

Chemical biology of methyltransferases

Capture compounds and cofactor analogues for functional proteomics and substrate labeling

Prof. Dr. Elmar Weinhold, Institute of Organic Chemistry, RWTH Aachen University, Germany

With the available genome sequences of many organisms we are faced with the task to assign molecular functions to thousands of predicted gene products. To address this problem we are developing trifunctional capture compounds for the isolation of functional protein families and subsequent protein identification. In particular we are interested in methyltransferases (MTases) which catalyse the transfer of the activated methyl group of the cofactor *S*-adenosyl-L-methionine (AdoMet) to various substrates, like DNA, RNA, proteins or small biomolecules and serve a broad variety of biological functions ranging from metabolism to epigenetic control of gene expression. We have synthesised capture compounds containing the well known product inhibitor *S*-adenosyl-L-homocysteine (AdoHcy) as a molecular bait and demonstrate effective functional enrichment of MTases from cell extracts.^[1]

Having identified proteins as previously unknown MTases leaves us with the question of their individual substrates. To answer this question we are applying synthetic AdoMet analogues. They carry extended chemical groups which are transferred by MTases to their substrates and can be modified in subsequent bioorthogonal reactions (e.g. click reaction). The feasibility of this approach is demonstrated by using various MTases for sequence-specific labelling of their DNA, RNA and protein substrates,^[2,3] which is also of interest for various applications in medical diagnosis and (nano)biotechnology.

- [1] C. Dalhoff, M. Hüben, T. Lenz, P. Poot, E. Nordhoff, H. Köster, E. Weinhold, "Synthesis of *S*-adenosyl-L-homocysteine capture compounds for selective photo-induced isolation of methyltransferases", *ChemBioChem* **2010**, *11*, 256–265.
- [2] W. Peters, S. Willnow, M. Duisken, H. Kleine, T. Macherey, K. E. Duncan, D. W. Litchfield, B. Lüscher, E. Weinhold, "Enzymatic site-specific functionalization of protein methyltransferase substrates with alkynes for click labeling", *Angew. Chem.* **2010**, *112*, 5296–5299; *Angew. Chem. Int. Ed.* **2010**, *49*, 5170–5173.
- [3] Y. Motorin, J. Burhenne, R. Teimer, R. Koynov, S. Willnow, E. Weinhold, M. Helm, "Expanding the chemical scope of RNA:methyltransferases to site-specific alkynylation of RNA for click labeling", *Nucleic Acids Res.* **2011**, *39*, 1943–1952