https://doi.org/10.1038/s41587-024-02375-0

EDITOR'S PICK: ATOMIC AI

Each year, *Nature Biotechnology* highlights companies that have received sizeable early-stage funding in the previous year. Atomic AI generates the structure data it needs for its AI model with the aim of RNA drug discovery. **By Vivien Marx**

Connecting AI and RNA for drug discovery takes more than to "somehow sprinkle some AI dust on things and it'll be great," says Atomic AI CEO and founder Raphaël Townshend. Some RNA therapeutics startups and spinouts choose to partner with big pharma fairly early on, but that's a path Atomic AI, founded in 2021, has not publicly disclosed to date. With its $7 million seed round and $35 million series A financing, 'AI-native' Atomic AI is generating the data it needs to train its artificial intelligence (AI)-based RNA structure model.

Atomic AI founder and CEO Raphaël Townshend.

To train AI algorithms, says Townshend, "95% of the work is getting the right data in the first place." Atomic AI's teams do their own wet-lab experiments to supplement the sparse public data on RNA structure. Unlike the Google DeepMind team that developed AlphaFold, which predicts protein structures and used data in the Protein Data Bank for its training data, Townshend and colleagues started from only 18 known structures when they co-developed a tool with the lab of Stanford biochemist Rhiju Das to predict the complex three-dimensional structure of RNA from an RNA sequence. Their neural network extrapolated molecular features from the training set and predicted RNA structures on the basis of sequence better than other existing platforms, with their Atomic Rotationally Equivariant Scorer published in 2021 in *Science*[1]. The software is available on Zenodo.

Atomic AI teams have been collecting data through wet-lab experiments to feed their Platform for AI-driven Structure Exploration (PARSE). PARSE includes ATOM-1, its model that predicts RNA structure and function from chemical mapping data. PARSE and ATOM-1, says CSO Manjunath Ramarao, "are the foundation for the company and the work that we do." He spent 12 years at Bristol Myers Squibb and joined Atomic AI in October 2023. ATOM-1, they note in a preprint[2], lets them model RNA structures despite the lack of ground truth data.

Successes that buoy new entrants in the RNA therapeutics space include mRNA-based vaccines for COVID-19 and approved drugs such as Spinraza (nusinersen), an antisense oligonucleotide that modifies RNA splicing to treat spinal muscular atrophy. Yet, according to a report[3] by the National Academies of Sciences, Engineering, and Medicine, "the use of RNA-based technologies for treating human diseases is in its infancy." Atomic AI wants to help the field grow up as it eyes applications in oncology and neurological and neurodegenerative disease.

Townshend's career might have led to a trajectory with self-driving cars given his PhD-focus on computer vision with Ron Dror at Stanford University. During his rotation through a structural biology lab, he remembers, "this looks like the right place to be." His sense about structural biology intensified in a research stint with DeepMind's AlphaFold team. As he stayed at the interface between structural biology, biophysics and AI, he deepened his skills in biology and computing and built the platform that Atomic AI now uses to predict the three-dimensional structure of RNA.

RNA is harder to drug than DNA, says University of California San Diego researcher Gene Yeo, who advises Atomic AI and who was interviewed jointly with Townshend. RNA forms complex three-dimensional structures, and perhaps as many as 140 different chemical modifications can tune RNA function and metabolism. For now, it is less clear how to read or alter most of these modifications, but Yeo thinks Atomic AI is well positioned for progress.

Atomic AI scientists use a library of compounds to modify specific RNA nucleotides, read out the changes with sequencing and assess how RNA's two- and three-dimensional structure was altered. Its core neural network, says Townshend, is a foundation model, such as those that underpin large language models like ChatGPT. In this case, the model is tuned to predict RNA's functional and structural properties. Rather than rely on public data, which can be of variable quality, Ramarao says, "We wanted to do our own experiments, generate our own data that can feed into the model building." Atomic AI aims to map the transcriptome to enable a scaled-up hunt for RNA on-targets and off-targets.

The wet-lab and modeling teams collaborate and iterate to build selectivity and potency traits into a lead molecule, says Ramarao. They address specifics about chemistry or structure together, says Atomic AI scientific advisor Percy Carter, who is CSO of Blueprint Medicines and who was interviewed together with Ramarao. With RNA, scientists can target regulation of translation, mRNA stability, RNA degradation or splicing, which can be mediated by proteins or by proteins interacting with RNA. A small molecule might interact directly with RNA or interfere with RNA–protein interactions to modulate function or degrade RNAs. Target types will differ, and so there might be direct binding to RNA, says Carter, or one has to consider activity of a protein-driven-process on RNA. Proteins that mediate splicing operate in a complex and bind to RNA as ribonucleoproteins. Thus, as they assess RNA structure, Atomic AI's teams also heed protein structure and behavior. RNA structures can be experimentally resolved, for instance with nuclear magnetic resonance (NMR) spectroscopy.

It is known what makes chemical compounds and ligands more likely than others to interact with RNA, says Yeo. Such traits include that they are positively charged, intercalating aminoglycoside-like, flexible molecules. But this knowledge alone is insufficient to find the most promising ones. In some cases, a protein, rather than an RNA, is a better target in one of the cell's many protein–RNA interactions. In other cases — for instance, where protein targeting has failed — RNA targeting offers a potential therapeutic benefit for previously undruggable targets.

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Targeting RNA also means navigating RNA's loops and bulges that form in two and three dimensions, says Matthew Disney from the University of Florida Scripps Institute for Biomedical Innovation & Technology, who is not affiliated with Atomic AI. The Protein Data Bank is not an RNA databank, and much more structural information about RNA is needed, especially ligand-bound structures, he says. Forcefields for small-molecule docking have been optimized for protein docking. RNA binding can be electrostatically similar, but it is less well-defined and can include high-energy interactions. Simulated structures help to assess forcefield interactions, but experimental validation with NMR, X-ray crystallography or other approaches is needed, says Disney, to flesh out the atomic details and learn what is essentially "the language of the best force field."

Potency of an RNA therapeutic is important, says Disney, but so, too, is selectivity. Disney and colleagues developed a computational approach to find on- and off-targets for small molecules that target RNA and consider how one might optimize them. When treating cancer, an off-target effect might be tolerated, he says, but that situation shifts in a genetic disease when patients take a drug all their lives. Another challenge is getting enough of the molecules into diseased tissue without too much toxicity.

With RNA therapeutics, as in biotech more generally, startups must balance platform-building with their hunt for bioactive compounds to ultimately get into the clinic, says Disney. It is better to have a compound in hand to advance toward a goal, he says, "but it may come back to platform," as balancing platform and bioactive compounds, he says, is critical for building value for investors.

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Published online: 26 August 2024

References

1. Townshend, R. J. L. et al. *Science* **373**, 1047–1051 (2021).
2. Boyd, N. et al. Preprint at *bioRxiv* https://doi.org/10.1101/2023.12.13.571579 (2023).
3. National Academies of Sciences, Engineering, and Medicine. *Charting a Future for Sequencing RNA and its Modifications: A New Era for Biology and Medicine* (National Academies Press, 2024); https://doi.org/10.17226/27165