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Review Article

Targeting RNA structures in diseases with small molecules

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RNA is crucial for gene expression and regulation. Recent advances in understanding of RNA biochemistry, structure and molecular biology have revealed the importance of RNA structure in cellular processes and diseases. Various approaches to discovering drug-like small molecules that target RNA structure have been developed. This review provides a brief introduction to RNA structural biology and how RNA structures function as disease regulators. We summarize approaches to targeting RNA with small molecules and highlight their advantages, shortcomings and therapeutic potential.

Introduction

RNA has traditionally been thought to simply carry genetic information from DNA to protein. However, with the accumulation of knowledge about RNA structures and functions, especially those of different types of non-coding RNAs, modern views have expanded RNA function a lot to gene expression regulation and human diseases. RNA structure is a bridge from primary sequence to biological function and is crucial for correct functioning, such as RNA transcription [1], splicing [2], translation [3], localization [4], protein interaction, and gene expression regulation [5]. For example, riboswitches rely a lot on structural changes to respond to metabolites and regulate gene expression. Riboswitches are typically found in the 5′ untranslated regions (5′-UTRs) of bacterial genes, and consist of an aptamer domain and an expression platform. Metabolites specifically bind to the aptamer domain and induce conformational changes to disturb either transcription terminators or translation initiation signals [6]. mRNA structure can also regulate translation initiation. The mRNA start codon must be single-stranded so that the mRNA can fit in the mRNA cleft of the ribosomal preinitiation complex and start translation [3]. RNA misfolding or aberrant RNA structures caused by mutations or abnormal interactions with other biomolecules can lead to human diseases, such as cancer, neurological diseases [7], cardiovascular diseases [8], chronic obstructive pulmonary disease (COPD), liver disease, and asthma [9]. In microbial infections, bacteria- or virus-specific ribosomal RNA, riboswitches, and RNA elements can serve as drug targets [10–13].

Although the relationship between RNA structure and diseases is not fully understood, RNA is emerging as a therapeutic target. Regular therapeutics targeting proteins face challenges of limited disease-related and druggable targets [14]. Only a small fraction of the human genome encodes proteins. Within a small subset of disease-related proteins, only part of them have specific pockets appropriate for small molecules binding. For therapeutics targeting DNA, toxicity is a severe problem such as some anti-cancer regents [15] and the CRISPR-Cas9 therapy [16]. Compared with proteins and DNA, however, RNA provides many more potential drug targets that constitute a much large fraction of genome, with very diverse functions and structures.

However, effective approaches for RNA-targeted drug discovery are limited. To date, the most commonly used methods to target disease-associated RNAs have been based on sequence complementarity, including single-stranded antisense oligonucleotides (ASOs) or double-stranded small interfering RNAs (siRNAs). A small number of oligonucleotide therapies have been approved by the Food and Drug

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Administration (FDA) [17]. But their application is limited by several shortcomings; for example, siRNAs can cause allergic reactions, have poor cell permeability, and are difficult to cross brain–blood barrier [18]. By contrast, small molecules, targeting RNA structure rather than complementary sequence, have good absorption, distribution, and bioavailability.

In this review, we first introduce RNA structures as regulators in human diseases and as drug targets, and then summarize approaches used to identify and design small molecules targeting disease-associated RNAs. We compare the advantages and shortcomings of different approaches and discuss future prospects of RNA-targeted drug discovery.

RNA structures as mediators in diseases

RNA is typically single-stranded, but complementary sequences in the strand can base pair intra- or inter-molecularly, creating secondary structures such as helices and loops, as well as more complex tertiary structures. Aberrant RNA structures can lead to human diseases through two mechanisms: loss-of-function or gain-of-function [7].

The loss-of-function mechanism involves mutations that alter RNA structural elements and disturb interactions between RNA and protein in normal cellular processes. For example, Halvorsen et al. investigated disease-associated SNPs mapped to UTRs in the human genome. SNPs that significantly change the structure of UTRs were identified and these UTR–SNP combinations were named 'RiboSNitches' [19]. They identified mutations in the 5′-UTR of the ferritin light chain (*FTL*) gene that disrupt the hairpin structure of the iron response element and thus alter the binding affinity of iron response proteins, leading to aberrant FTL regulation in hyperferritinemia cataract syndrome [19]. Another example is RNA structure-mediated deficiency of α-1-antitrypsin expression which is associated with COPD, liver disease, and asthma [9]. Splicing generates distinct local 5′-UTR secondary structures and the inclusion of long upstream open reading frames (ORFs) in *SERPINA1* (α-1-antitrypsin gene) transcripts, altering the translational efficiencies. Two cardiovascular disease-related SNPs in 3′-UTRs were shown to regulate gene expression by altering RNA structure and thus microRNA binding [8]. The first is in the miR-155-binding site of the Angiotensin II type 1 receptor (*AGTR1*) 3′-UTR and correlates with changes of the secondary structure of the 3′-UTR and *AGTR1* gene expression. The second is in the muscle RAS oncogene homolog (*MRAS*) 3′-UTR. Although this SNP is outside microRNA binding sites, it influences microRNA-mediated gene regulation by altering local RNA structure.

The gain-of-function mechanism involves the emergence of pathogenic RNA structures not present in normal conditions. The most common example is that abnormal RNA repeat expansion leads to sequestration of RNA-binding proteins and induces non-ATG translation to produce short neurotoxic peptides. In neurological diseases, taking type 1 myotonic dystrophy (DM1) as an example, the r(CUG)^{exp} (expanded r(CUG) repeats) in the DM1 protein kinase (*DMPK*) transcripts can bind to and sequester splicing regulators, such as muscleblind-like (MBNL) proteins, and cause incorrect pre-mRNA splicing [20]. The r(CUG)^{exp} and r(CAG)^{exp} generated multivalent base-pairing, which could cause phase transition in some neurological and neuromuscular disorders [21]. In other cases, r(GGGGCC)^{exp} from the *C9orf72* gene in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) [22], and r(CAG)^{exp} from the *htt* gene in Huntington's disease [23] cause neurotoxicity through similar mechanisms.

RNA structures as drug targets

Early strategies to identify RNA-binding molecules were mainly based on complementary sequence rather than structure, such as siRNAs [24] and ASOs [25]. However, approaches based on nucleic acids involve large, often highly charged molecules, and present limitations in delivery, bioavailability, specificity, toxicity, and immune response.

Small molecules are more 'drug-like' than nucleic acids and have better physicochemical properties. Structure-based identification of small molecules that bind to RNA would provide higher specificity than sequence-based strategies. Linezolid antibiotics are the only class of small molecules designed to target RNA that are used clinically [14]. They are broad-spectrum antibacterial agents that bind to ribosomal RNA of the large ribosomal subunit and perturb correct tRNA positioning [26,27]. Other small-molecule drugs have been studied in research and clinical experiments; they target multiple classes of RNAs, including ribosomal RNA, riboswitches, repeated RNA expansions, microRNAs, viral elements, and RNA splicing (Table 1).

To identify effective drug-like small molecules targeting RNA, common principles of drug design must be considered. Lipinski's rule of five is well known to evaluate the drug-likeness of a molecule: a molecular mass less than 500 Daltons, an octanol–water partition coefficient log P not greater than 5, no more than five hydrogen bond donors, and no more than ten hydrogen-bond acceptors [28]. Although these criteria are based on orally active drugs that target proteins, they could be applicable to RNA-targeted drugs since drug-likeness is mainly based on bioavailability and human physiology [14]. Considering physicochemical and structural differences between protein and RNA,

Table 1 Small molecules targeting RNA

RNA targets	Example	Related diseases	Small molecules
Ribosomal RNA	23S rRNA	Gram-positive bacteria	Linezolid [26]
	16S rRNA	Bacteria	Aminoglycosides [31,32]
Riboswitch	Riboflavin riboswitch	Bacteria	Ribocil [33]
	Thiamin pyrophosphate (TPP) riboswitch	Bacteria and fungi	Pyrithiamine [34]
	Lysine riboswitch	Gram-positive bacteria	L-aminoethylcysteine and DL-4-oxalysine [35]
Viral elements	Transactivation response (TAR) element	Human immunodeficiency virus (HIV)	Netilmicin [36]
	Frameshift site (FS)	HIV	DB213 (RG501) [37]
	Internal ribosome entry site (IRES)	Hepatitis C virus	Benzimidazole inhibitor [38]
Oligonucleotide repeat expansion	r(CUG) repeat expansion	Myotonic dystrophy type 1	Bisamidinium inhibitor [39]
	r(CAG) repeat expansion	Huntington's disease and spinocerebellar ataxia	Myricetin [40]
	r(GGGGCC) repeat expansion	Frontotemporal dementia and amyotrophic lateral sclerosis	Ligand 1a [41]
microRNA	miR-544 precursor	Cancer	Ligand 1 [42]
	miR-96 precursor	Cancer	Compound 1 (Benzimidazole) [43]
	miR-21 precursor	Cancer	Streptomycin [44]
	primary miR-21	Cancer	Compound 2 (Diazobenzene) [45]
	miR-122	Hepatocellular carcinoma and hepatitis C virus infection	Compound 1-3 [46]
RNA splicing	RNA duplex between U1 and SMN2 pre-mRNA	Spinal muscular atrophy	Branaplam (NVS-SM1) [47] SMN-C5 [48]

RNA-targeted small molecules could have distinct structural properties such as rod-like shape [29], and kinetic properties such as slow molecular recognition [30]. Warner et al. discussed principles for discovering small molecules that target RNA and argued that disease-related RNAs that have high information content and appropriate ligand-binding pockets should be focused on as RNA targets [14].

Approaches to targeting RNA structure in drug development

Despite the highly anionic nature and the flexible and dynamic structure of RNA, a number of promising approaches to identify small molecules targeting RNA have been developed. They can be categorized roughly into experimental and computational approaches, as well as into different strategies, e.g., structure-based, fragment-based, and similarity-based. The following approaches discussed are not necessarily independent and there could be overlapping techniques.

Biochemical screening

Biochemical screenings are target-based approaches dependent on biochemical techniques, such as fluorescence resonance energy transfer (FRET) [49], fluorescent indicator displacement [50], click chemistry [51], and mass spectrometry [52], to report the potency of RNA–ligand interaction in high-throughput screening.

Small molecule microarray (SMM) is a valuable biochemical screening approach for RNA-targeted drug discovery. It was originally developed to identify inhibitors of 'undruggable' proteins [53–56]. For application for identification of RNA-binding ligands, a library of small molecules is arrayed and linked to glass slides. Fluorescently labeled RNAs are incubated with the slides and bound to some small molecules. The slides are then washed with buffer to remove unbound RNA and imaged with a fluorescence scanner for quantification of fluorescence intensity for each spot. Spots with significant fluorescence increases indicate interactions between the RNA and small molecules [57] (Figure 1A).

Aminoglycoside microarrays were developed for the high-throughput screening of saccharides that bind to the prokaryotic 16S ribosomal aminoacyl site [58]. The Disney laboratory also developed a microarray platform to screen RNA motif–ligand interactions from RNA and chemical space simultaneously [59,60]. This RNA–ligand database can also be used for informatics-based drug discovery which will be discussed later. The Schneekloth group used small molecule microarrays to screen a library of drug-like small molecules against the HIV transactivation response (TAR) RNA hairpin and identified a novel chemotype that selectively bound the target [61].

This approach can cover many different RNA structures and achieve higher throughput than cell-based screening. It can identify compounds that bind targets directly. The biggest problem is that the small molecules identified from *in*

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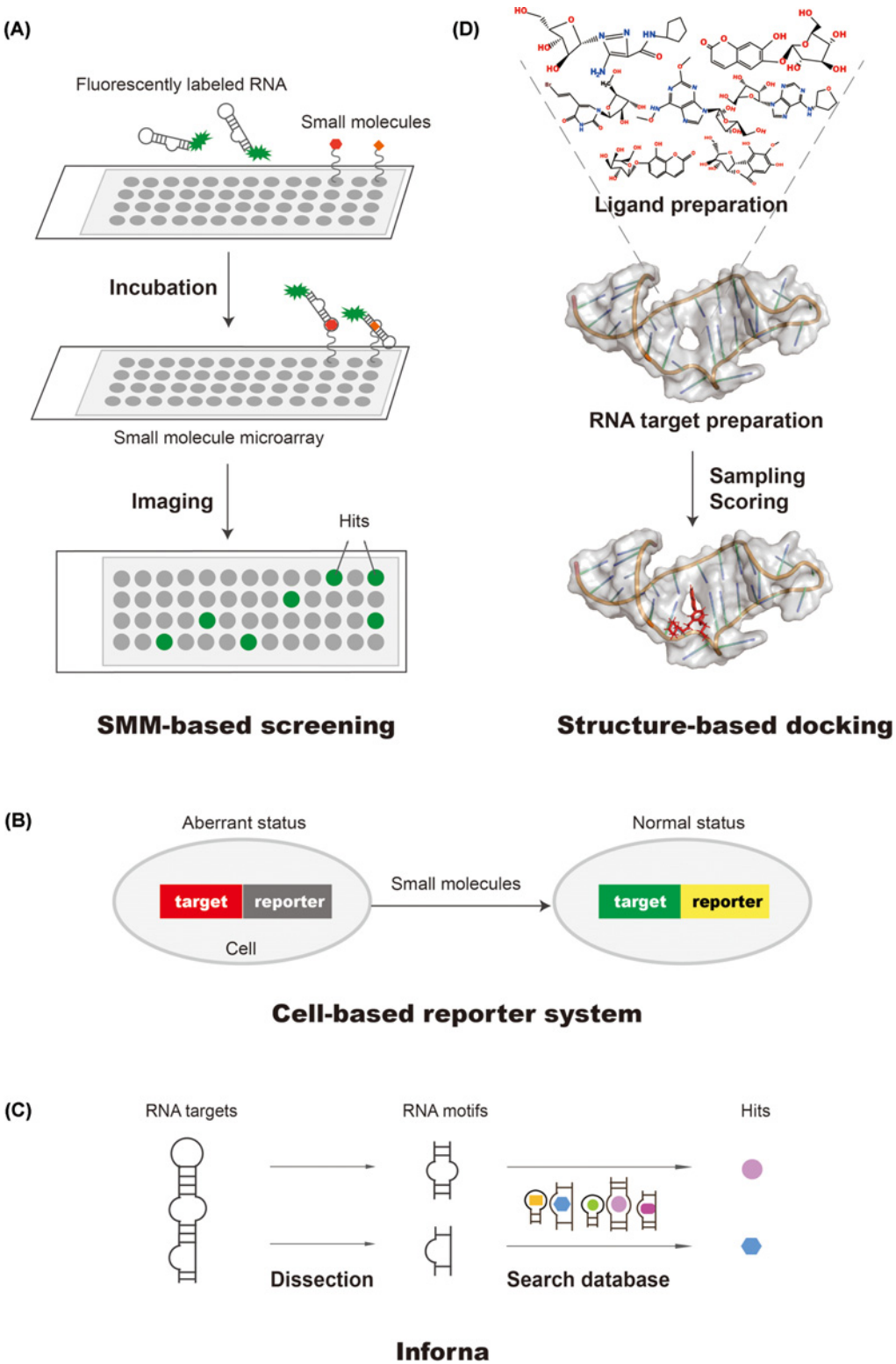

Figure 1. Approaches based on high-throughput screening

(**A**) Small molecules are arrayed and linked to a glass slide, incubated with a fluorescently labeled RNA, and then imaged for identification of hit compounds. (**B**) Reporter system in cell-based screening indicates ligand potency. (**C**) A database of RNA motif-small molecule interactions is created. By comparing the motifs found in the target RNA structure to those in the database, lead compounds can be identified from the annotated RNA motif–small molecule interactions. (**D**) Small molecules are docked on to the known 3D structure of an RNA target and the binding energies are evaluated by a scoring function.

vitro screening usually have poor cell permeability and bioactivity. Validation and modification are therefore needed for further drug development.

Cell-based screening

Cell-based high-throughput screening applies phenotypic readout, like gene expression and cell survival rate, to report the effect of small molecules. Reporter systems are constructed in cells and then are incubated with small molecules for phenotypic readout [62] (Figure 1B). Although phenotypic assays are not used for identification of small molecules that specifically target RNA, most effective and well-known RNA-targeted drugs have been identified by this approach, including ribocil, branaplam and SMN-C5 [33,47,48]. They were identified by phenotypic screening, but only during validation were they shown to bind to RNA targets.

An example is Novartis's work on spinal muscular atrophy (SMA) [47], a debilitating motor neuron disease caused by deficiency of survival of motor neuron (SMN) protein and death of α-motor neurons. SMN can be produced by both *SMN1* and *SMN2* genes, but a single-nucleotide transition in *SMN2* causes altered splicing and exon 7 exclusion, which decreases full-length SMN mRNA and protein [63,64]. Researchers from Novartis used phenotype-based high-throughput screening to identify small molecules that can reduce SMN2 exon 7 exclusion, using a pair of SMN2-matched reporter constructs in an NSC34 motor neuron cell line. The reporter constructs indicated exon 7 inclusion (full-length reporter) or exon 7 exclusion (Δ7 reporter). Hits that both increased full-length and decreased Δ7 reporter activity were selected. They identified two active compounds, NVS-SM1 (renamed branaplam) and NVS-SM2, with good efficacy, bioavailability, and distribution to the brain. Branaplam is now in a Phase II clinical trial.

This strategy can efficiently identify small molecules that cause phenotypic changes and contribute more to drug discovery than target-based strategies [65]. However, the direct targets and molecular mechanisms of effective compounds are unknown—only after their identification are efforts made to explore the biological targets and mechanisms.

In silico screening

With the development of bioinformatics, computational approaches have been used for drug discovery. Computer-aided structure-based docking and optimization, Inforna platform and machine learning-based approaches are promising bioinformatics-based approaches for identification of RNA-targeted small molecules.

Structure-based docking

Structure-based virtual screening by docking is a powerful, fast, and cost-effective tool for discovery of RNA-binding small molecules. Small molecules are docked on to the known 3-dimensional (3D) structure of an RNA target elucidated using X-ray crystallography or nuclear magnetic resonance and the binding energies are evaluated by a scoring function. Compounds that are most likely to bind to the target are selected for further validation. Many docking programs have been developed for virtual screening of small molecules against RNA; they include DOCK6 [66], rDock [67], DrugScore^{RNA} [68], and Internal Coordinate Mechanics (ICM) [69].

Docking programs originally developed for proteins are not particularly accurate for RNA, due to distinct physicochemical and structural properties, e.g., greater structural flexibility and higher negative charge of RNA, which produces a different surface in terms of electrostatic potentials and solvation [70]. To enhance the prediction efficiency, efforts have been made to develop scoring functions for specific evaluation of RNA–small molecule interactions [71] and docking programs that allow more flexibility [72]. Studies also show that docking small molecules on to RNA dynamic ensembles by combining molecular dynamics (MD) and NMR residual dipolar couplings, rather than a single conformation, can increase prediction accuracy [73,74].

The Al-Hashimi laboratory used an RNA dynamic ensemble to virtually screen small molecules that target the HIV type 1 (HIV-1) TAR element using the ICM docking program [36]. They docked ~51000 small molecules against 20 conformers of the RNA dynamic ensemble and identified six compounds that bind TAR with high affinity (K_d = 55 nM–122 μM) and inhibit the interaction with Tat (K_i = 710 nM–169 μM) *in vitro*. Among these compounds, netilmicin bound TAR with high selectivity, inhibited Tat activation of HIV-1 long terminal repeat, and inhibited HIV-1 replication. This research first validated the *in vivo* activity of the compound identified from virtual screening, demonstrating it as a promising approach to identify small molecules targeting RNA.

Virtual screening enables testing of an extremely broad variety of compounds with few limitations, which is a double-edged sword because more possibilities mean lower hit rates. Other limitations include inaccurate pose scoring and binding energy prediction, long running times, and lack of consideration of flexibility [75].

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Inforna

Inforna is a sequence-based approach that designs lead small molecules targeting RNA using sequence information alone [76]. Inforna constructs a library of interactions between small molecules and small RNA motifs including bulges, hairpins, and internal loops, by two-dimensional combinatorial screening (2DCS) based on small molecule microarray [60,77]. Then, structure–activity relationships through sequencing (StARTS) is used to score the fitness of the interactions between small molecules and RNA motifs [78]. By comparing the motifs found in the target RNA structure with those in the database, lead compounds can be identified from the annotated RNA motif–small molecule interactions (Figure 1C). Lead compounds are then validated for biological function.

The Disney lab has used Inforna to identify small molecules for several RNA targets, including RNA repeat expansions [41] and microRNA precursors [42,43,79]. For example, they applied Inforna to human microRNA precursors that are up-regulated in diseases and identified 27 lead small molecules that bind Dicer or Drosha processing sites [43]. Twelve small molecules were validated to inhibit biogenesis of the microRNA from targeted precursors in primary cell lines. The strongest interaction was that between a benzimidazole and pre-miR-96. The benzimidazole selectively inhibited the biogenesis of miR-96, up-regulated its target protein FOXO1, and induced apoptosis in cancer cells, which suggests that Inforna can be useful for RNA-targeted drug discovery.

Inforna applies a simple and straightforward strategy that involves only sequence and secondary structure of RNA targets and relies on the RNA motif-small molecule database. However, the database covers very limited types of small molecules and RNA motifs, so it is only applicable in some conditions.

Machine learning

Machine learning-based approaches predicting drug–target interactions can be categorized into three types: (1) feature vector-based approaches, which generate features by combining representation of drug properties and target sequence; (2) similarity-based approaches, which assume that similar drugs tend to share similar targets and *vice versa*; and (3) other approaches based on integration of various profiles including pharmacological information of drugs and co-occurrent drug–target relationship [80].

Many approaches based on machine learning have been developed [81–85], but these approaches are based on big data mainly from protein targets. With increasing understanding of RNA structure and RNA–small molecule interactions, machine learning would be a promising approach to predicting RNA–drug interactions.

Rational design

Rational design is an efficient and interdisciplinary method for drug development, combining computer science, statistics, biophysics, biochemistry, molecular biology, pharmacokinetics, and pharmacodynamics [86]. It designs small molecules with desired properties for targets with known 3D structural information. Rational design comprehensively examines many aspects of small molecules, including their absorption, distribution, metabolism, excretion, toxicity, and quantitative structure–activity relationship (QSAR), as well as whether they are electrophilic or nucleophilic. [87]. It depends a lot on knowledge and experience, based on full characterization of drug targets. Ingenious design can save time and money, and drive novel drug discovery.

An example is the rational design of small molecules binding to r(CUG)^{exp} in DM1. DM1 is a multisystemic neuromuscular disease caused by abnormal CTG^{exp} in the 3′-UTR of the *DMPK* gene. r(CUG)^{exp} in *DMPK* transcripts can bind to and sequester MBNL proteins, and cause deficient pre-mRNA splicing [88]. Originally, the Baranger lab designed ligand 1 with an acridine to intercalate DNA and a triaminotriazine unit to recognize U–U through Janus-wedge hydrogen bonding (Figure 2A) [89,90]. It showed high selectivity and nanomolar affinity to r(CUG), but it was poorly water-soluble and cell-permeable, and was cytotoxic. Then they made improvements based on ligand 2 (Figure 2A) binding to the HIV-1 frameshift site RNA stem-loop [37], which is very similar to the structure of CUG repeats. They kept the bisamidinium unit of ligand 2 as a groove-binding scaffold and replaced the dimethylammonium groups with triaminotriazine units for U-U recognition [39]. The new ligand 3 (Figure 2A) exhibited low micromolar affinity (KD = 8 ± 2 mM) for r(CUG)$_{12}$ and high selectivity over other targets. It showed good cell permeability, reduced MBNL1-r(CUG)^{exp} ribonuclear foci in a DM1 cell culture model, partially corrected the defective splicing of pre-mRNAs and suppressed CUG-induced toxicity in a DM1 transgenic *Drosophila* model. This ligand was further used for the rational design of multitarget agents that targeted DM1 *in vitro* in three distinct ways: (1) by binding CTG^{exp} and inhibiting formation of the r(CUG)^{exp} transcript, (2) by binding r(CUG)^{exp} and inhibiting sequestration of MBNL1, and (3) by cleaving r(CUG)^{exp} in an RNase-like manner [90].

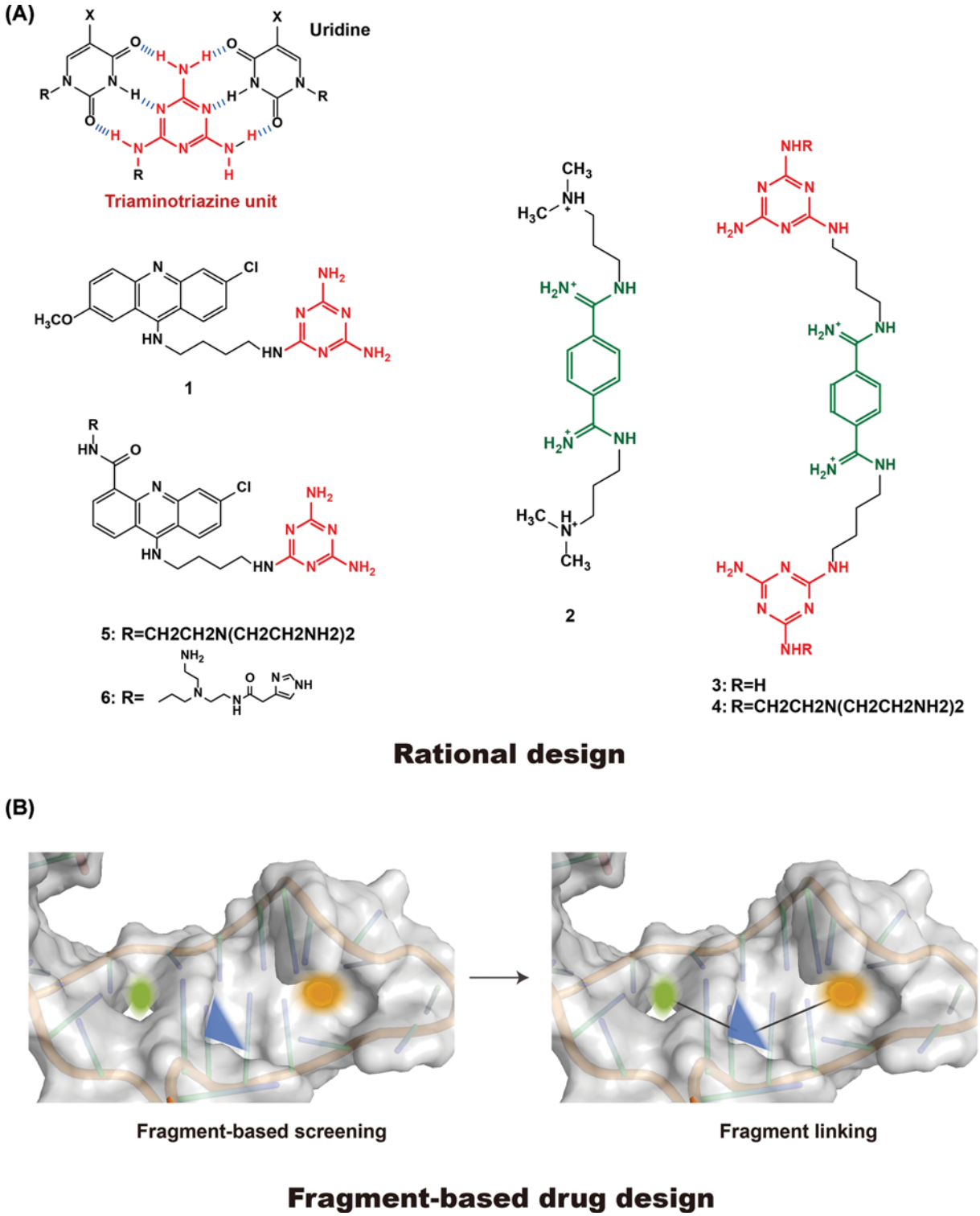

Figure 2. Approaches based on design

(**A**) Ligand 1 binds to r(CUG)^{exp} with an acridine intercalating DNA and a triaminotriazine unit recognizing U–U through Janus-wedge hydrogen bonding. Ligand 2 binds to HIV-1 frameshift site with a bisamidinium unit and two dimethylammonium groups. Ligand 3 binds to r(CUG)^{exp} with a bisamidinium unit binding to groove and two triaminotriazine units recognizing U–U. Ligands 4–6 were designed as multitarget agents to target the DM1 *in vitro* in three distinct ways. (**B**) Fragment library is experimentally or computationally screened against an RNA target. Identified fragments are linked or optimized for higher affinity and specificity.

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Fragment-based drug design

Fragment-based drug design (FBDD) is a rapid and resource-efficient approach for drug discovery. It focuses on identifying fragments of low molecular weight and chemical complexity that bind subpockets of targets with weak affinity. By adding functional groups or linking two fragments together, the initially identified fragments are optimized to produce potent and selective lead compounds (Figure 2B). FBDD not only covers better chemical diversity space, but also achieves higher hit rates than conventional high-throughput screening [91].

FBDD has also been combined with computational methods, like molecular docking and computer-aided fragment optimization. Several programs have been developed for optimization of hit fragments, such as GANDI [92], COMFIRM [93], BREED [94], and FOG [95]. These programs look for similar compounds in commercially available or public small molecule databases, or search for linker molecules to join fragments identified to binding targets, to help fragment growing, linking, and optimization.

An example is Novartis' work to identify compounds that interact with dengue viral RNA-dependent-RNA polymerase (RdRp) and show antiviral activity [96]. They screened Novartis' fragment collection against dengue viral RdRp and identified a biphenyl acetic acid fragment binding to the palm subdomain of RdRp with an IC_{50} of 734 μM. Then, they optimized the fragment hit using computer-aided structure-based design, resulting in >1000-fold improvement in potency. Physicochemical properties were then modified to increase cell permeability and anti-dengue activity was achieved in cell-based assays against all four serotypes with low micromolar EC_{50}. This research identified promising leads against all dengue serotypes, suggesting that FBDD can be an effective approach for identification of RNA-targeted small molecules.

Conclusion

This review briefly introduces RNA structures as mediators in diseases and as drug targets and then focuses on different approaches to identify small molecules targeting RNA, corresponding to three key components in RNA-targeted drug discovery: (1) identification of disease-related targets and dissection of their structures, (2) evaluation of druggability for identified targets, and (3) drug discovery based on high-throughput screening or rational design.

With increasing understanding of RNA structures and biological functions, more and more RNAs are identified as important mediators in multiple diseases. But the lack of information about RNA 3D structures and RNA–small molecule interactions limit our insights into RNA druggability and RNA-targeted drug discovery. A small subset of human proteins is thought to be druggable, and currently approved drugs target only 667 human proteins [97], ∼3% of total. By contrast, only a single class of small molecules targeting RNA, the linezolid antibiotics, is used clinically [14]. There is much room for exploration, but principles for the assessment of RNA druggability and RNA–small molecule interactions are required for guidance of RNA-targeted drug discovery.

Traditional strategies for drug discovery such as high-throughput screening and rational drug design originally designed for protein targets also apply to RNA targets, but subtle modifications are needed according to specific physicochemical properties and structures of RNA. Approaches developed to specifically target RNA structures efficiently like Inforna would be of great value if they could be used for a wide range of RNA and small molecules. RNA with stable structure of high complexity and ligand-binding pockets are more valuable targets for ligands with high affinity and specificity. Interactions between RNA and protein could also be paid more attention, which would have more stable structure and functional significance. For future studies, the development effective therapeutics that effectively targets RNA structure will largely anchored on our knowledge on RNA structure, which may come from probing experiments [98] and computational prediction [99], and more importantly, understanding the mechanism of RNA structure-related diseases. With the development of novel technologies to study RNA structures in biological context, we envision that their successful applications in the study of disease samples will acquire much knowledge of the regulatory role of RNA structure in human disease, and powered by the innovative new RNA structure-based methods, finally lead to the discovery of many more potential therapeutic targets and drugs.

Summary

- RNA is increasingly appreciated as regulators of human diseases and consequently as potential drug targets.
- Novel methods to target RNA structure with small molecules rather than RNA sequence have been developed.

- Knowledge and principles of RNA structure are highly desired to develop more effective RNA structure-targeting drugs.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Abbreviations

AGTR1, angiotensin II type 1 receptor; ASO, antisense oligonucleotide; Cas9, CRISPR associated protein 9; COPD, chronic obstructive pulmonary disease; CRISPR, clustered regularly interspaced short palindromic repeats; *DMPK*, DM1 protein kinase; DM1, type 1 myotonic dystrophy; FBDD, fragment-based drug design; *FTL*, ferritin light chain; FOXO1, forkhead box protein O1; HIV-1, HIV type 1; ICM, Internal Coordinate Mechanics; MBNL, muscleblind-like; pre-mRNA, precursor messenger RNA; RdRp, RNA-dependent-RNA polymerase; $r(CUG)^{exp}$, expanded r(CUG) repeat; siRNA, small interfering RNA; SMN, survival of motor neuron; SNP, single-nucleotide polymorphism; TAR, transactivation response; 3D, 3-dimensional; 5′-UTR, 5′ untranslated region.

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