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AI-Driven Tools and Methods for Small Molecule Ligand Discovery and Prediction for RNA Interactions

Andrea Ruiz Escudero

Department of Pharmacology, Faculty of Medicine and Nursing, University of the Basque Country (UPV/EHU), Leioa, Biscay, Spain.

Department of Information and Communication Technologies, Computer Science Faculty, University of A Coruña, Campus de Elviña, A Coruña, Spain.

IKERDATA S.L INVESTIGO Next-generation Researcher.

Abstract. RNA molecules are crucial in many biological processes, therefore, they have become potential targets for disease diagnosis and treatment. The design of small molecules that can target RNA structures is a promising approach, as they are tunable and easily taken up by cells. However, it can be challenging without knowing the RNA structure. In this review three different examples will be discussed of research groups combining AI to predict the interactions between RNA molecules and small molecules to address the challenges in designing RNA-targeted ligands due to the difficulty in obtaining accurate RNA structures and the lack of understanding of binding kinetics.

RNA molecules have emerged as potential targets for disease treatment and diagnosis, since they are essential in many biological processes. A promising approach is the design of small molecules that can specifically target RNA structures, because they are adaptable and easy for cells to take up. Nevertheless, it might be challenging if the RNA structure is unknown. There are several methods that can provide information about RNA molecular recognition properties, topology and dynamics, such as enzymatic probing, NMR, X-ray diffraction, cryo-electron microscopy and chemical probing. High-throughput techniques like patron recognition of RNA by small molecules (PRRSM) can accelerate the discovery of RNA-druggable motifs and molecular scaffolds.[1] Computational modeling advances have made it possible to model RNA tertiary structures with coordinate information. A better understanding of RNA structures enables the engineering of RNAs with specific functions and designing drugs that can selectively target structured RNA molecules. Accurate RNA structural determination will be crucial for RNA biotechnology and biomedical applications.[2]

As previously mentioned, any RNAs can be selectively targeted with small molecules, offering an unlimited potential target for chemical probes and lead medicines. The use of small molecules to modulate RNA expression offers an exciting opportunity for biomedical research. While antisense technologies have been effective, researchers are exploring the same level of control and selectivity using small molecules. To achieve bioactivity of small molecule ligands, it is essential to validate their transcriptome- and downstream proteome-wide selectivity through selective molecular recognition of structured RNA motif regions. This may lead to a new paradigm in chemical biology and launch research into new therapeutic modalities and viable medicines. A druggable transcriptome project can be proposed to provide chemical probes for functional RNAs on a transcriptome-wide scale.[3]

Three different examples will be reviewed of research groups combining AI to predict the interactions between RNA molecules and small molecules to address the challenges in designing RNA-targeted ligands due to the difficulty in obtaining accurate RNA structures and the lack of understanding of binding kinetics.

On one side, Cai Z. et al. developed a new method by a systematic quantitative structure-activity relationships (QSAR) workflow using HIV-1 transactivation response as a model system to predict RNA-targeted ligand binding parameters. The study trained the models by using 36 small molecules from DMZ, DMA, DPF, AG and nucleic acid dye classes. By predicting 12 untested compounds, they found that MLR models can accurately predict binding affinity and kinetics, providing information on how to modify ligand properties for lead optimization. Although the method has limitations, such as the small number of molecules to train the chemical space, it can be applied to other biomacromolecular targets with little structural information. Overall, the study provides a valuable tool for identifying hits

and optimizing leads in RNA-targeted small-molecule development.[4]

On the other side, Philips A. et al. created a tool called LigandRNA that can predict how RNA molecules and small molecules interact. They used a method that looks at the shapes of the molecules and how they fit together. LigandRNA takes in files that describe the RNA and the small molecule, and it ranks the different ways they could fit together. They suggest using LigandRNA along with a different tool called Dock6 to improve the results of native-like ligand identification. A major limitation of the study is the lack of a wide variety of examples of RNA-small molecule interactions to learn from, therefore, LigandRNA will be continually updated as new examples become available.[5]

In addition to these methods, Wan Y. et al. made another approach to studying RNA structural dynamics and ligand recognition is through AI-augmented molecular simulations. This article discusses the feasibility of using AI-augmented molecular simulations to gain detailed and robust insights into RNA structural dynamics, specifically focusing on the Tte-PreQ$_1$ riboswitch aptamer system using the RAVE sampling method to observe ligand dissociation. The simulations are able to accurately model ligand dissociation from RNA and provide validatable hypotheses regarding structural features that impact small molecule recognition of RNA. Understanding a variety of human diseases requires the capacity to create precise and effective predictions regarding the effects of mutations on RNA structure dynamics and ligand recognition procedures. The approach will have broad use for understanding not only natural systems like riboswitches but also the structural characteristics and dynamics that control how synthesized small molecules interact with RNA.[6]

In conclusion, the use of AI-driven tools for predicting and discovering small molecule compounds that can interact with RNA has made significant progress in the development of RNA-targeted ligands. These tools provide a valuable opportunity for modulating RNA expression, thereby creating new possibilities for biomedical research.

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