ligand discovery

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Over the past 15 years, fragment based discovery has become established as an important addition to the armoury of ligand discovery methods within the pharmaceutical industry. The methods are also very attractive for academic groups, as they require relatively low investment in compound libraries and can utilise biophysical screening methods avaiable at most institutions.

In this presentation, I will briefly summarise the current approach to fragment based discovery used by most organisations. I will illustrate their application with some recent examples of drug discovery and then spend some time discussing the use of the methods for the identification of chemical tools for rapidly assessing features of proteins and their binding sites. I will conclude with a discussion of some of the current hot topics in fragments, to include 3D fragments and how to progress fragments in the absence of a crystal structure.

Keywords: fragment screening, structure-based discovery