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## Functional protein conformation networks probed by NMR nanorulers

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The function of a protein is tightly connected to its conformational network. Often, subtle differences distinguish interchanging states with distinct properties. One major challenge in structural biology is a sufficiently complete description of the structural landscape and the exchange dynamics between structural states at atomic resolution. We have replaced the standard NMR structure determination by an approach that generates multi-state ensembles from a dense network of tight averaged distance restraints derived from exact measurements of nuclear overhauser enhancements. Here, we present the identification of conformational networks harbored by two-human cis/trans isomerases cyclophilin A and Pin1 using the nanorulers provided by eNOEs. We have previously presented an eNOE-based ensemble description of cyclophilin that reveals the presence of a closed and an open state, the latter of which pre-organizes the catalytic site for catalysis. Based on this finding, we demonstrate here a ligand-selective change of the binding affinity to the active site by tuning the dynamics of a highly flexible loop. We show that the binding affinity is increased upon substitution of double glycines to alanines at either of the hinge regions of a loop. The equilibrium distribution is shifted towards more binding-competent conformations. Comparison of the eNOE-based ensembles of the free and ligand-bound WW domain of Pin1 reveals a conformational network that extends into the interface formed with the enzymatically active PPIase domain. This finding may offer an atomic-picture explanation for the previously discovered communication between the two domains.

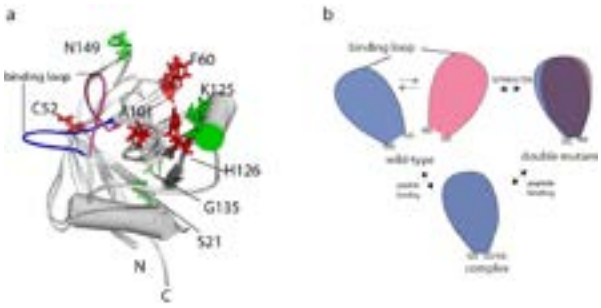


**Figure1:** *Conformational network of cyclophilin A. a) Structural two-state eNOE ensemble representation of the residues affected by the dynamics of the binding loop shown in the open (blue) and closed state (magenta). b) Mechanistic representation for loop opening and closing for the wildtype, G74A/G75A mutant and the complex.*

### Biography

Beat Vögeli has his expertise in nuclear magnetic resonance (NMR) spectroscopy of biomacromolecules. He develops methodology for the elucidation of conformation and communication networks within and between proteins and nucleic acids. He received his PhD degree at the ETH Zürich in the group of Konstantin Pervushin. After a postdoctoral stay at the National Institutes of Health, Bethesda USA, in the group of Ad Bax, he returned to ETH Zürich to become Oberassistant in the group of Roland Riek and Privatdozent. He is currently an Assistant Professor at the University of Colorado at Denver in the Department of Biochemistry and Molecular Genetics.

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