Therapeutic targeting of long non-coding RNAs in cancer using synthetic small molecules

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Long non-coding RNAs (lncRNAs) are a recently identified class of regulatory RNAs greater than 200 nucleotides in length that constitute the largest portion of the mammalian non-coding transcriptome. They play an essential role in regulating the expression of target genes in normal biological contexts as well as pathologic processes including expression of oncogenes [1]. MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) is a highly conserved lncRNA involved in metastasis and tumor proliferation in multiple cancer types. Upon folding, the 3'-terminal end assumes a triple-helical conformation that promotes the nuclear accumulation and persistent function of MALAT1 and can be targeted by synthetic small molecules [2]. The aim of our project is to develop new fluorescence-based screening assays suitable for medium-throughput analysis to identify potential selective interactions between the MALAT1 triple helix and compounds from various libraries including RNA binders [2,3]. A first screening of an in-house focused library of RNA ligands allowed for the identification of efficient MALAT1 binders. The mechanism of action at the molecular level of the identified hits is currently under study by using biochemical and biophysical assays as well as intracellular studies. The screening of larger libraries (50-10000 compounds) is also ongoing. Therapeutic targeting of tertiary structure of MALAT1 with selective small molecules represents a relevant model to explore the druggability of RNAs as well as a very original and promising anticancer approach. Once validated, we envisage to apply similar screening strategies to other lncRNA targets.

[1] Morris, K., Mattick, J. The rise of regulatory RNA. Nat Rev Genet 15, 423–437 (2014)

[2] ACS Chem. Biol. 2019, 14, 223−235

[3]Angew Chem Int Ed Engl. 2018 Oct 1; 57(40): 13242–13247