Advancing RNAi therapeutics: Integrating Strategies for Optimal Lead Identification and Effective Tissue Delivery

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RNAi-based therapy is a powerful approach to reach previously undruggable targets and opens new options for treating a wide range of diseases. As an emerging modality, its development still faces two central hurdles: designing molecules with the right potency, specificity, and safety profile, and delivering them efficiently to the tissue of interest. Here we describe an integrated pipeline that addresses both. On the molecule design side, we developed a machine-learning framework for predicting the activity of chemically modified siRNAs (FENNEC), trained on the largest patent-derived collection of chemically modified siRNAs assembled to date. To evaluate the model prospectively, we ran a high-throughput screen against a target in a dose response, using automated and scalable workflow, allowing us to robustly screen large siRNAs libraries. HTS results are analysed using a robust automated pipeline with fit quality classification module that allows robust compound selection. The results suggest that FENNEC outperforms other algorithms and identifies both known and novel optimization rules, providing a powerful tool to streamline siRNA design. For in vivo delivery, we present a Brain Shuttle (BrS) conjugate strategy that shuttles the selected siRNAs for efficient uptake in the central nervous system, enabling robust knockdown in Brain. Together, the design, screening, and delivery components form a scalable end-to-end platform that shortens the path from target to lead and is expected to accelerate the identification of safe and effective RNAi therapies.