***In Silico* Design And Evaluation Of Potential siRNA For Hepatocellular Carcinoma Treatment**

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**Background and aims.** Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for over 70% of liver cancer cases. It remains a major global health challenge, with more than 800,000 deaths annually and little improvement in survival rates over the past decade. Small interfering RNA (siRNA) offers high specificity in silencing oncogenes but requires careful design and delivery. Therefore, this study aims to apply *in silico* to the design and evaluation of potential siRNA for HCC treatment.

**Methods.** The study was conducted in four stages: (1) Construction of a protein–protein interaction (PPI) network and functional analysis using GO and KEGG to identify key genes; (2) Identification of core pathways and potential siRNA targets; (3) Design and evaluation of siRNA sequences using multiple bioinformatics tools; (4) Molecular docking and molecular dynamics simulations (MDs) of siRNA–Ago2 complexes and delivery systems to assess stability.

**Results.** From predicted HCC-associated targets, PPI network with 5,794 nodes and 291,517 edges was constructed. Three major clusters of hub genes were identified, highlighting key roles in HCC pathogenesis. Among enriched pathways, the cancer pathway was most significantly involved, leading to the selection of *PIK3R1*, *PIK3R2*, and *PIK3CA* as primary targets. Fifteen siRNA sequences were designed and filtered based on thermodynamic stability, structural features, and off-target potential. Molecular docking and MDs identified three lead candidates: A7 (*PIK3R1*), B2 (*PIK3R2*), and C10 (*PIK3CA*), with strong Ago2 binding and post-simulation stability. The sequences of these siRNAs are shown in Table 1. Notably, B2 also showed spontaneous interaction with polyethylenimine, suggesting delivery feasibility.

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| Name | Guide strand 5' -3' | Target strand 5' - 3' |
| A7 (PIK3R1) | UUAUGACACAAUGCUUUACUU | AAGTAAAGCATTGTGTCATAAAC |
| B2 (PIK3R2) | UUGAUAGUCUCAUUGAAGGCC | CGAGUAUGACCAGCUUUAUGA |
| C10 (PIK3CA) | UAAUUCAGCCAUUCAUUCCAC | GTGGAATGAATGGCTGAATTATG |

**Table 1.** Sequences of top siRNA candidates targeting PIK3R1, PIK3R2, and PIK3CA

**Conclusion/Discussion.** A7, B2, and C10 are promising siRNA candidates targeting *PIK3R1, PIK3R2,* and *PIK3CA*, respectively. This study highlights the utility of *in silico* methods for siRNA design, functional assessment, and early evaluation of delivery mechanisms, contributing to the future development of siRNA-based therapies for HCC.

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