

A Search for Hydride Shift Mechanism in Enzymatic Synthesis of TetrahydrobiopterinE. Bozkurt¹, R. Hovius¹, K. Johnsson^{1,2}, U. Röthlisberger^{1*}¹EPF Lausanne, ²Max Planck Institute for Medical Research Heidelberg

Sepiapterin reductase (SR) is a homodimeric enzyme responsible for the synthesis of tetrahydrobiopterin (BH₄), a multifunctional cofactor associated with neuropsychiatric diseases^{1,2,3}. Based on biochemical and crystallographic data^{4,5}, it has been hypothesized that SR reduces the C1' carbonyl and then catalyses an isomerization reaction shifting the C2' carbonyl group to the C1' position. The final catalytic step includes NADPH-dependent reduction of the carbonyl group and generates *L-erythro*-BH₄. However, underlying mechanistic details of every step are not completely understood. In this computational study, we seek an answer for the following outstanding question: Is there a potential hydride shift mechanism in the isomerization step? Molecular dynamics and QM/MM molecular dynamics are in progress to provide precise information for enzymatic formation of BH₄. The underlying chemistry of this intriguing reaction may facilitate drug design for diseases such as Alzheimer's and Parkinson's disease.

[1] Friedman, J.; Roze, E.; Abdenur, J. E.; Chang, R.; Gasperini, S.; Saletti, V.; Wali, G. M.; Eiroa, H.; Neville, B.; Felice, A.; Parascandalo, R.; Zafeiriou, D. I.; Arrabal-Fernandez, L.; Dill, P.; Eichler, F. S.; Echenne, B.; Gutierrez-Solana, L. G.; Hoffmann, G. F.; Hyland, K.; Kusmierska, K.; Tijssen, M. A. J.; Lutz, T.; Mazzuca, M.; Penzien, J.; Poll-The, B. T.; Sykut-Cegielska, J.; Szymanska, K.; Thöny, B.; Blau, N. Sepiapterin reductase deficiency: A Treatable Mimic of Cerebral Palsy. *Annals of Neurology*, **2012**, 71, 520-530.

[2] Lohmann, E.; Köroğlu, Ç.; Hanagasi, H. A.; Dursun, B.; Taşan, E.; Tolun, A. *Parkinsonism and Related Disorders* **2012**, 18, 191.

[3] Smith, G. K. *Archives of Biochemistry and Biophysics* **1987**, 255, 254.

[4] Auerbach, G.; Herrmann, A.; Gütlich, M.; Fischer, M.; Jacob, U.; Bacher, A.; Huber, R. *EMBO Journal* **1997**, 16, 7219.

[5] Supangant, S.; Choi, Y K.; Son, D.; Han, C.; Lee, K. H. *Act Crystallographica Section F Structural Biology and Crystallization Communications* **2005**, 61, 202.