Complex I (NADH:ubiquinone oxidoreductase) is crucial to respiration in many aerobic organisms. In mitochondria it oxidises NADH (regenerating NAD$^+$ for the tricarboxylic acid cycle and fatty-acid oxidation), reduces ubiquinone (the electrons are used to reduce oxygen to water), and translocates protons across the inner mitochondrial membrane (contributing to the proton motive force that supports ATP synthesis and transport processes). Complex I is also a major contributor to cellular reactive oxygen species production.

The mechanism of complex I comprises four ‘sequential’ steps. NADH oxidation by the flavin mononucleotide, and intramolecular electron transfer to bound quinone (along a chain of iron-sulphur clusters), are increasingly well understood. Conversely, the mechanisms of quinone reduction and proton translocation remain poorly defined, although recent structural analyses of the membrane domain of complex I (R. G. Efremov, R. Baradaran & L. A. Sazanov (2010) Nature 465, 441-7) have revealed intriguing features, including a lateral helix running in the plane of the membrane, and the ‘elevation’ of the proposed quinone binding site, above the membrane plane. This talk will present and discuss recent data to address the mechanisms of quinone reduction and proton translocation by complex I.