# Syrna Therapeutics Comes Out of Stealth with Covalent Translation Inhibitors Targeting mRNA

Shutting down the production of disease-causing proteins - by interfering with cellular translation - is the next great frontier in small-molecule drug discovery. Syrna Therapeutics was founded on the conviction that realizing this vision requires a fundamentally new approach and transformative capabilities. The company is leading this evolution by pioneering *3D structure-guided drug discovery for mRNA*, coupled with a powerful universal mechanism for inhibiting translation that operates independently of the complex biology of each mRNA target.

Directly targeting mRNA with a small molecule to reduce production of disease-causing proteins is not a new idea. Preventing production of a protein by targeting its mRNA provides a powerful drug amplification effect relative to inhibitors that block the protein's function after it is made: each mRNA produces many protein copies, so each molecule of mRNA that is blocked stops hundreds to thousands of protein copies from being made. Despite its enormous potential, aside from splice modifiers, direct targeting mRNA with a small molecule has remained elusive.

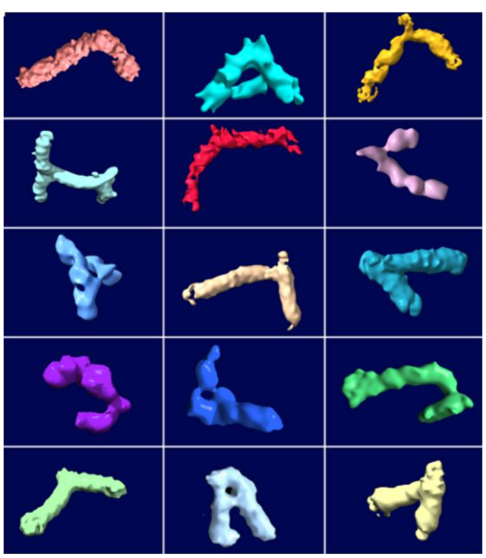
## Two founders converge on a shared vision

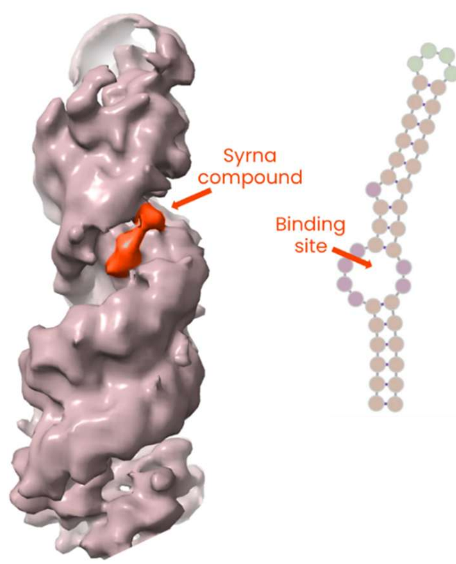
Syrna Therapeutics was founded by David Weitz and Thomas Hermann. David's drug discovery career began at Syrrx, a pioneer in structure-based drug design that was acquired by Takeda in 2005. He stayed post-acquisition to build up and ultimately lead Takeda's research site in San Diego. In the process, he watched structure-guided drug discovery grow and evolve. He saw how soluble protein drug discovery was catalyzed by the automation Syrrx pioneered, and later how membrane protein drug discovery was boosted by novel X-ray crystallography and cryo-EM techniques. Convinced by these experiences, David knew that it was time for structural biology to tackle targeting mRNA. Thomas, both by working in biotech and as a professor at UC San Diego since 2005, helped to establish the field of small-molecule modulation of RNA function from a structural perspective. His pioneering research on RNA molecular recognition demonstrated that a 3D-fold in the mRNA-like genome of the hepatitis C virus can present a pocket accessible to rationally designed small molecules that block viral translation [1-8]. Together, David and Thomas converged on a shared vision that involved doing what the literature said was impossible: find where mRNA forms highly stable structures, solve the structures to enable structure-guided drug discovery, and design covalent translation inhibitors using those capabilities.

**Proof that structure-guided design of covalent translation inhibitors can be achieved**

Syrna has made three scientific breakthroughs to become the first structure-guided company to target mRNA with small molecules and the first covalent translation inhibitor company:

1) **Discovery of structured mRNA domains:** Using cryo-electron microscopy (cryo-EM), Syrna has identified druggable structured domains in the mRNAs of over 25 high-value protein drug targets (15 of these structures are shown in the collage image below). All the structured domains are novel - identified without prior knowledge of their existence.
2) **Structural visualization of a drug-RNA complex:** Syrna has already achieved first high resolution cryo-EM structures for two of its novel structured domains with a bound small molecule. These landmark structures confirm the feasibility of structure-guided design for RNA-targeted drugs, revealing exactly how the compound binds and guiding further inhibitor optimization.
3) **Translation inhibition through formation of a covalent small molecule – mRNA adduct:** Using 3D-structural information, Syrna has designed compounds that selectively bind and form a covalent adduct with the mRNA target in cells to effectively silence protein production.





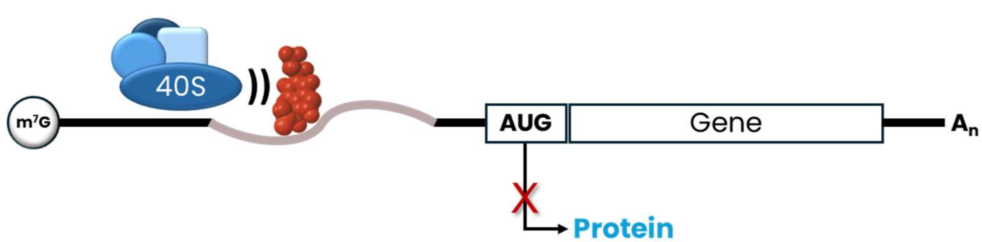
**Limitations of current RNA-targeting methods**

Drugging mRNA to shut down protein expression has advanced to the clinic only with antisense oligonucleotides (ASOs), RNA interference (siRNA), and with a few small molecules that modify splicing efficiency. While these approaches prove that mRNA can be a therapeutic target, they have limited therapeutic reach and effectiveness: Oligonucleotide therapies (ASOs and siRNAs) face major challenges with cellular delivery and stability, often requiring special formulations or delivery vehicles to reach their targets inside cells, and splice modulators only work on a narrow subset of targets.

A wide swath of disease-causing proteins remain beyond the reach of current RNA-targeting approaches. This creates a tremendous opportunity for a new modality that can address a much broader range of protein targets.

**Syrna is pioneering a new approach: Covalent translation inhibition**

Syrna's ability to identify structured domains in the mRNA of a large number of proteins and advance small molecule programs in a structure-guided manner opens the door to rational discovery of covalent translation inhibitors. First, a unique structured domain in the mRNA of the targeted protein is identified. Small molecule screening then delivers selective hits that validate the druggability of the structured domain. Those hits are expanded into a chemical series and electrophiles are introduced to arrive at compounds that form site-selective covalent adducts at the RNA target. Guidance provided by 3D structural information narrows the chemistry space that needs to be explored for developing hits into optimized translation inhibitors. The covalent adduct formed on the mRNA is irreversible and functions as a roadblock for translation. A ribosome attempting to translate mRNA that has been covalently modified will run into the bound inhibitor and stall. The stalled ribosome triggers cellular quality control mechanisms that degrade the aberrant RNA.




Covalent inhibitors modify the mRNA as it is made during transcription and prevent translation of the target. The protein is never synthesized, achieving the same outcome as gene silencing but with a small molecule.

Because covalent inhibition is permanently effective when the adduct is formed, this mechanism solves important problems that have hampered drugging mRNA in the past. Once a compound is covalently attached to the mRNA, it blocks any ribosome that approaches, even if the RNA's structure unfolds under the force of translation. Importantly, covalent translation inhibition provides a universal mechanism of action that is effective independent of the structured domain's native functional role for the mRNA target. Hence, Syrna's approach to covalent translation inhibitors obviates the need to understand why the structured domain exists or whether there are any natural binders.

Covalent inhibition is superior in many cases to traditional enzyme inhibitors and receptor antagonists because the protein which causes disease due to over-production is never made to begin with.

**Defying the conventional wisdom about RNA structural biology**

A prevailing assumption in the RNA targeting field has been that stable structured domains are rarely found in mRNA molecules – they were thought to be floppy and unstructured, unless bound by a protein to adopt a biologically relevant conformation. Because of this, detailed 3D structural information on mRNA has been scarce, aside from a few special cases like bacterial riboswitches and aptamers, where RNA structures have been determined. Syrna challenged this notion. The founders hypothesized that portions of an mRNA may fold into complex structured domains, and cryo-EM imaging would reveal the most persistent structured domains with the best small molecule binding sites.

Another frequently held view posits that obtaining 3D structures of mRNA is prohibitively difficult. In contrast, the Syrna team was convinced that the 3D structures obtained during target identification could be advanced to high resolution in support of a structure-guided drug discovery approach. Challenging prevailing assumptions head-on, Syrna developed techniques to directly image domains within mRNA by cryo-EM and made several eye-opening discoveries:

1) Persistent RNA folds exist in many mRNA: Syrna demonstrated that regions within an mRNA do form stable tertiary structures independently, without needing a protein to fold or stabilize them.
2) Complex folds create druggable pockets: The RNA domains that Syrna identifies comprise hundreds of nucleotides and form intricate folds with clefts and pockets that a small molecule can potentially bind.
3) High-resolution structures are attainable: Syrna's work shows that isolated mRNA domains can be advanced to high-resolution, further demonstrating how stable and ordered the domains are.

The results speak for themselves. Syrna has screened segments of different mRNAs encoding high-value targets across a wide range of protein classes: enzymes, GCPRs, receptors, ion channels, transcription factors, CD proteins and cytokines. We found stable, structured domains in 25 of them, indicating that many mRNA across the proteome contain structured domains that can be exploited as small molecule binding sites.

Notably, mRNA structured domains discovered by Syrna often span hundreds of nucleotides and lie outside the reach of current computational structure prediction methods. The scarcity of known RNA–small molecule complex structures makes it especially challenging for machine learning approaches to predict which mRNA regions will form stable folds or where a ligand might bind. This underscores the importance of Syrna's experimental approach to identify druggable 3D-folds in mRNA.

**Advancing a new therapeutic modality for mRNA inhibitors**

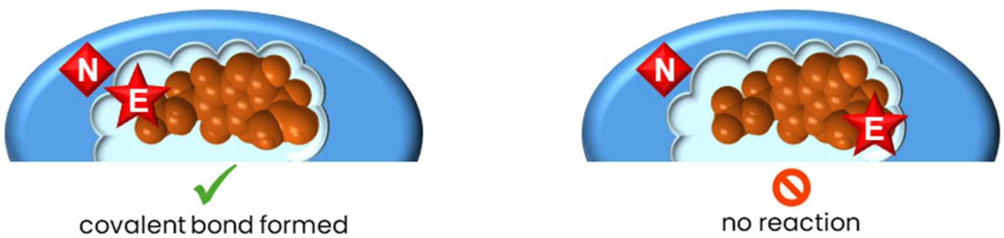
Until very recently, little was written on binding site-directed covalent modification of mRNA. The few published examples were based on RNA where the structure was already known with established non-covalent binders. We think that widely held assumptions have kept people away: a lack of RNA 3D-structural information, poor binding selectivity, and the perception that nucleobases provide poor nucleophilic sites, to name a few.

By identifying structured domains that are stable and persistent, Syrna discovered high quality small molecule targets to work with that yielded improved high throughput screening success: hit molecules were identified that are progressible to drug-like chemical series and yield high affinity binders. By cross-screening compounds against many RNA targets, Syrna developed a strong understanding of non-covalent binding selectivity. With 3D structural information in hand, Syrna greatly narrows the chemistry space to be explored to properly place an electrophilic warhead in a non-covalent binder. Through iterative design, guided by structure activity relationships, we can optimize the compound's shape and binding groups to maximize affinity and selectivity for the RNA pocket. We also demonstrated strategic placement of an electrophile warhead so that it reacts with a specific nucleotide in the RNA structure. Syrna's work is supported by a full suite of technology that provides a deep understanding of RNA target-compound engagement: non-covalent ligand binding by affinity screening, adduct formation by mass spectrometry, adduct-induced reverse transcriptase primer stops by next generation sequencing, 3D structures of RNA-compound complexes by cryo-EM, and translation inhibition by human cell-based reporter assays.

**Achieving selectivity through combining inhibitor proximity and geometry**

A critical advantage of covalent translation inhibitors is their exceptional selectivity for the target mRNA. This selectivity results from two synergistic factors:

1) Selectivity for the binding-site (proximity): Covalent reactivity requires the small molecule to first bind non-covalently to a target RNA which provides a unique pocket. Syrna's work across many different target RNAs informs the selectivity of compounds for a specific RNA.
2) Proper warhead positioning (geometry): The electrophilic warhead must be precisely oriented relative to the nucleophilic target sites in the mRNA. Syrna scientists take advantage of the high-resolution images of the RNA-compound complexes to iteratively refine the positioning of the electrophile warheads to achieve optimal activity. By fine-tuning the reactivity of the warhead to be just right – reactive enough to engage the target nucleotide, but not so reactive that it attacks any RNA at random – Syrna's chemists can further refine selectivity. If the warhead is too hot or the ligand binding is too weak, off-target reactions could occur, but with the right balance, the covalent inhibitor becomes selective for its intended RNA target.




High-resolution structural data is key to achieving this balance. Knowing exactly how the compound sits in the RNA pocket allows vectoring of an electrophile toward a specific nucleophilic group in an RNA base at the correct distance and angle. This precision in design translates to both on-target potency and off-target selectivity.

**Broad potential and outlook**

Syrna is using its structure-enabled platform to chart a path to effectively targeting mRNA with broad protein target reach. Covalent translation inhibitors can be made for many different transcripts, regardless of the protein's class, function, or disease area. Essentially, any disease-causing protein is a potential target if its mRNA contains suitable structured domains. This is a leap forward in expanding the reach of small molecule drugs broadly to the human transcriptome and beyond traditional protein targets.

Syrna Therapeutics raised a seed financing round in 2023 co-led by *Insight Partners* and *Innovation Endeavors*, to refine its platform and advance discovery programs to lead optimization. For partnership inquiries, contact: bd@syrnatx.com

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