



Wednesday 28 September 2016  
at 11:15 in the FKF Meeting-room

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*“Oncogenic microRNAs biogenesis as a drug  
target: New applications for synthetic RNA  
ligands”*

Web: <http://www.unice.fr/icn-s/spip.php?rubrique102>

**Abstract:**

MicroRNAs (miRNAs) are a recently discovered category of small RNA molecules that regulate gene expression at the post-transcriptional level. Accumulating evidence indicates that miRNAs are aberrantly expressed in a variety of human cancers, thus being oncogenic and that the inhibition of oncogenic miRNAs (defined as the blocking of miRNAs' production or function) would find application in the therapy of different types of cancer in which these miRNAs are implicated [1].

The purpose of the work that will be presented is the development of small-molecule drugs targeting specific oncogenic miRNAs production. In particular, we chose to target two oncogenic miRNAs (miRNA-372 and miRNA-373) implicated in gastric cancer, which is the fourth most common cancer and the second leading cause of cancer death in the world. These two oncogenic miRNAs are overexpressed in gastric cancer cells starting from their precursors (pre-miRNA-372 and pre-miRNA-373): two stem-loop structured RNAs which lead to mature miRNAs after cleavage by the enzyme Dicer in the cytoplasm [2]. A compound able to interfere with the cleavage of these pre-miRNAs by the enzyme Dicer will inhibit the production of oncogenic miRNAs and restore normal mRNA translation finally leading to cancer regression.

In order to discover new and efficient inhibitors of oncogenic miRNA production, we have (i) designed and synthesized new RNA ligands conceived in order to bind at the stem-bulge and/or stem-loop junction sites on the pre-miRNA sequence (Focused design approach) and (ii) screened a library of 640 compounds

(Chimiothèque Essentielle belonging to 56000-compounds French National Chemical Library) (Library screening approach). Both these approaches were based on a high throughput in vitro assay and demonstrated to be successful in identifying compounds able to interfere with the biogenesis of oncogenic miRNAs. The most active compounds discovered using the in vitro assay have been further studied for their activity on adenocarcinoma gastric cancer cells (AGS cells) overexpressing targeted miRNAs. Some of the studied compounds demonstrated the ability to inhibit AGS cells proliferation in a dose-dependent manner and this effect has been directly correlated to the decrease in the production of oncogenic miR-372 and miR-373 [3].

[1] Garzon R, Marcucci G, Croce CM (2010) Targeting microRNAs in cancer: rationale, strategies and challenges. *Nat. Rev. Drug Discov.* 2010 9, 775-789.

[2] a) Cho, W. J., Shin, J. M., Kim, J. S., Lee, M. R., Hong, K. S., Lee, J. H., Koo, K. H., Park, J. W., and Kim, K. S. miR-372 regulates cell cycle and apoptosis of ags human gastric cancer cell line through direct regulation of LATS2. *Mol. Cells* 2009 28, 521-527.

[3] a) Vo, D.D., Staedel, C., Zehnacker, L., Benhida, R., Darfeuille F., Duca, M. Targeting the Production of Oncogenic MicroRNAs with Multimodal Synthetic Small Molecules. *ACS Chem. Biol.* 2014 9, 711-21; b) Tran, T.P.A., Vo, D.D., Di Giorgio, A., Duca, M. Ribosome-targeting antibiotics as inhibitors of oncogenic microRNAs biogenesis: old scaffolds for new perspectives in RNA targeting *Bioorg. Med. Chem.* 2015 23, 5334-44; c) Vo, D.D., Tran, T.P.A., Staedel, C., Benhida, R., Darfeuille F., Di Giorgio, A., Duca, M. Oncogenic MicroRNAs Biogenesis as a Drug Target: Structure-Activity Relationship Studies on New Aminoglycoside Conjugates. *Chem. Eur. J.* 2016 22, 5350-62.