Universität Basel

Research Project

Optimizing a family of lanthanide ....

Third-party funded project

Project title Optimizing a family of lanthanide ....
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Determination of the three-dimensional structure of proteins in solution is a stronghold of modern bio-molecular NMR spectroscopy. Even more important for understanding processes in the living cell is the characterization of interaction sites and surfaces of protein-protein and protein-ligand complexes. NMR can provide not only structural but also dynamic information on this subject. Classical determination of NOE distant restraints has recently been complemented by techniques, which utilize paramagnetic lanthanide ions that are tagged covalently to the suitably modified protein. Besides residual dipolar couplings (RDCs) and paramagnetic relaxation enhancement (PRE) the focus of this proposal is aimed at pseudo contact shift (PCS) NMR spectroscopy. PCS NMR has unique properties as it is a long-range method that can cover distances of more than 50 Å, in combination with precise angle information. The very sensitive measurements are simple 2D-NMR experiments that can be performed even on larger proteins. We have recently presented a new lanthanide chelating tag ”M8”, based on a sterically overcrowded DOTA framework that shows PCS of unprecedented size when linked to ubiquitin. This project is aimed at further improving the properties of the new ligand by systematically fine-tuning the type and the rigidity of the linker between the DOTA core and the protein. In a second step, variation of the donor atoms of the chelator should trigger a strong crystal field distortion for the lanthanide ion and might result in a more pronounced anisotropy of the susceptibility tensor and hence stronger PCS. Finally a screening of at least a number of different lanthanides should yield, together with the variation of the first two parameters, a family of lanthanide chelating tags that should be suitable for tackling a variety of different problems in structural biology. As the stereospecific synthesis of the macrocyclic ligand is tedious and demanding, a number of interesting collaborations with other groups is already underway or is planned for the near future. We will therefore have a chance to study the individual benefits of the various members of our LCT family by applying them to a number of challenging bio-molecular questions.

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