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RNA Degraders

Small Molecule RNA Degraders

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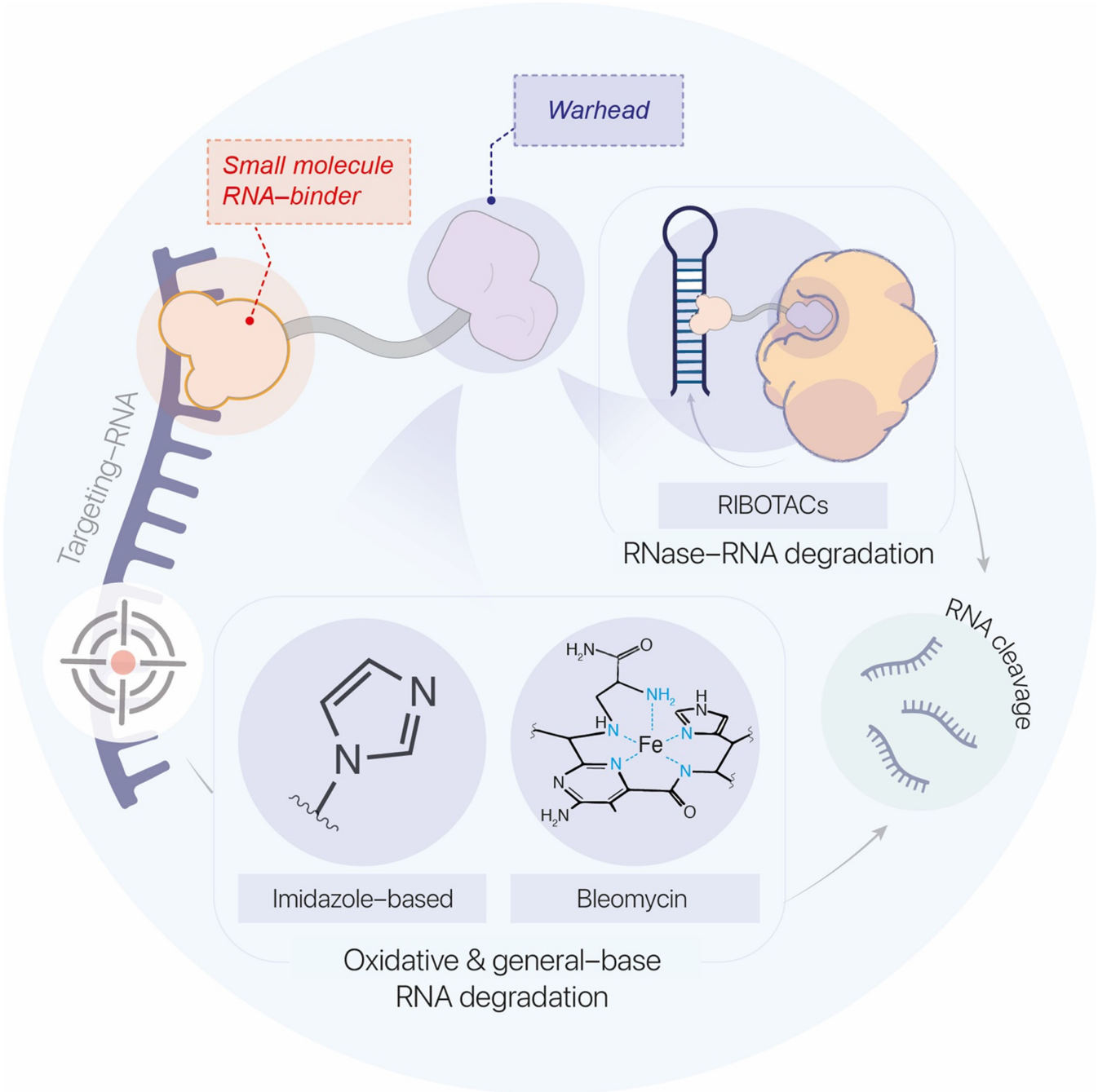

Abstract: RNA is a central molecule in life, involved in a plethora of biological processes and playing a key role in many diseases. Targeting RNA emerges as a significant endeavor in drug discovery, diverging from conventional protein-centric approaches to tackle various pathologies. Whilst identifying small molecules that bind to specific RNA regions is the first step, the abundance of non-functional RNA segments renders many interactions biologically inert. Consequently, small molecule binding does not necessarily meet stringent criteria for clinical translation, calling for solutions to push the field forward. Converting RNA-binders into RNA-degraders presents a promising avenue to enhance RNA-targeting. This mini-review outlines strategies and exemplars wherein simple small molecule RNA binders are reprogrammed into active degraders through the linkage of functional groups. These approaches encompass mechanisms that induce degradation via endogenous enzymes, termed RIBOTACs, as well as those with functional moieties acting autonomously to degrade RNA. Through this exploration, we aim to offer insights into advancing RNA-targeted therapeutic strategies.

1. Introduction

Nucleic acids are essential components that underpin all life processes. While DNA encodes the information to build and maintain an organism, RNA functions as both a messenger between DNA and proteins and a regulator of genome organization and gene expression.[1] RNA occupies the pivotal position in the so-called "central dogma of molecular biology," which describes the flow of information within a living system, from DNA to the final protein. The central role of RNA in cell biology[2] makes this intermediary molecule a unique target with immense potential to target numerous diseases, as defects or dysregulation of certain RNAs are implicated in many pathologies.[3] Targeting RNA will also expand the existing druggable genome (Figure 1a). This stems from the extensive transcription (~70 %) of the human genome into non-coding RNA (i.e. RNAs without protein-coding regions) with only 1.5 % encoding proteins,[4] which are the target of most of small molecule drugs. Given that, out of ~20,000 human proteins, fewer than 700 have been targeted by approved drugs,[5] this indicates that only 0.05 % of the human genome has been drugged so far.[6]

Drugging RNA can be conventionally achieved either through use of synthetic oligonucleotides which base pair to a target sequence, used in siRNA and antisense oligonucleotide (ASOs) strategies, or by binding its folded tertiary structures, usually with small molecules.[7,8] By 2023, up to eight ASOs and five siRNA are currently approved by the FDA for the treatment of a diverse range of diseases, including spinal muscular atrophy, atherosclerotic cardiovascular disease or acute hepatic porphyria, among others.[9] Although binding to target RNA is usually highly specific, this strategy faces important challenges. First, the highly negatively charged backbone present in most synthetic oligonucleotides typically entails poor cell and/or tissue permeability and, ultimately, delivery issues.[8,10] Additionally, therapeutic oligonucleotides are prone to be degraded by endogenous RNases intracellularly or by serum nucleases,[9] leading to low metabolic stability.[11] Finally, clinical trials have revealed myriad adverse reactions, renal clearance, and immunogenicity issues.[11]

Targeting RNA with small molecules may negate many of these limitations. In general, the use of small molecules improves pharmacokinetic properties, especially in terms of metabolic stability and cell permeability.[12] The first example of targeting RNA with this approach dates from 1940 with the discovery of streptomycin, whose antimicrobial activity was derived from its binding to the prokaryotic ribosomal RNA.[13] Since then, important milestones were reached in the 60s, 2000 and 2020 with the discovery of RNA binders, such as macrolides, oxazolidinones or pre-mRNA splicing modulators, respectively.[14] Small molecules which bind to a functional site of RNA aim to disrupt downstream biology in a controlled way, ultimately leading to a therapeutic benefit (Figure 1b).

The discovery of small molecule binders can be challenging due to RNA's inherent properties. Firstly, its negatively charged sugar-phosphate backbone restricts the number of compatible structures,[15] and the number of possible combinations of the four nucleobases that comprise RNA (A, U, G, C) is considerably lower than the 20 major amino acids that form proteins.[16] Despite this, the combination of computational tools, large databases gathered from high-throughput experimentation, and novel screening assays have driven the discovery of new RNA-small molecule binders.[17] Secondly, the binding event must occur at a functional RNA site; otherwise, it will be biologically silent, and no phenotypic effect is expected to be observed. For some small molecule binders, it has been predicted that 70 % of binding sites are non-functional.[18] Converting RNA binders into degraders allows the exploitation of these non-functional binding sites, facilitating therapeutic targeting.[19] Considerable efforts have been directed towards degrading RNA instead of merely binding to it since the early 1990s, particularly using ASOs.[20] Recent findings in the field suggest that the use of small molecule RNA degraders will have an even stronger effect on the downregulation of disease-causing RNAs.[18,21]

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All known small molecule degraders have a common architecture (Figure 1c). This involves the utilization of bifunctional molecules comprising three separate parts: (1) a small molecule moiety that recognizes the target RNA, referred to as the binder; (2) another moiety which triggers —directly or indirectly—the degradation of the targeted RNA; and (3) a linker between the binder and the degrader. This approach encompasses sequential two-stage RNA targeting: first, the binder attaches to a specific region of an RNA target (Figure 1c-**1**); subsequently, the degrader moiety promotes the cleavage of RNA (Figure 1c-**2**). Degradation of RNA has been successful using three different elements so far: (i) a RNase recruiter, or (ii–iii) an organic cleavage unit, termed as warhead, which act through (ii) a base-mediated mechanism (particularly using imidazole) or (iii) through metal-mediated catalysis. Based on this, our review aims to summarize and categorize the existing small molecule RNA degraders, highlighting their current advantages and limitations to provide a motivation for further development of the field.

2. Ribonuclease Targeting Chimeras

RNases are ubiquitous enzymes found in every organism, which catalyze the degradation of RNA and can be exploited for targeted RNA degradation, a strategy termed Ribonuclease Targeting Chimeras (RIBOTACs). This approach draws lessons from Proteolysis Targeting Chimera (PROTACs) technology, initially conceptualized in 2001 by Craig M. Crews[26] group. In PROTACs, a bifunctional molecule induces proximity between the targeted protein and an endogenous ubiquitin E3 ligase to trigger protein ubiquitination, ultimately leading to protein degradation.[27] RIBOTACs work in an analogous fashion, using bifunctional molecules to sequentially i) bind the targeted RNA and ii) recruit an endogenous RNase, mostly RNase L, to degrade the target (Figure 2a). RNase L is part of our innate immune defense, predominantly against viruses. Typically, it is found as two inactive monomers (Figure 2a). Upon viral infection, a short oligonucleotide sequence is produced, 2', 5 oligoadenylate (2'-5' poly(A)), which interacts with RNase L monomers and fosters their dimerization into an active dimeric complex.[28] The activated RNase L finally cleaves the viral RNA to inhibit further infection. RNase L also cleaves other substrates such as rRNA, mRNA, or tRNA, aiding regulation of their diverse biological functions.[29] The first example of in vitro recruitment of RNase L for targeted RNA degradation dates to 1993,[20] but used an ASO rather than a small molecule. A tail of 2'-5' poly(A) was covalently linked to an ASO, allowing recognition of a specific region of HIV RNA while recruiting endogenous RNase L, mimicking the natural response mentioned above. These conjugates even achieved positive results in African Green Monkeys infected with respiratory syncytial virus,[37] reducing viral replication.

However, these 'protoRIBOTACs' had to deal with the limitations of using oligonucleotides as binding ligands,[8,10] as mentioned in *Section 1*. The first use of RIBOTACs was reported in 2018 by the M. Disney group,[30] targeting

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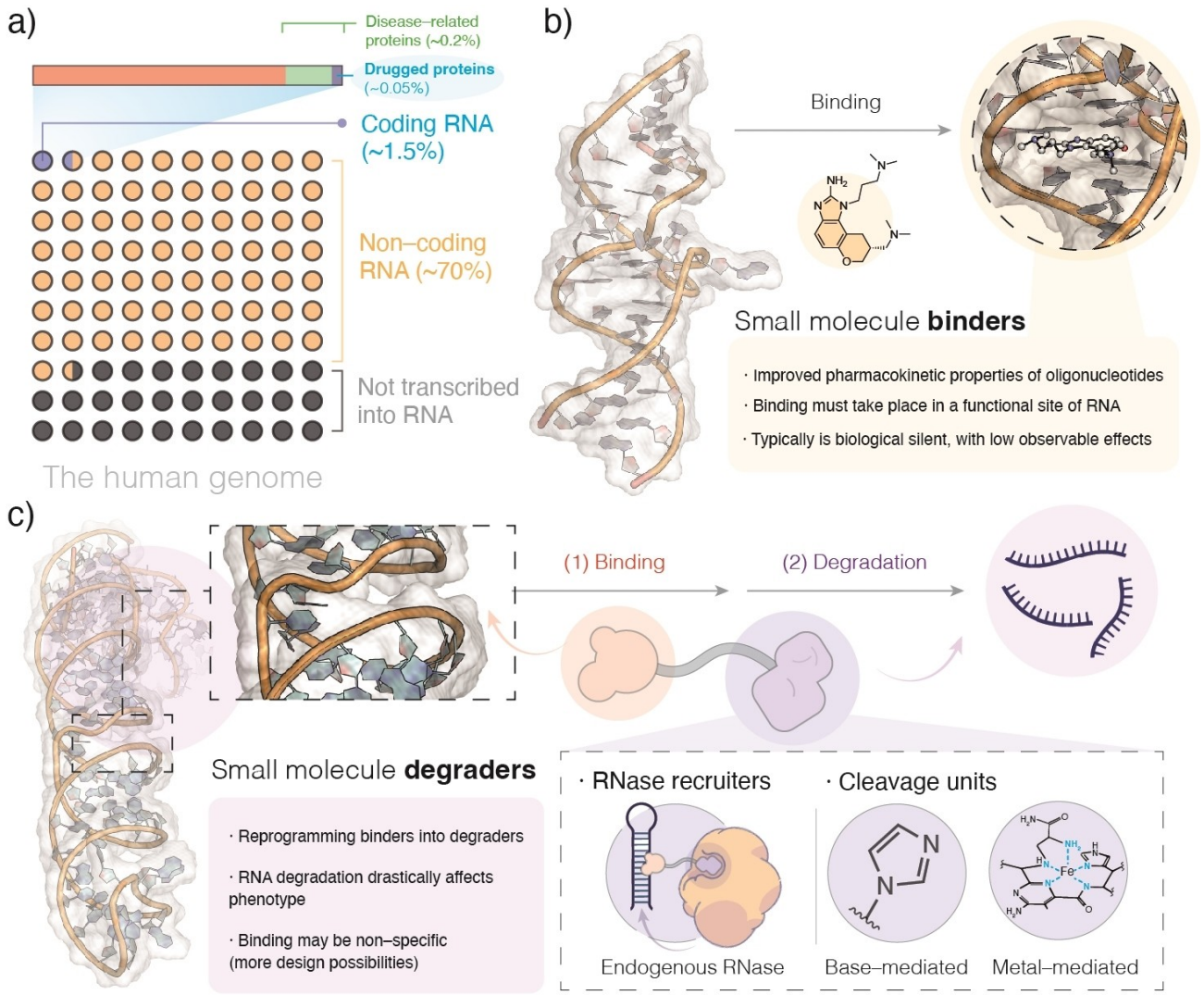

Figure 1. **Drugging RNA with small molecules.** (a) The potential to combat diseases increases significantly when RNA is targeted instead of proteins. In essence, only a small fraction (~1.5%) of the human genome contains the information to synthesize coding RNA, which is ultimately translated into a protein. Additionally, only a small percentage of the approximately 2,000–3,000 proteins associated with a disease[22] have been successfully targeted with drugs.[6] (b) Small molecule binders exert their action by binding to a specific region of an RNA target. Example shown consists of a benzimidazole[23] binding to the internal ribosomal entry site in the Hepatitis C virus RNA (PDB: 3tzr)[24] to inhibit translation. (c) Small molecule degraders consist of a binder group, which recognizes a structural site of RNA, and a degrader domain, which triggers the degradation of the targeted RNA either by recruiting an endogenous RNase or by the action of a cleavage unit. This can be mediated by an organic base, such as an imidazole- or by a metal-binding unit which enables oxidative cleavage, such as bleomycin. Represented RNA is pre-miR-31, an oncogenic RNA[25] (PDB:8fcs).

oncogenic miRNA-96, which plays important roles in breast[38] and pancreatic[39] cancers with functions including regulation of apoptotic response and cell proliferation. They combined the 2'-5' poly(A) recruiter (Figure 2b) with two binders (Figure 2c, *RIBO-1*) reported to target the miR-96 hairpin precursor.[40] In vitro treatment of MDA-MB-231 with 200 nM (48 h) of RIBOTAC RIBO-1 + R1 led to 2-fold increased expression of FOXO1, a protein repressed by miRNA-96 involved in promoting apoptosis via Bcl–xl proteins.[41] Comparing the biological activity of this RIBOTAC with the binder alone, the authors concluded that recruitment of RNase L led to a 5-fold increased activity.[30] The use of 2'-5' poly(A) recruiter (Figure 2b) has also been combined with a single ligand (Figure 2b, RIBO-2) to target pre-miR-210,[42] a ncRNA overexpressed in hypoxic tumors which, essentially, represses Glycerol-3-phosphate dehydrogenase 1-like (GDP1L) mRNA. GDP1L encodes a protein that binds to prolyl hydroxylase, an enzyme which triggers hydroxylation of the Hypoxia-Inducible factor 1-alpha (HIF1α) and its ultimate polyubiquitination for proteasomal-induced degradation.[43] Therefore, overexpression of miR-210 yields reduced degradation of HIF1α, and the expression of HIF-related genes related to proliferation and metastasis.[44] By using a ligand with high affinity for pre-miR-210 (Figure 2b, RIBO-2), other RNAs present in the cell remained unchanged upon the treatment with

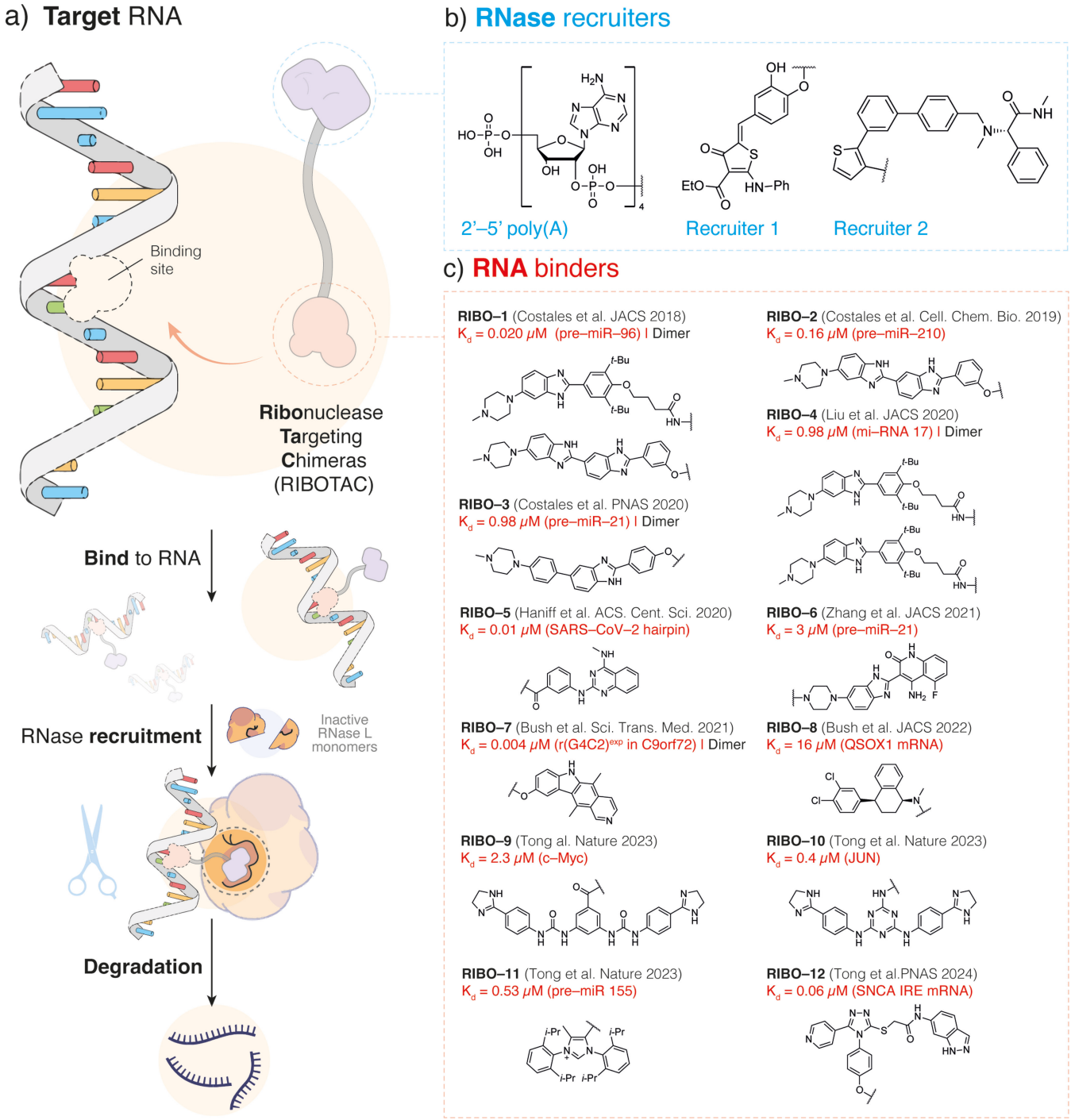

Figure 2. **Targeted RNA degradation by exploiting endogenous nucleases**. (a) Overview of RIBOTAC strategy. RIBOTACs utilize bifunctional small molecules, composed of a binding ligand with a high affinity for a specific structure of a particular RNA, and an RNase recruiter to target and degrade RNA. After the RIBOTAC binds to the RNA through the ligand, the free recruiter moiety interacts with endogenous RNase, ultimately degrading the RNA. (b) Summary of the discovered RNase recruiters linked to small molecule binders to date. References for the first use of R1, R2, and R3 linked to small molecules are,[30,31] and,[32] respectively. (c) Outline of the binders tested in RIBOTAC strategy along with their K_d for the targeted RNA, mentioned in parentheses. References for RIBO-6, RIBO-7, RIBO-8 and RIBO-12 are,[33,34,35] and,[36] respectively.

RIBOTAC.[42] An alternative to 2'-5' poly(A) was reported in 2020 by the M. Disney group to recruit an endogenous RNase L.[31] The structure (see Figure 2b, Recruiter 1) was previously identified in 2007 to activate RNase L.[45] Interestingly, the introduction of Recruiter 1 in the structure of the final RIBOTAC (R2+RIBO-4) did not negatively affect drug uptake by the MDA-MB-231 cells,[46] whilst the use of 2'-5' poly(A) as an RNase recruiter decreased RIBOTAC uptake by the same cell line.[30,42] Reflecting this, the RNase recruiter of most RIBOTACs reported to date is Re-

cruiter 1. Diseases such as SARS-CoV-2 infection have also been approached through RIBOTAC strategy,[47] even using non-biological RNase recruiters (for example, Recruiter 1+ RIBO-5[47b]), demonstrating the broad applicability of this new family of therapeutics.

A breakthrough for RIBOTACs came in 2023. Tong et al.[18] identified a novel class of compounds, mainly containing azolium groups (Figure 2c, RIBO-11), which bind to a 3D-fold RNA library by using a high-throughput screening approach. However, only ~30% of the targetable sites within screened RNAs are functional, reducing significantly the potential biological effect of the small molecule-RNA interaction.[18] Transforming the binders into RIBOTACs by including Recruiter 1 into their molecular structure can overcome the above limitation: three oncogenic RNAs were targeted using this strategy, including c-MYC (RIBO-9), JUN (RIBO-10), and pre-miR 155 (RIBO-11).[18] Additionally, Zhang et al.[48] improved the selectivity of a RIBOTAC which targets G-quadruplex enriched oncologic mRNAs by caging a RNase recruiter, similar to Recruiter 1, through different strategies. By masking the RNase recruiter with different functional groups which can be in situ activated by NQO1, an enzyme biomarker in tumors, or tumor overexpressed metabolites such as H_2O_2 or selenocysteine, it is possible to tune the selectivity of the RIBOTAC towards a specific cell line under or towards specific chemical conditions. Preliminary therapeutic results obtained with RIBOTACs are promising, as this technology has the potential to transform an inactive RNA-ligand interaction into active degradation, improving the final biological effect. RIBOTACs' main limitation lies in their dependence on intracellular RNase L levels, which are typically low[49] and some studies suggest depending on cell type.[50] Thus, some cell types may not be compatible with RIBOTAC approach. In addition, although transforming a small molecule binder into a RIBOTAC partially overcomes the non-functional binding site issue, binding must take place close to an RNA position susceptible to RNase L cleavage. Taken together, these caveats can limit the therapeutic efficacy of RIBOTACs in some scenarios.

3. Mimicking Natural RNases using Imidazole-Based Warheads

Achieving an autonomous RNA degradation is highly attractive to remove the dependency of endogenous elements such as RNase L. Many artificial approaches at RNA cleavage are inspired by the mechanism of natural RNase A (Figure 3a), a strategy pioneered by Breslow et al. in the 1970 s.[51] The active site is composed of two histidine residues, His12 and His119, whose side chains containing imidazole rings act as acid-base catalysts,[52] in addition to Lys41, which stabilizes the increasing negative charge on nonbridging phosphoryl oxygen in both transition structures.[52a] In the first step (Figure 3b, (1)), the pyrrolic N of His12 abstracts an H from the 2'-OH subsequently forming a 2',3'-cyclic phosphodiester. The acidic pyrrolic N of His119 facilitates the displacement of the reaction by

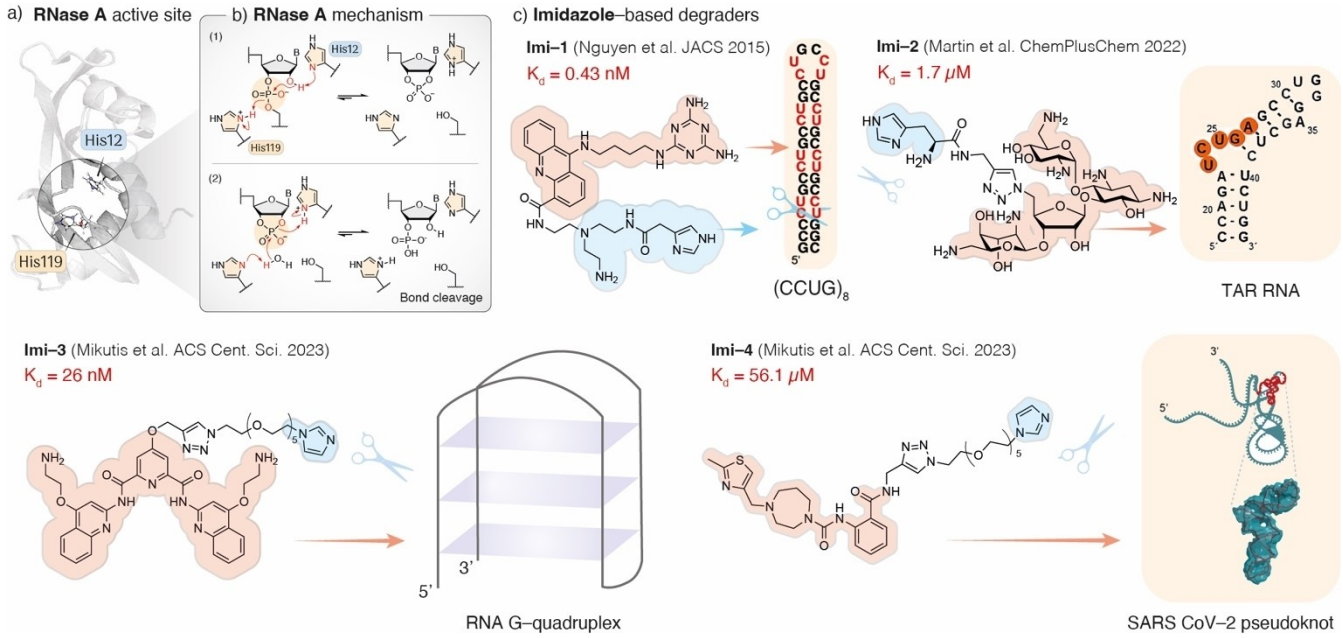

Figure 3. **Autonomous RNA degradation using imidazole-based warheads**. (a) Illustration of the active site in RNase A, highlighting the catalytic role of the histidine residues His12 and His119 (PDB: 7rsa). (b) Mechanism of catalytic cleavage of RNA assisted by His12 and His119 residues of RNase A, involving step (1) where the pyrrolic N of His12 abstracts the H from the 2' OH group, complemented by the acidic properties of the pyrrolic NH of His119[52a] and leading to the cleavage of RNA. In a step (2), the His119 catalyzes the hydrolysis of the cyclic phosphodiester to recover the active catalytic species.[52a] (c) Summary of the chemical structures of RNA degraders based on imidazole warheads and their target RNA.

protonating the 5'-oxygen of the next nucleoside, ultimately leading to the cleavage of two nucleoside units (Figure 3b). Finally, the basic imidazole from His119 catalyzes the hydrolysis of the cyclic phosphodiester to recover the active catalytic species (i.e. a deprotonated pyrrolic N in His12 and an acidic pyrrolic N in His119, Figure 3b).[52a]

Following this strategy, small molecule RNA degraders can be synthesized by linking an RNA binder (Figure 3c, highlighted in red) with an imidazole containing warhead (Figure 3c, highlighted in blue). The mechanism of action works in a sequential manner: first, the binder recognizes a specific region of the targeted RNA; then, induced proximity allows the imidazole warhead to cleave the RNA.[53] Numerous attempts have been made to cleave RNA with metal free organic molecules based on imidazole[54] or guanidium,[55] but these required a large concentration and led to inefficient degradation in vitro. This is probably due to the lack of a binding ligand incorporated in the molecule structure, thus emphasizing the importance of the proximity induced effect.[56] The first use of a liganded imidazole-based RNA degrader was reported in 2015 by Nguyen et al.[57] (Figure 3c, Imi-1) for targeting myotonic dystrophy type 1 (DM1). In this disease, an abnormal expansion of CTG trinucleotide repeats (referred to as (CTG)exp) occurs in the 3'-untranslated region of the DMPK gene.[58] This expansion is transcribed into a $(CUG)^{exp}$ RNA transcript, which sequesters the alternative-splicing regulator muscleblind-like protein (MBNL), ultimately leading to disease symptoms. Developing binding competitors of $(CUG)^{exp}$ with oligonucleotides, peptides or small molecules has been demonstrated to improve DM1-associated defects.[59] In their work, Nguyen et al. designed bifunctional molecules by combining a binder with a high affinity for $(CUG)^{exp}$, previously identified by the same research group,[60] with a cleavage subunit containing an imidazole.[57] Treatment with 50 μM of Imi-1 for 72 h in DM1 model cells led to a reduction of the 60–70 % of CUG^{exp} mRNA levels in cell culture, and in Drosophila disease phenotypes. Similar to RIBOTACs, imidazole-based degraders have also been used to degrade viral RNA. In 2022, M. Duca's group reported a small molecule degrader to target the trans-activating region (TAR) of the HIV-1 virus RNA[61] (Figure 3c, Imi-2) based on a neomycin binder, reported to recognize the TAR region of HIV-1 RNA.[62] They connected a histidine residue via Copper-catalyzed Azide-Alkyne Cycloaddition (CuAAC) to the neomycin unit to form Imi-2 compound. The small size of the degradation warhead (i.e., histidine) yielded a negligible effect on the K_d value for the TAR region of HIV-1 RNA (1.7 μM for neomycin vs. 1.4 μM for Imi-2, respectively[61]), while providing the cleavage of the target RNA, achieving a IC_{50} value for the inhibition of Tat/TAR interaction below 0.5 μM in vitro. Improved activity was observed at basic pH, suggestive of histamine acting as a general base.

Two further examples of targeting viral RNA were reported by our laboratory and collaborators in 2023.[21] Two small molecules, termed Proximity Induced Nucleic Acid Degraders (PINADs), were validated to target two key structures found in SARS CoV-2 genome:[63] G-quadruplexes (Imi-3, Figure 3c) and betacoronaviral pseudoknots (Imi-4, Figure 3c). These RNA structures play key roles in stabilizing viral proteins[63a] and producing vital enzymes for viral replication,[64] respectively, and are therefore appealing targets for novel antiviral therapeutics. The selection of Imi-3 binder was motivated by its high affinity for G-quadruplexes, with a K_d of 26 nM,[65] while Imi-4 binder was previously demonstrated to bind SARS-CoV-2 pseudoknot.[66] As proof of its good performance, the incubation of Imi-4 with pseudoknot oligomers resulted in a ~75 % degradation after 3 h, without affecting levels of a mutated control strand, demonstrating the absence of off-targeting. In vivo experiments with Imi-4 showed a significant reduction of the lung viral load, and a marked reduction in the expression of p38 protein, a biomarker of SARS-CoV-2 infection and replication.[67] PINAD-assisted RNA degradation may take place following two different mechanisms: (1) a general base mechanism, mimicking RNase A activity (Figure 3b) and (2) a copper-mediated mechanism, where the imidazole warhead is prone to coordinate copper ions that may ultimately cleave the RNA through the production of ROS.[53] This latter mechanism is further discussed in the next section.

4. Transition-Metal Catalysis for RNA Cleavage

In fact, the combination of transition-metal catalysis and organic molecules has been an area of exploration for RNA degradation since the early '80s. Several molecules containing a metal-coordinating group such as amines[68] or pyridines[69] have been demonstrated to cleave RNA in a test tube but rarely in cells. Again, for an efficient RNA degradation it is imperative to use a binder to achieve proximity. Prior to small molecules, the design was based on a metal-coordinating group attached to an oligonucleotide which provides the recognition, and ultimately the proximity-induced effect. Some examples of metal coordinating groups utilized include phenanthroline-copper,[70] pyridine-zinc[71] or amine crown-zinc system,[72] as well as various lanthanide chelates,[73] to the corresponding antisense oligonucleotide.

Joyner et al. conducted a systematic analysis of different metal-coordinating ligands (DOTA, EDTA or NTA, among others) linked to a Rev peptide,[74] known for binding to HIV-1 RNA,[75] with different metal ions such as Cu^{2+}, Co^{2+}, Fe^{2+} or Ni^{2+}. The presence of the oxidative system with ascorbate/H_2O_2 promoted a fast cleavage of RRE RNA, especially in the Cu-NTA-Rev system. The authors explain this trend by analyzing the reduction potential, E^0, of the conjugates. The most active complexes had their E^0 between 380 and −66 mV which matched with the E^0 values of H_2O_2/$HO^{\bullet}$ and ascorbyl/ascorbate reactions,[76] so multiple-turnover single-electron oxidation and reduction reactions are thermodynamically favored for the complexes with their E^0 in this range. Further investigations by the same research group concluded that the RNA cleavage was through 5'-hydrogen abstraction, but hydrolysis and 2'-OH endonucleolysis also contributed to degradation.[77]

Transforming an RNA small molecule binder into an active, autonomous degrader by using imidazole-containing or metal-containing warheads has the potential to provide a high turnover in terms of therapeutic action. Ideally, a complete turnover cycle would involve (i) selective recognition and interaction with the desired RNA target through the binder, (ii) the irreversible degradation of RNA via either general acid/base or transition-metal catalysis, (iii) dissociation from the degraded RNA and (iv) regeneration of the active catalytic species to repeat the cycle. This 'catalytic' mechanism of action could offer important advantages over traditional drug-binding systems. Apart from the improvement entailed by the irreversible RNA degradation, a cyclic oxidative cleavage of RNA has the potential to reduce the amount of drug required to reach the target organ/tissue, as one molecule can cleave multiple RNAs. Moreover, no mechanisms of repair of mRNA are known,[78] thereby reducing the possibility of chemoresistance by target cells, especially in cancer disease. An important challenge in this perspective is achieving fast reaction kinetics of RNA cleavage to provoke a strong biological response. The use of transition metal catalysis in cells is sometimes restricted by the precise regulation cells exert on metals, ultimately leading to their intracellular deactivation. Glutathione (GSH) is the main antioxidant molecule present in mammalian cells, with very large intracellular concentrations in the range of 2–10 mM.[79] Apart from preventing oxidative damage via GPX4 enzyme, GSH is a major compound in regulating the trafficking of intracellular metal ions due to its strong coordinating properties,[80] transferring the captured metal to metallothionein for further disposal.[81] Therefore, GSH is mostly responsible for the deactivation of transition metal catalysis within cells.[82] In this way, significant attention should be paid to synergies of PINADs or metal-coordinating warheads with GSH-depleting systems to drive efficient RNA degradation.

Naturally produced by the fungus *Streptomyces verticillus*, bleomycin is a drug currently used to treat various cancers such as testicular or ovarian cancer, or Hodgkin lymphoma.[83] Bleomycin's primary mechanism of action involves inducing cleavage of DNA strands in a process dependent on iron and oxygen.[84] This CP450-like activity led to the exploration of bleomycin for targeted RNA degradation in the early '90 s.[85] The structure of bleomycin-based RNA degraders consist of three domains (Figure 4a). The carbohydrate moiety facilitates cell internalization[86] (Figure 4a). Then, the metal-binding domain can interact with iron ions via N-coordination.[84a,87] The bleomycin-Fe complex can activate molecular O_2 to produce oxidative cleavage of RNA through formation of Fe^{V}=O centers.[84] To achieve the proximity induced effect, a third domain (Figure 4a, highlighted in red), was linked to bleomycin through one of its terminal amines, consisting of an RNA binder. The first example of a Bleomycin A5-binder conjugate was reported by M. Disney group in 2017 for treatment of DM1 by cleaving r(CUG)^{exp} (see Section 2).[59] Interestingly, small molecules (Figure 4b, Bl-1) showed a 100-fold increase in potency when compared to antisense oligonucleotides. Apart from lower cell uptake, oligonucleotides are prone to suffering slow kinetics of binding to structured RNAs[88] highlighting the advantages of using small molecules over ASOs. Moreover, no cleavage of r(CUG)^{exp} RNA was observed in the presence of bleomycin alone, showcasing again the pivotal importance of a binder to achieve a proximity-induced effect[59] and target selectivity. It is also possible to tune the chemical structure of bleomycin to gain selectivity and reduce off-targeting.[89] As mentioned above, bleomycin has partial affinity by DNA that may provoke undesired damage.[84a] By removing the carbohydrate domain of bleomycin-A5, the amount of phosphorylated histone H2 A variant H2AX (γ-H2AX), which forms foci in response to DNA damage, was reduced significantly.[89] In terms of the linker between the binder and the bleomycin unit, a peptoid linker containing proline units performed better in RNA degradation than others containing alanine, tyrosine or hydroxylated proline, and reduced the off-target DNA cleavage.[90] Although the efficacy of using bleomycin as a warhead has been demonstrated, these types of RNA degraders depend on endogenous iron and oxygen levels, which may be a limitation depending on the targeted disease. For example, numerous tumors are hypoxic,[91] where the efficacy of bleomycin may be limited due to oxygen scarcity. Consequently, we believe it is imperative to consider optimizations not only in terms of the chemical structure, but also the endogenous fuel availability (i.e. iron ions and oxygen) of the targeted cell type to achieve the desired reaction kinetics and, thus, the successful therapeutic outcome.

5. Conclusions and Outlook

Recent breakthroughs in the discovery and design of small molecule RNA binders pave the way to developing active RNA degraders by adding small functional groups which induce RNA cleavage. Depending on the degradation mechanism and the nature of the functional group, we have classified the existing small molecule degraders into three categories: (1) RIBOTACs, where the functional group is a RNase L recruiter which drives RNA degradation through dimerization of an endogenous RNase L; (2) base-mediated warheads and (3) metal-based which degrade RNA through a specific mechanism involving metal coordination to the warhead and subsequent ROS production. When targeting RNA, the advantages of using small molecule ligands over traditional oligonucleotides are significant, especially in terms of pharmacokinetic properties and cell permeability, as well as due to the high stability of duplexed RNA. Furthermore, recent in vitro and in vivo experimental results strongly suggest the necessity of transforming RNA binders into RNA degraders for maximum functionality[18,21]—ideally one would be able to cleave the targeted RNA specifically and catalytically. This would result in maximum therapeutic efficacy using low amounts of a small molecule drug. We anticipate that the insights described at the end of each section of this minireview will foster further developments of small molecule warheads that add function—degradation

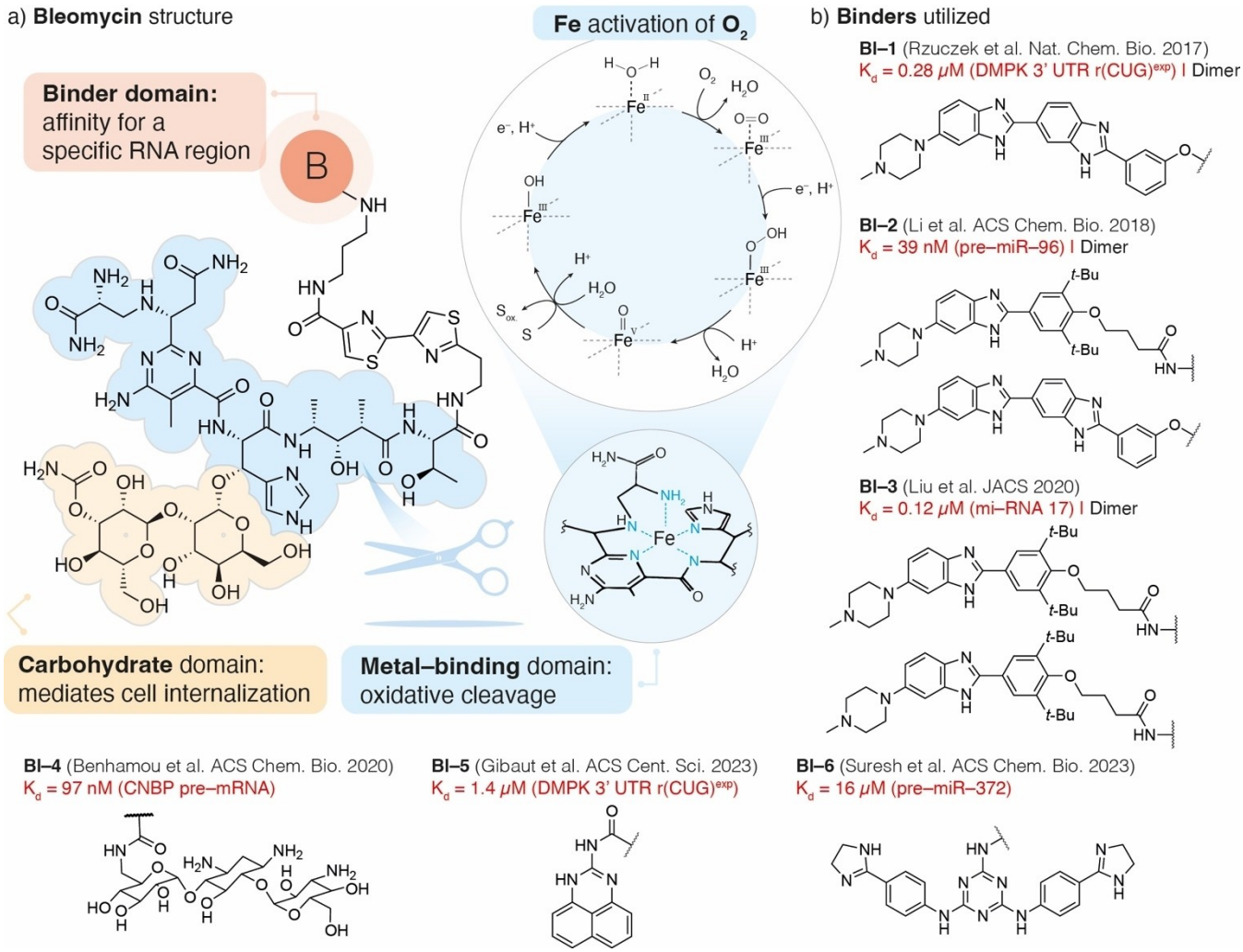

Figure 4. **Bleomycin assisted targeted RNA degradation**. (a) The architecture of bleomycin-based RNA degraders consists of three different domains: a carbohydrate domain (highlighted in pale-yellow) which facilitates cell internalization;[86] a metal-binding domain with high affinity for iron ions[92] responsible for inducing oxidative damage to RNA; and the binder domain, consisting of a small molecule with high affinity for a specific region of an specific RNA. The active site was adapted from reference.[87] Iron-mediated catalysis involves the coordination of O_2 to an iron(II) centre and the further formation of Fe^{V}=O species which causes oxidative damage to nucleic acids.[84] (b) Overview of the binders linked to a bleomycin unit utilized to target different RNAs and their K_d, highlighted in red. References for Bl-2, Bl-3, Bl-4, Bl-5 and Bl-6 are,[93,46,46,94,95] and,[96] respectively.

—to neutral RNA binders, especially if these novel technologies are well integrated with existing research using ASOs to direct RNA cleavage. The discovery of novel RNA binders, especially aided by high-throughput experimentation and tools as ML/AI has the potential to expand the number of targets exponentially. Such research will assist the development of small molecule RNA degraders as valuable drugs.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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[1] K. V. Morris, J. S. Mattick, *Nat. Rev. Genet.* **2014**, *15*, 423–437.
[2] P. A. Sharp, *Cell* **2009**, *136*, 577–580.

[3] a) T. A. Cooper, L. Wan, G. Dreyfuss, *Cell* **2009**, *136*, 777–793; b) S. Lin, R. I. Gregory, *Nat. Rev. Cancer* **2015**, *15*, 321–333; c) M. Esteller, *Nat. Rev. Genet.* **2011**, *12*, 861–874.
[4] I. Dunham, A. Kundaje, et al., *Nature* **2012**, *489*, 57–74.
[5] R. Santos, O. Ursu, A. Gaulton, A. P. Bento, R. S. Donadi, C. G. Bologa, A. Karlsson, B. Al-Lazikani, A. Hersey, T. I. Oprea, J. P. Overington, *Nat. Rev. Drug Discovery* **2017**, *16*, 19–34.
[6] K. D. Warner, C. E. Hajdin, K. M. Weeks, *Nat. Rev. Drug Discovery* **2018**, *17*, 547–558.
[7] A.-M. Yu, Y. H. Choi, M.-J. Tu, *Pharmacol. Rev.* **2020**, *72*, 862–898.
[8] T. C. Roberts, R. Langer, M. J. A. Wood, *Nat. Rev. Drug Discovery* **2020**, *19*, 673–694.
[9] A. Sparmann, J. Vogel, *EMBO J.* **2023**, *42*, e114760.
[10] S. T. Crooke, B. F. Baker, R. M. Crooke, X.-h. Liang, *Nat. Rev. Drug Discovery* **2021**, *20*, 427–453.
[11] C. F. Bennett, *Annu. Rev. Med.* **2019**, *70*, 307–321.
[12] J. L. Childs-Disney, X. Yang, Q. M. R. Gibaut, Y. Tong, R. T. Batey, M. D. Disney, *Nat. Rev. Drug Discovery* **2022**, *21*, 736–762.
[13] D. N. Wilson, *Nat. Rev. Microbiol.* **2014**, *12*, 35–48.
[14] S. Kovachka, M. Panosetti, B. Grimaldi, S. Azoulay, A. Di Giorgio, M. Duca, *Nat. Chem. Rev.* **2024**, *8*, 120–135.
[15] A. Di Giorgio, M. Duca, *MedChemComm* **2019**, *10*, 1242–1255.
[16] J. P. Falese, A. Donlic, A. E. Hargrove, *Chem. Soc. Rev.* **2021**, *50*, 2224–2243.
[17] M. D. Disney, A. M. Winkelsas, S. P. Velagapudi, M. Southern, M. Fallahi, J. L. Childs-Disney, *ACS Chem. Biol.* **2016**, *11*, 1720–1728.
[18] Y. Tong, Y. Lee, X. Liu, J. L. Childs-Disney, B. M. Suresh, R. I. Benhamou, C. Yang, W. Li, M. G. Costales, H. S. Haniff, S. Sievers, D. Abegg, T. Wegner, T. O. Paulisch, E. Lekah, M. Grefe, G. Crynen, M. Van Meter, T. Wang, Q. M. R. Gibaut, J. L. Cleveland, A. Adibekian, F. Glorius, H. Waldmann, M. D. Disney, *Nature* **2023**, *618*, 169–179.
[19] Y. Song, J. Cui, J. Zhu, B. Kim, M.-L. Kuo, P. R. Potts, *Cell Chem. Biol.* **2024**, *31*, 1101–1117.
[20] P. F. Torrence, R. K. Maitra, K. Lesiak, S. Khamnei, A. Zhou, R. H. Silverman, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 1300–1304.
[21] S. Mikutis, M. Rebelo, E. Yankova, M. Gu, C. Tang, A. R. Coelho, M. Yang, M. E. Hazemi, M. Pires de Miranda, M. Eleftheriou, M. Robertson, G. S. Vassiliou, D. J. Adams, J. P. Simas, F. Corzana, J. S. Schneekloth Jr., K. Tzelepis, G. J. L. Bernardes, *ACS Cent. Sci.* **2023**, *9*, 892–904.
[22] S. J. Dixon, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2009**, *13*, 549–555.
[23] P. P. Seth, A. Miyaji, E. A. Jefferson, K. A. Sannes-Lowery, S. A. Osgood, S. S. Propp, R. Ranken, C. Massire, R. Sampath, D. J. Ecker, E. E. Swayze, R. H. Griffey, *J. Med. Chem.* **2005**, *48*, 7099–7102.
[24] S. M. Dibrov, K. Ding, N. D. Brunn, M. A. Parker, B. M. Bergdahl, D. L. Wyles, T. Hermann, *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 5223–5228.
[25] T. Yu, P. Ma, D. Wu, Y. Shu, W. Gao, *Biomed. Pharmacother.* **2018**, *108*, 1162–1169.
[26] K. M. Sakamoto, K. B. Kim, A. Kumagai, F. Mercurio, C. M. Crews, R. J. Deshaies, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 8554–8559.
[27] M. Békés, D. R. Langley, C. M. Crews, *Nat. Rev. Drug Discovery* **2022**, *21*, 181–200.
[28] S. E. Brennan-Laun, H. J. Ezelle, X. L. Li, B. A. Hassel, *J. Interferon Cytokine Res.* **2014**, *34*, 275–288.
[29] a) A. Karasik, G. D. Jones, A. V. DePass, N. R. Guydosh, *Nucleic Acids Res.* **2021**, *49*, 6007–6026; b) J. M. Burke, S. L. Moon, T. Matheny, R. Parker, *Mol. Cell* **2019**, *75*, 1203–1217. e1205.
[30] M. G. Costales, Y. Matsumoto, S. P. Velagapudi, M. D. Disney, *J. Am. Chem. Soc.* **2018**, *140*, 6741–6744.
[31] M. G. Costales, H. Aikawa, Y. Li, J. L. Childs-Disney, D. Abegg, D. G. Hoch, S. Pradeep Velagapudi, Y. Nakai, T. Khan, K. W. Wang, I. Yildirim, A. Adibekian, E. T. Wang, M. D. Disney, *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 2406–2411.
[32] S. M. Meyer, T. Tanaka, P. R. A. Zanon, J. T. Baisden, D. Abegg, X. Yang, Y. Akahori, Z. Alshakarchi, M. D. Cameron, A. Adibekian, M. D. Disney, *J. Am. Chem. Soc.* **2022**, *144*, 21096–21102.
[33] P. Zhang, X. Liu, D. Abegg, T. Tanaka, Y. Tong, R. I. Benhamou, J. Baisden, G. Crynen, S. M. Meyer, M. D. Cameron, A. K. Chatterjee, A. Adibekian, J. L. Childs-Disney, M. D. Disney, *J. Am. Chem. Soc.* **2021**, *143*, 13044–13055.
[34] J. A. Bush, H. Aikawa, R. Fuerst, Y. Li, A. Ursu, S. M. Meyer, R. I. Benhamou, J. L. Chen, T. Khan, S. Wagner-Griffin, M. J. Van Meter, Y. Tong, H. Olafson, K. K. McKee, J. L. Childs-Disney, T. F. Gendron, Y. Zhang, A. N. Coyne, E. T. Wang, I. Yildirim, K. W. Wang, L. Petrucelli, J. D. Rothstein, M. D. Disney, *Sci. Transl. Med.* **2021**, *13*, eabd5991.
[35] Y. Tong, Q. M. R. Gibaut, W. Rouse, J. L. Childs-Disney, B. M. Suresh, D. Abegg, S. Choudhary, Y. Akahori, A. Adibekian, W. N. Moss, M. D. Disney, *J. Am. Chem. Soc.* **2022**, *144*, 11620–11625.
[36] Y. Tong, P. Zhang, X. Yang, X. Liu, J. Zhang, M. Grudniewska, I. Jung, D. Abegg, J. Liu, J. L. Childs-Disney, Q. M. R. Gibaut, H. S. Haniff, A. Adibekian, M. M. Mouradian, M. D. Disney, *Proc. Natl. Acad. Sci. USA* **2024**, *121*, e2306682120.
[37] D. W. Leaman, F. J. Longano, J. R. Okicki, K. F. Soike, P. F. Torrence, R. H. Silverman, H. Cramer, *Virology* **2002**, *292*, 70–77.
[38] I. K. Guttilla, B. A. White, *J. Biol. Chem.* **2009**, *284*, 23204–23216.
[39] S. Yu, Z. Lu, C. Liu, Y. Meng, Y. Ma, W. Zhao, J. Liu, J. Yu, J. Chen, *Cancer Res.* **2010**, *70*, 6015–6025.
[40] S. P. Velagapudi, M. D. Cameron, C. L. Haga, L. H. Rosenberg, M. Lafitte, D. R. Duckett, D. G. Phinney, M. D. Disney, *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 5898–5903.
[41] Z. Fu, D. J. Tindall, *Oncogene* **2008**, *27*, 2312–2319.
[42] M. G. Costales, B. Suresh, K. Vishnu, M. D. Disney, *Cell Chem. Biol.* **2019**, *26*, 1180–1186.e1185.
[43] X. Huang, L. Ding, K. L. Bennewith, R. T. Tong, S. M. Welford, K. K. Ang, M. Story, Q.-T. Le, A. J. Giaccia, *Mol. Cell* **2009**, *35*, 856–867.
[44] R. Y. Ebright, M. A. Zachariah, D. S. Micalizzi, B. S. Wittner, K. L. Niederhoffer, L. T. Nieman, B. Chirn, D. F. Wiley, B. Wesley, B. Shaw, E. Nieblas-Bedolla, L. Atlas, A. Szabolcs, A. J. Iafrate, M. Toner, D. T. Ting, P. K. Brastianos, D. A. Haber, S. Maheswaran, *Nat. Commun.* **2020**, *11*, 6311.
[45] C. S. Thakur, B. K. Jha, B. Dong, J. Das Gupta, K. M. Silverman, H. Mao, H. Sawai, A. O. Nakamura, A. K. Banerjee, A. Gudkov, R. H. Silverman, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 9585–9590.
[46] X. Liu, H. S. Haniff, J. L. Childs-Disney, A. Shuster, H. Aikawa, A. Adibekian, M. D. Disney, *J. Am. Chem. Soc.* **2020**, *142*, 6970–6982.
[47] a) X. Su, W. Ma, D. Feng, B. Cheng, Q. Wang, Z. Guo, D. Zhou, X. Tang, *Angew. Chem. Int. Ed.* **2021**, *60*, 21662–21667; b) H. S. Haniff, Y. Tong, X. Liu, J. L. Chen, B. M. Suresh, R. J. Andrews, J. M. Peterson, C. A. O'Leary, R. I. Benhamou, W. N. Moss, M. D. Disney, *ACS Cent. Sci.* **2020**, *6*, 1713–1721; c) Y. Min, W. Xiong, W. Shen, X. Liu, Q. Qi, Y. Zhang, R. Fan, F. Fu, H. Xue, H. Yang, X. Sun, Y. Ning, T. Tian, X. Zhou, *Sci. Adv.* **2024**, *10*, eadl4393.

[48] Y. Zhang, L. Wang, F. Wang, X. Chu, J.-H. Jiang, *J. Am. Chem. Soc.* **2024**, *146*, 15815–15824.
[49] M. Drappier, T. Michiels, in *Encyclopedia of Signaling Molecules* (Ed.: S. Choi), Springer New York, New York, NY, **2017**, pp. 1–9.
[50] A. Zhou, R. J. Molinaro, K. Malathi, R. H. Silverman, *J. Interferon Cytokine Res.* **2005**, *25*, 595–603.
[51] a) R. Breslow, M. Labelle, *J. Am. Chem. Soc.* **1986**, *108*, 2655–2659; b) R. Breslow, J. B. Doherty, G. Guillot, C. Lipsey, *J. Am. Chem. Soc.* **1978**, *100*, 3227–3229.
[52] a) R. T. Raines, *Chem. Rev.* **1998**, *98*, 1045–1066; b) H. Lönnberg, *Org. Biomol. Chem.* **2011**, *9*, 1687–1703.
[53] S. Mikutis, M. Gu, E. Sendinc, M. E. Hazemi, H. Kiely-Collins, D. Aspris, G. S. Vassiliou, Y. Shi, K. Tzelepis, G. J. L. Bernardes, *ACS Cent. Sci.* **2020**, *6*, 2196–2208.
[54] a) I. Kuznetsova, F. Tuzikov, N. Tuzikova, N. Tamkovich, M. Zenkova, V. Vlassov, *Nucleos., Nucleot. Nucl.* **2004**, *23*, 907–913; b) N. Tamkovich, L. Koroleva, M. Kovpak, E. Goncharova, V. Silnikov, V. Vlassov, M. Zenkova, *Bioorg. Med. Chem.* **2016**, *24*, 1346–1355.
[55] U. Scheffer, A. Strick, V. Ludwig, S. Peter, E. Kalden, M. W. Göbel, *J. Am. Chem. Soc.* **2005**, *127*, 2211–2217.
[56] P. Dogandzhiyski, A. Ghidini, F. Danneberg, R. Strömberg, M. W. Göbel, *Bioconjugate Chem.* **2015**, *26*, 2514–2519.
[57] L. Nguyen, L. M. Luu, S. Peng, J. F. Serrano, H. Y. E. Chan, S. C. Zimmerman, *J. Am. Chem. Soc.* **2015**, *137*, 14180–14189.
[58] J. R. Gatchel, H. Y. Zoghbi, *Nat. Rev. Gen.* **2005**, *6*, 743–755.
[59] S. G. Rzuczek, L. A. Colgan, Y. Nakai, M. D. Cameron, D. Furling, R. Yasuda, M. D. Disney, *Nat. Chem. Biol.* **2017**, *13*, 188–193.
[60] a) C.-H. Wong, L. Nguyen, J. Peh, L. M. Luu, J. S. Sanchez, S. L. Richardson, T. Tuccinardi, H. Tsoi, W. Y. Chan, H. Y. E. Chan, A. M. Baranger, P. J. Hergenrother, S. C. Zimmerman, *J. Am. Chem. Soc.* **2014**, *136*, 6355–6361; b) J. F. Arambula, S. R. Ramisetty, A. M. Baranger, S. C. Zimmerman, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 16068–16073.
[61] C. Martin, M. Bonnet, N. Patino, S. Azoulay, A. Di Giorgio, M. Duca, *ChemPlusChem* **2022**, *87*, e202200250.
[62] S. Wang, P. W. Huber, M. Cui, A. W. Czarnik, H.-Y. Mei, *Biochemistry* **1998**, *37*, 5549–5557.
[63] a) C. Zhao, G. Qin, J. Niu, Z. Wang, C. Wang, J. Ren, X. Qu, *Angew. Chem. Int. Ed.* **2021**, *60*, 432–438; b) J. A. Kelly, A. N. Olson, K. Neupane, S. Munshi, J. San Emeterio, L. Pollack, M. T. Woodside, J. D. Dinman, *J. Biol. Chem.* **2020**, *295*, 10741–10748.
[64] P. R. Bhatt, A. Scaiola, G. Loughran, M. Leibundgut, A. Kratzel, R. Meurs, R. Dreos, K. M. O'Connor, A. McMillan, J. W. Bode, V. Thiel, D. Gatfield, J. F. Atkins, N. Ban, *Science* **2021**, *372*, 1306–1313.
[65] R. Rodriguez, S. Müller, J. A. Yeoman, C. Trentesaux, J.-F. Riou, S. Balasubramanian, *J. Am. Chem. Soc.* **2008**, *130*, 15758–15759.
[66] D. B. Ritchie, J. Soong, W. K. A. Sikkema, M. T. Woodside, *J. Am. Chem. Soc.* **2014**, *136*, 2196–2199.
[67] M. Bouhaddou, D. Memon, et al., *Cell* **2020**, *182*, 685–712.e619.
[68] O. Iranzo, A. Y. Kovalevsky, J. R. Morrow, J. P. Richard, *J. Am. Chem. Soc.* **2003**, *125*, 1988–1993.
[69] G. Feng, J. C. Mareque-Rivas, N. H. Williams, *Chem. Commun.* **2006**, 1845–1847.
[70] a) C. H. B. Chen, D. S. Sigman, *J. Am. Chem. Soc.* **1988**, *110*, 6570–6572; b) J. Wang, P. G. Schultz, K. A. Johnson, *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E4604–E4612.
[71] S. Matsuda, A. Ishikubo, A. Kuzuya, M. Yashiro, M. Komiyama, *Angew. Chem. Int. Ed.* **1998**, *37*, 3284–3286.
[72] K. Michaelis, M. Kalesse, *Angew. Chem. Int. Ed.* **1999**, *38*, 2243–2245.
[73] B. F. Baker, S. S. Lot, J. Kringel, S. Cheng-Flournoy, P. Villiet, H. M. Sasmor, A. M. Siwkowski, L. L. Chappell, J. R. Morrow, *Nucleic Acids Res.* **1999**, *27*, 1547–1551.
[74] J. C. Joyner, J. A. Cowan, *J. Am. Chem. Soc.* **2011**, *133*, 9912–9922.
[75] N. W. Luedtke, Y. Tor, *Biopolymers* **2003**, *70*, 103–119.
[76] a) H. Borsook, G. Keighley, *Proc. Natl. Acad. Sci. USA* **1933**, *19*, 875–878; b) P. M. Wood, *Biochem. J.* **1988**, *253*, 287–289.
[77] J. C. Joyner, K. D. Keuper, J. A. Cowan, *Chem. Sci.* **2013**, *4*, 1707–1718.
[78] E. J. Wurtmann, S. L. Wolin, *Crit. Rev. Biochem. Mol. Biol.* **2009**, *44*, 34–49.
[79] a) J. Bonet-Aleta, M. Sancho-Albero, J. Calzada-Funes, S. Irusta, P. Martin-Duque, J. L. Hueso, J. Santamaria, *J. Colloid Interface Sci.* **2022**, *617*, 704–717; b) A. Bansal, M. C. Simon, *J. Cell Biol.* **2018**, *217*, 2291–2298.
[80] L. Banci, I. Bertini, S. Ciofi-Baffoni, T. Kozyreva, K. Zovo, P. Palumaa, *Nature* **2010**, *465*, 645–648.
[81] A. Santoro, J. S. Calvo, M. D. Peris-Díaz, A. Krężel, G. Meloni, P. Faller, *Angew. Chem. Int. Ed.* **2020**, *59*, 7830–7835.
[82] a) H. D. Nguyen, R. D. Jana, D. T. Campbell, T. V. Tran, L. H. Do, *Chem. Sci.* **2023**, *14*, 10264–10272; b) A. M. Pérez-López, B. Rubio-Ruiz, V. Sebastián, L. Hamilton, C. Adam, T. L. Bray, S. Irusta, P. M. Brennan, G. C. Lloyd-Jones, D. Sieger, J. Santamaría, A. Unciti-Broceta, *Angew. Chem. Int. Ed.* **2017**, *56*, 12548–12552.
[83] J. Chen, J. Stubbe, *Nat. Rev. Cancer* **2005**, *5*, 102–112.
[84] a) F. Neese, J. M. Zaleski, K. Loeb Zaleski, E. I. Solomon, *J. Am. Chem. Soc.* **2000**, *122*, 11703–11724; b) J. Peisach, *Int. Congr. Ser.* **2002**, *1233*, 511–517.
[85] B. J. Carter, E. de Vroom, E. C. Long, G. A. van der Marel, J. H. van Boom, S. M. Hecht, *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 9373–9377.
[86] S. A. Kane, S. M. Hecht, in *Progress in Nucleic Acid Research and Molecular Biology, Vol. 49* (Eds.: W. E. Cohn, K. Moldave), Academic Press, **1994**, pp. 313–352.
[87] L. V. Liu, C. B. Bell, S. D. Wong, S. A. Wilson, Y. Kwak, M. S. Chow, J. Zhao, K. O. Hodgson, B. Hedman, E. I. Solomon, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 22419–22424.
[88] W. F. Lima, B. P. Monia, D. J. Ecker, S. M. Freier, *Biochemistry* **1992**, *31*, 12055–12061.
[89] A. J. Angelbello, M. E. DeFeo, C. M. Glinkerman, D. L. Boger, M. D. Disney, *ACS Chem. Biol.* **2020**, *15*, 849–855.
[90] R. I. Benhamou, M. Abe, S. Choudhary, S. M. Meyer, A. J. Angelbello, M. D. Disney, *J. Med. Chem.* **2020**, *63*, 7827–7839.
[91] Z. Chen, F. Han, Y. Du, H. Shi, W. Zhou, *Signal Transduct Target Ther.* **2023**, *8*, 70.
[92] a) R. M. Burger, *Chem. Rev.* **1998**, *98*, 1153–1170; b) S. M. Hecht, *Acc. Chem. Res.* **1986**, *19*, 383–391.
[93] Y. Li, M. D. Disney, *ACS Chem. Biol.* **2018**, *13*, 3065–3071.
[94] R. I. Benhamou, A. J. Angelbello, R. J. Andrews, E. T. Wang, W. N. Moss, M. D. Disney, *ACS Chem. Biol.* **2020**, *15*, 485–493.
[95] Q. M. R. Gibaut, J. A. Bush, Y. Tong, J. T. Baisden, A. Taghavi, H. Olafson, X. Yao, J. L. Childs-Disney, E. T. Wang, M. D. Disney, *ACS Cent. Sci.* **2023**, *9*, 1342–1353.
[96] B. M. Suresh, Y. Tong, D. Abegg, A. Adibekian, J. L. Childs-Disney, M. D. Disney, *ACS Chem. Biol.* **2023**, *18*, 2385–2393.

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Minireview

RNA Degraders

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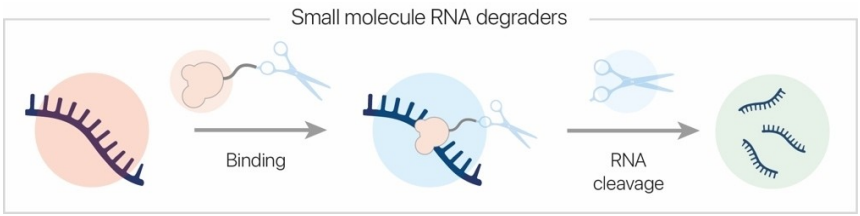
Small Molecule RNA Degraders



As one of the central molecules for life, RNA is connected to various processes involved in disease. Achieving a targeted, specific and irreversible RNA degradation is both a challenge and a highly valuable goal for pushing forward the development of new therapeutics. This minireview aims to summarize and provide mechanistic insights into every approach so far to drug and irreversibly degrade disease-associated RNA using small molecules.