

## **Molecular mechanism of light-regulated phosphodiesterase activity in BlrP1.**

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BlrP1 is a multi-domain protein from *Klebsiella Pneumoniae* consisting of photosensing (BLUF, blue light using flavin) and catalytic (EAL) domains. The rate of catalytic reaction, namely hydrolysis of c-di-GMP (cyclic dimeric guanosine monophosphate) that takes place in the EAL domain, depends on the regulatory BLUF domain. C-di-Gmp is a secondary messenger which is of great importance for bacterial organization. C-di-GMP regulates cell surface-associated traits and community behavior such as biofilm formation. We apply modern quantum chemistry methods, molecular dynamics simulations, and the combined quantum mechanical – molecular mechanical (QM/MM) approaches to formulate detailed mechanistic picture of events in BlrP1 at the atomic resolution. Knowledge of the atomic coordinates recently available from the crystal structure is an important starting point for understanding molecular mechanisms of this biological machine which should be succeeded by molecular modeling. In present study we use molecular dynamics with the CHARMM force field parameters for protein and c-di-GMP and GAFF for flavin. We study the influence the conformational changes in the BLUF domain on the catalytic activity of the EAL domain. We study the role of point mutations of key residues near the substrate binding site and of those remote from it for the conformational changes that occur in EAL domain. For modeling elementary stages in the mechanism of hydrolysis of c-di-GMP inside the catalytic domain we use the combined quantum mechanical – molecular mechanical (QM/MM) approach. This work was partially supported from the grant from the Russian Foundation for Basic Research (#08-03-91104-AFGIR).