Combined experimental and theoretical studies of the catalytic activity of RPE65 enzyme using biomimetic active centre models (CatVis).

Retinoids form a class of fat-soluble chemical compounds closely related to vitamin A (trans-retinol). The species display a variety of biological functions such as regulation of cell differentiation (e.g. in the development of a human embryo) or hormone secretion. Moreover, they play crucial role in the vision process where the 11-*cis*-retinal serves as a chromophore precursor for rod and cone photoreceptor cells. Upon light absorption the geometrical isomer called *cis* is transformed into trans form. Sustained vision requires constant *cis* form regeneration. This transformation is carried out by the protein called RPE65.

Whereas genetic disorders that lead to lack of the active RPE65 enzyme causes blindness, controlled inhibition of the protein was recently shown to be promising in macular degeneration treatment. In the CatVis project we will investigate this crucial regeneration step, i.e. the mechanism of all-*trans*-retinyl ester transformation into 11-*cis*-retinol carried out by the RPE65 protein. We will use a unique combination of methods: computer simulations based on quantum physics will provide us with plausible reaction mechanism while experimental investigation of biomimetic model of the active site will allow us to study RPE65 active site properties in great details.

Knowledge-driven drug discovery requires the knowledge of mechanism of the target biochemical step that will be influenced by the new drug. The key impact of the CatVis project will be the molecular basis for future drugs that target visual cycle modulation. Moreover, by studying RPE65 activity we also hope to provide an efficient catalyst for *cis*-retinoids synthesis to pave way to a cost-effective synthesis of drugs that target disorders related to retinoid deficiencies.