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Combined X-ray crystallographic, in-situ UV-Vis and QM/MM studies highlight alternate retinal binding modes in CRALBP

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11-cis-retinal is the photon accepting cofactor of rhodopsin in the primary light reaction within rod- and cone receptor cells. Persistent vision affords the enzymatic re-isomerization of accumulating all-trans-retinal to 11-cis-retinal in the retinal pigment epithelium (RPE). Cellular retinaldehyde binding protein (CRALBP) is essential for vision by routing 11-cis-retinoids for the conversion of photobleached opsin molecules into photosensitive rhodopsin pigments.
Here, we report the high-resolution (1.8 Å) crystal structure of the R234W mutant of CRALBP (R234W) in complex with its less abundant isomer 9-cis-retinal, a naturally occurring alternate isomer that is used in retinal replacement therapies. A structural overlay with the known 11-cis:R234W complex reveals alternate binding for the 9-cis-aldehyde tail and a strong deformation of the ligand arround position C11/C12. We have complemented our structural study with single crystal UV/Visible spectroscopy of the 9-cis:R234W complex, as well as spectrally characterizing crystals of the 11-cis:WT and the 11-cis:R234W complexes. The single crystal spectral data has provided detailed information as to the nature of the bound ligand within the crystal through the observation of a dose dependent X-ray induced radical peak at 545nm. The chemical nature of the 9-cis-retinal has been further probed by QM/MM simulation and has allowed us to propose a mechanism for the stabilization of a ground-state radical of retinal within R234W.

Primary author: Dr STOCKER, Achim (Uni Bern)

Co-authors: Dr PEARSON, Arwen R (University of Leeds); Ms BOLZE, Christin S (University of Bern); Dr DWORKOWSKI, Florian (Swiss Light Source); Dr POMPIDOR, Guillaume (Swiss Light Source); Prof. PALCZEWSKI, Krzysztof (Case Western Reserve University); Dr GOLCZAK, Marcin (Case Western Reserve University); Dr FUCHS, Martin (Swiss Light Source); Prof. CASCELLA, Michele (University of Bern); Ms HELBLING, Rachel (University of Bern); Dr OWEN, Robin (Diamond Light Source); Mr AESCHIMANN, Walter (University of Bern); Dr HE, Xiaoqin (PSI Villigen)

Presenter: Dr STOCKER, Achim (Uni Bern)

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