FENNEC: Fine-Tuned Ensemble Neural Networks Accelerate Chemically Modified siRNA Screening and Design

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Small interfering RNAs (siRNAs) are a clinically validated therapeutic modality, but designing potent chemically modified siRNAs remains costly and iterative due to limited public data. Computational prediction of siRNA efficacy can accelerate rational design and preclinical development. However, despite the importance of chemical modifications in therapeutic performance, current machine-learning methods either do not account for this or generalize poorly beyond their training data. Here, we present FENNEC (Fine-Tuned Ensemble of Neural Networks for siRNA Efficiency Characterization), a machine-learning framework for predicting chemically modified siRNA activity. We curate the largest publicly available patent-derived dataset of modified siRNAs from 42 patents using OCR-based table extraction and stringent quality filtering. FENNEC combines temporal convolutional networks with thermodynamic features, experimental covariates, and RNA foundation-model embeddings to capture sequence- and transcript-level determinants of efficacy. We show that foundation-model embeddings encode transferable biological information, particularly benefiting prediction in data-scarce settings. FENNEC achieved robust gene- and siRNA-level performance, including independent validation on a novel AHSA1-targeting dataset, and consistently outperformed existing approaches. Model interpretation recovers modification-specific effects, while in silico perturbation analyses demonstrate its utility for both prediction and design optimization of chemically modified siRNAs. Together, these results establish FENNEC as a chemically aware framework for data-driven siRNA design. We have FENNEC which will be publicly available for non-commercial use at https://github.com/marsico-lab/fennec.

Competing Interest Statement

D.B., R.R., D.Y., J.B., and P.B. are employees and shareholders of F. Hoffmann-La Roche Ltd. A.L. was a PhD student at Helmholtz Munich/TUM and employed by Roche during the course of this work. A.M. and J.G. declare no competing financial interests.