# Ribozymes for site-specific RNA modification


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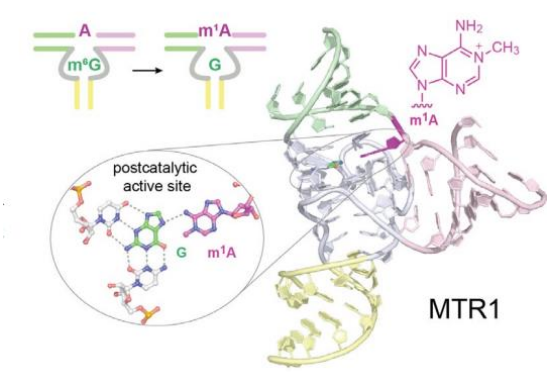
**Abstract**

Natural RNA modifications are known to expand the structural and functional diversity of RNA, and many of them are highly conserved throughout evolution. Methylated nucleotides belong to the most abundant RNA modifications and have implications in the regulation of gene expression. Besides modulating the RNA modification landscape, post-transcriptional RNA labelling and visualization are critical prerequisites for studying RNA localization, folding and structural dynamics. Ribozymes and aptamers generated by in vitro selection provide enabling tools for studying RNA labelling in vitro and in cells.

Using a direct in vitro selection strategy, we discovered the first methyltransferase ribozyme (MTR1) that catalyzes the site-specific installation of 1-methyladenosine ($m^1A$) in a target RNA. The ribozyme uses $O^6$-methylguanine ($m^6G$) as a small-molecule cofactor and shows a broad RNA sequence scope, as exemplified by site-specific adenosine methylation in native tRNAs and synthetic mRNAs. Recently, we solved the crystal structure of MTR1, which represents the post-catalytic state of a split ribozyme in complex with the $m^1A$-containing RNA product and the demethylated cofactor guanine. The structure revealed an active site reminiscent of natural guanine riboswitches and suggested the mechanistic involvement of a protonated cytidine. A synergistic effect of two 2'-*O*-methylated ribose residues in the active site resulted in accelerated catalysis and tolerance of larger alkyl groups. These results encourage the development of alkyl-transferase ribozymes using established benzylguanine substrates for site-specific fluorescent labelling of RNA, as well as the development of additional ribozymes using alternative bioorthogonal cofactors.




The presentation will also highlight some additional examples of ribozymes for RNA-catalyzed fluorescent labelling of RNA, and discuss strategies for the accelerated discovery of nucleic acid catalysts to examine the modification states of target RNAs.

**Biography**

Claudia Höbartner studied Chemistry in Vienna (Austria) and in Zürich (Switzerland), and earned a PhD degree from the Leopold-Franzens-University Innsbruck (Austria). After postdoctoral research at the University of Illinois at Urbana-Champaign (UIUC, USA) funded by an Erwin Schrödinger fellowship, she was supported by the Hertha Firnberg career development fellowship of the Austrian Science Fund (FWF). In 2008, Claudia joined the Max Planck Institute for biophysical Chemistry in Göttingen as a Max Planck research group leader. In 2014, she was appointed professor for biomolecular label chemistry at the faculty of chemistry at the Georg-August-University Göttingen. Since July 2017 she holds the Chair of Organic Chemistry I at the Julius-Maximilians-University Würzburg. In 2022 she was elected to the German National Academy of Sciences Leopoldina, and she was awarded the Gottfried-Wilhelm-Leibniz Prize in 2023. Her major research interests include the synthetic, biomolecular and structural chemistry of natural and artificial nucleic acids, with a focus on natural RNA modifications and in vitro selection of ribozymes and other catalytic and functional nucleic acids.