AN INTERDISCIPLINARY APPROACH TO OPTIMIZE APTAMER-MEDIATED SIRNA DELIVERY FOR LIVER CANCER CELLS

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Résumé

The tumor microenvironment significantly influences cancer development, progression, and therapeutic resistance. We are interested in targeting in a secreted molecule found to be highly overexpressed in a large proportion of hepatocellular carcinoma (HCC), suggesting it plays a critical role in tumor biology. Our project aims to inhibit its expression, using small interfering RNAs (siRNAs). They are a powerful molecule for gene silencing, but their clinical application is limited by challenges such as instability in biological fluids and poor cellular uptake. To overcome these barriers, this study focuses on developing a targeted delivery system using aptamer-based approaches, which offer high specificity and low immunogenicity. Aptamers are short, single-stranded DNA or RNA molecules that can fold into defined three-dimensional structures to bind specific cellular targets with high affinity. Aptamers targeting cell-surface receptors are also capable of cellular internalization, making them promising carriers for the delivery of therapeutic molecules like siRNAs. Our objective is to evaluate the potential of siRNA delivery thanks to aptamers that target a cell surface marker overexpressed in HCC, using two strategies:

- Aptamer–siRNA Conjugates (AsiCs) – Direct chemical linkage of siRNA to the aptamer
- Aptamer-Functionalized Nanoliposomes (AsiNLs) – Liposomes encapsulating siRNA and decorated with surface aptamers

Our preliminary data provide information on the stability of the aptamer and of the AsiC in different buffers and medium. To facilitate the delivery of siRNA, various prototypes of Neutral and cationic liposomes, decorated with aptamers have been formulated, exhibiting an average size of approximately 100 nm with variety in zeta range conferring to the composition. Currently, the project is progressing, the formulations of interest possess low toxicity

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and we are focusing on optimizing the delivery of AsiNL into the cells.

We next plan to optimize siRNA cytosolic delivery thanks to photochemical and pharmacological approaches. Hence, Liposomes emerges as a promising concomitant delivery system to enhance the internalization and bioavailability of siRNA guided by aptamer towards specific HCC cell-surface receptors.

Mots-Clés: Hepatocellular carcinoma, Aptamer, siRNA, Liposomes