RNA as a small-molecule drug target: doubling the value of genomics

David J. Ecker and Richard H. Griffey

Recent advances in the determination of RNA structure and function have led to new opportunities that will have a significant impact on the pharmaceutical industry. RNA, which, among other functions, serves as a messenger between DNA and proteins, was thought to be an entirely flexible molecule without significant structural complexity. However, recent studies have revealed a surprising intricacy in RNA structure. This observation unlocks opportunities for the pharmaceutical industry to target RNA with small molecules. Because both proteins and their specific mRNAs are potential drug-binding sites, the number of targets revealed from genome sequencing efforts is effectively doubled. Perhaps more importantly, drugs that bind to RNA might produce effects that cannot be achieved by drugs that bind to proteins.

Targeting RNA for drug discovery is not an entirely new concept. Indeed, antisense is an approach to targeting RNA that has matured over the past decade as a result of the focused efforts of a few specialty companies. A recently achieved milestone was the first approval of an antisense drug in 1998 (Vitravene™, discovered and developed by Isis Pharmaceuticals, Carlsbad, CA, USA). The discovery of complex three-dimensional (3D)-structure in mRNA was not necessary for antisense drug discovery, in which oligonucleotides are used to bind to RNA by well-known Watson–Crick interactions in single-stranded regions. In fact, the existence of 3D-structures in mRNA could be one reason why many oligonucleotides fail to work, as internal structures compete with oligonucleotides for binding sites on mRNA.

Although exciting new antisense oligonucleotides will continue to be developed, they are a very specialized class of drugs that are not within the traditional scope of drugs produced by major pharmaceutical companies. The notion that RNA might be targeted with small molecules will undoubtedly result in considerable attention in the industry once the value of the concept is more widely appreciated.

Small-molecule drugs that bind to RNA

The notion that small molecules that bind to RNA can be used as drugs opens up a whole new line of investigation for the pharmaceutical industry (Fig. 1). In contrast to many early-stage concepts in drug discovery, targeting RNA with small molecules has no major conceptual hurdles to overcome. Proof of principle has already been provided by the success of several classes of drugs obtained from natural sources that have been shown to work by binding to RNA or RNA–protein complexes. These drugs include thiostrepton, the aminoglycoside-family and the macrolide-family of antibiotics, which represent three different structural classes. The macrolide antibiotics, which include erythromycin, azithromycin and the streptogramin family, work by binding to the large ribosomal subunit. Macrolides interfere with the peptidyl transfer function of the ribosome, although the molecular details of the binding site for macrolides are not well understood. Evidence

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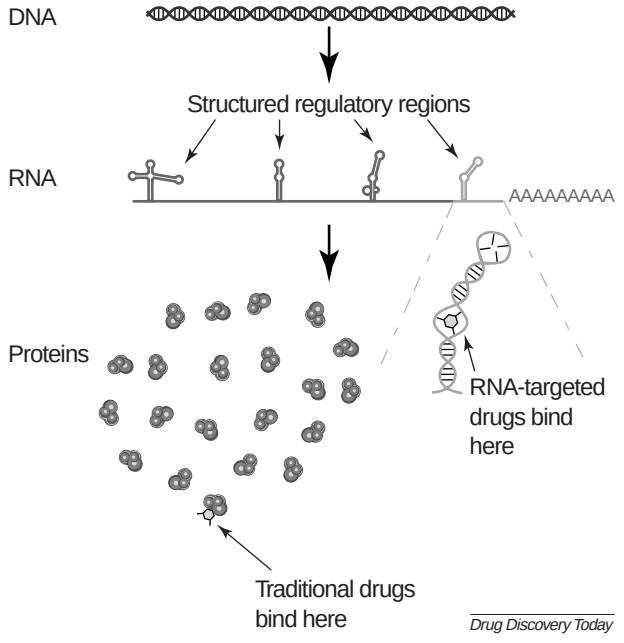

Figure 1. *Paradigm for drugs that bind to mRNA in structured regulatory regions.*

that RNA is a component of its binding site comes from data showing that resistance to macrolide antibiotics is mediated by methylation of adenosine 2058 (A2058) of the large rRNA subunit. In mycobacteria, macrolide resistance is mediated by a point mutation of A2058 to G and no alteration of any of the proteins is involved[1]. Whether RNA, protein, or the interface of RNA with the protein provide the binding site for macrolide antibiotics is unclear. However, macrolide structures have very attractive pharmaceutical properties having good lead shapes for the design of new compound motifs that interact with RNA or RNA–protein complexes.

The aminoglycoside family includes neomycin, paromomycin, lividomycin, kanamycin and gentamicin, which are very potent, bactericidal compounds that bind to the RNA of the small ribosomal subunit. This bactericidal action is mediated by binding of the compound to the bacterial RNA in a way that leads to misreading of the genetic code[2]. Misreading of the code whilst translating integral membrane proteins is thought to produce abnormal proteins that compromise the barrier properties of the bacterial membrane. This is a very interesting mechanism because bactericidal action is highly desired in new antimicrobial drugs and there are few ways of achieving it. The cascade of events that lead to bacterial cell death is:

- Uptake of a small quantity of the aminoglycoside into the cell
- A minor quantity of misreading results in mutant membrane proteins
- This facilitates more aminoglycoside penetration into the cell, which, in turn, produces more misreading
- The membrane barrier becomes so compromised that the cell is unable to recover and lyses.

Another reason why the aminoglycosides are interesting is that they target binding sites on the RNA that appear to be difficult for cells to change by mutation. Even after chemical mutagenesis, it is difficult to obtain aminoglycoside-resistant ribosomes. Hence, natural resistance to aminoglycosides is mediated mostly by enzymes that deactivate the compounds, which are transferred among bacterial species via plasmids. Since there are multiple copies of ribosomal RNA genes, it is difficult to have resistance mediated by mutations, since misreading is a dominant effect. Thus, new chemical entities that bind these same ribosomal target sites might produce the same desired bactericidal effects but be immune to the current set of deactivating enzymes.

The misreading function of aminoglycosides has been considered for use in a therapeutic mode for situations in which some misreading is desired. In cystic fibrosis, a single recessive mutation produces a premature stop codon in a critical membrane protein – the cystic fibrosis transmembrane conductance regulator (CFTR). Aminoglycosides have been used to induce some misreading of this erroneous stop codon, resulting in a small amount of full-length CFTR (Ref. 3). Apparently, having a general low level of misreading in these cells and some functional CFTR balances out to produce a net benefit for cystic fibrosis patients. Drugs that bind to RNA might have a similar use in other disorders where loss of function is caused by erroneous stop codons, although the diseases might need to be as severe as cystic fibrosis.

In contrast to the macrolides, the structure of the key RNA binding site for some of the aminoglycosides is known, as are details of the molecular interactions between the aminoglycoside and the RNA. Puglisi and coworkers have determined the nuclear magnetic resonance (NMR) structure of some aminoglycosides and their target RNA subdomain in the ribosome (Fig. 2)[4–6]. Recognition is based on a combination of shape recognition and electrostatic and hydrogen-bonding interactions. The aminoglycosides provide four hydrogen-bond donors from primary amines or hydroxyl groups to specific nucleotide acceptors on the target, which is a widened and distorted

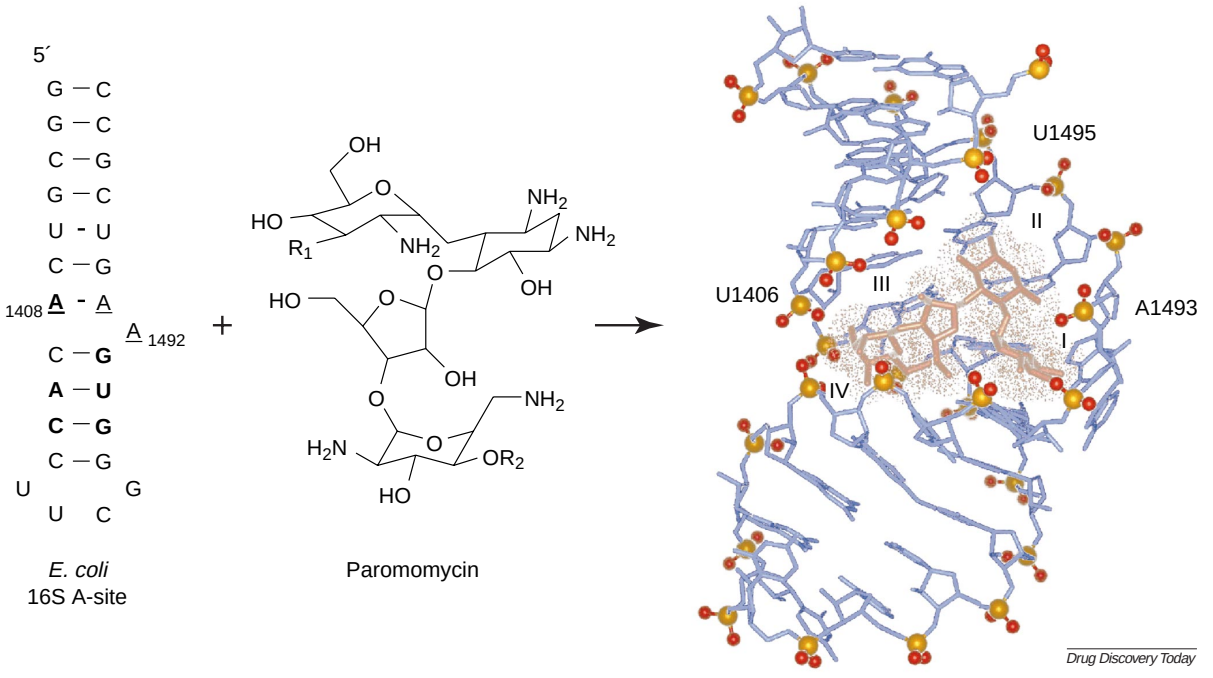

Figure 2. *Paromomycin binding to the A-site subdomain of 16S ribosomal RNA (modified from Ref. 4).*

major groove. The sugar rings provide 'scaffolding' to deliver these donors in precisely the correct orientation for recognition.

The peptide antibiotics thiostrepton and micrococcin work through a different mechanism. Instead of disrupting the interaction between L11 protein and its 23S RNA binding site, thiostrepton stabilizes the RNA–protein interaction associated with elongation factor G. Such targeting of the ribosomal 'machinery' involved in protein synthesis opens up new opportunities for novel therapeutic mechanisms.

Strategic and tactical advantages of RNA as a drug target

A key strategic advantage of RNA as a drug target is that it essentially doubles the opportunities provided by genome sequencing[7–9], a technique that reveals the sequences of both the proteins and the mRNAs that encode them. Because all proteins are synthesized using an RNA template, formation of all the proteins can be inhibited by preventing their production through interference with the translation of the mRNA.

A new method of inhibiting proteins

Many proteins are extremely difficult to isolate and purify in a form that is appropriate for use in assays for drug screening. Moreover, many proteins require post-translational modifications that occur only in certain cell types under specific conditions. Almost invariably, obtaining biologically active forms of proteins is the most expensive and reagent-limiting step of high-throughput screening (HTS). By contrast, all RNAs are essentially equivalent in their solubility, ease of synthesis and use in assays. The physical properties of RNAs are independent of the protein they encode, they can be readily prepared in large quantities through chemical or enzymatic synthesis and they are not extensively modified *in vivo*.

Although classical drug discovery approaches have worked well with enzymes and membrane surface-receptors, other kinds of proteins have caused more problems. For example, the 'hit-rate' for HTS with protein–protein interactions is much lower than for other assays[10]. There are also very few successful examples of screening for inhibitors of proteins that bind to DNA. There will undoubtedly be many attractive new protein targets revealed by genomic sequencing, for which the development of a protein-based assay will not be technically feasible. In these situations, inhibiting the RNA may be an attractive alternative.

Unique effects are possible

Small molecules that bind to RNA have the potential to achieve results that cannot be achieved by binding to

proteins. Besides inhibiting the production of proteins, it might also be possible to increase the level of protein production by binding drugs to RNA. There are now several known examples in which regulatory proteins bind specific mRNAs to inhibit translation. Drugs that interfere with this process can potentially cause an increase in protein levels, rather than a decrease, hence producing unprecedented opportunities for these small-molecule drugs that were previously restricted to replacement strategies such as gene therapy or the direct administration of therapeutic proteins.

New opportunities for specificity

There are some unique opportunities to achieve specificity for drugs at the RNA level that are derived from aspects of cell biology unique to RNA. When a gene is expressed in different tissues, the cells frequently create variations in mRNAs. Processes such as alternative initiation, splicing and polyadenylation generate transcripts that might be unique to (or enriched in) specific tissues. These alternative transcripts sometimes encode an alternative form of the protein or might encode an identical protein, depending on whether the sequence variation affects the reading frame. This diversity provides the opportunity to make drugs that bind to the region of RNA that is unique to the desired tissue and do not affect the RNA in other tissues.

This opportunity for an additional level of drug specificity is not generally available when targeting proteins. An analogous opportunity for specificity at the protein level might be to target post-translational modifications of proteins that are tissue specific. In practice, however, this variation in proteins has been difficult to exploit because of the lack of good analytical tools to differentiate tissue-specific protein modifications. In contrast, finding alternative transcript forms in RNA is accomplished by straightforward sequencing of cDNA libraries obtained from different tissues. The potential to find alternative transcript forms is one of the unappreciated strategic advantages of RNA as a drug target.

New drug-discovery tactics

The pharmaceutical industry has developed a set of tactical approaches to drug discovery that has evolved significantly in recent years. The historical foundation of the industry was its proprietary collection of chemicals, which has recently been supplemented by combinatorial chemistry. Although the relative value of the combinatorial versus historical collections has been debated, the need for HTS is without question. Molecular targets were historically derived from pharmacological and biochemical research, and are now being augmented or supplanted by genomics. Although the production of more targets and chemicals has driven the development of innovative new tools, the process of screening for drug leads has remained fundamentally the same for the past 30 years. The process invoves the preparation of the protein target from biological sources and the development and validation of a solution assay. The process is miniaturized to the maximum extent without compromising reproducibility and lead identification, and as many compounds as possible are screened.

With RNA as the target, these classical tactics of the pharmaceutical industry no longer make sense. Strategies to identify the best molecular targets need to be modified and can be dramatically improved. For example, targets for which increased protein expression is desired can be considered. This new opportunity requires strategic rethinking of the classical mindset in which a molecular target is considered only in the context of inhibiting it.

When a gene product is determined to be of interest, its natural pattern of expression in different tissues and its transcript forms need to be identified. Fortunately, the expressed sequence tags (ESTs) database is available, with an extensive and expanding list of sequences (http://www.ncbi.nlm.nih.gov/dbEST/dbEST_summary.html). Although only a small percentage of the human genome has been sequenced, the EST database of expressed RNAs has over a million entries. Thus, of 80,000–100,000 human genes, a much higher percentage of the expressed genome is already known relative to the whole genome. Clustering ESTs derived from the same gene into virtual mRNA transcripts[11], gives information on the transcript forms that are present in different tissues and facilitates the identification of drug targets.

Impact on high-throughput screening

To discover compounds that bind to RNA targets, the classical screening methods used for proteins can be superseded by newer approaches. Proteins fold into globular domains, with hydrophobic cores and hydrophilic and charged groups on the surface. Multiple subunits frequently form complexes, which might be required for a valid drug screen. Membrane proteins usually need to be embedded in a membrane to retain their proper shape. The smallest practical unit of a protein that can be used in drug screening is a globular domain. The idea of removing a single α-helix or a turn of a β-sheet and using it in a drug screen is not practical, because only the intact protein has the appropriate 3D-shape for drug binding. Preparation of biologically active protein for screening is a

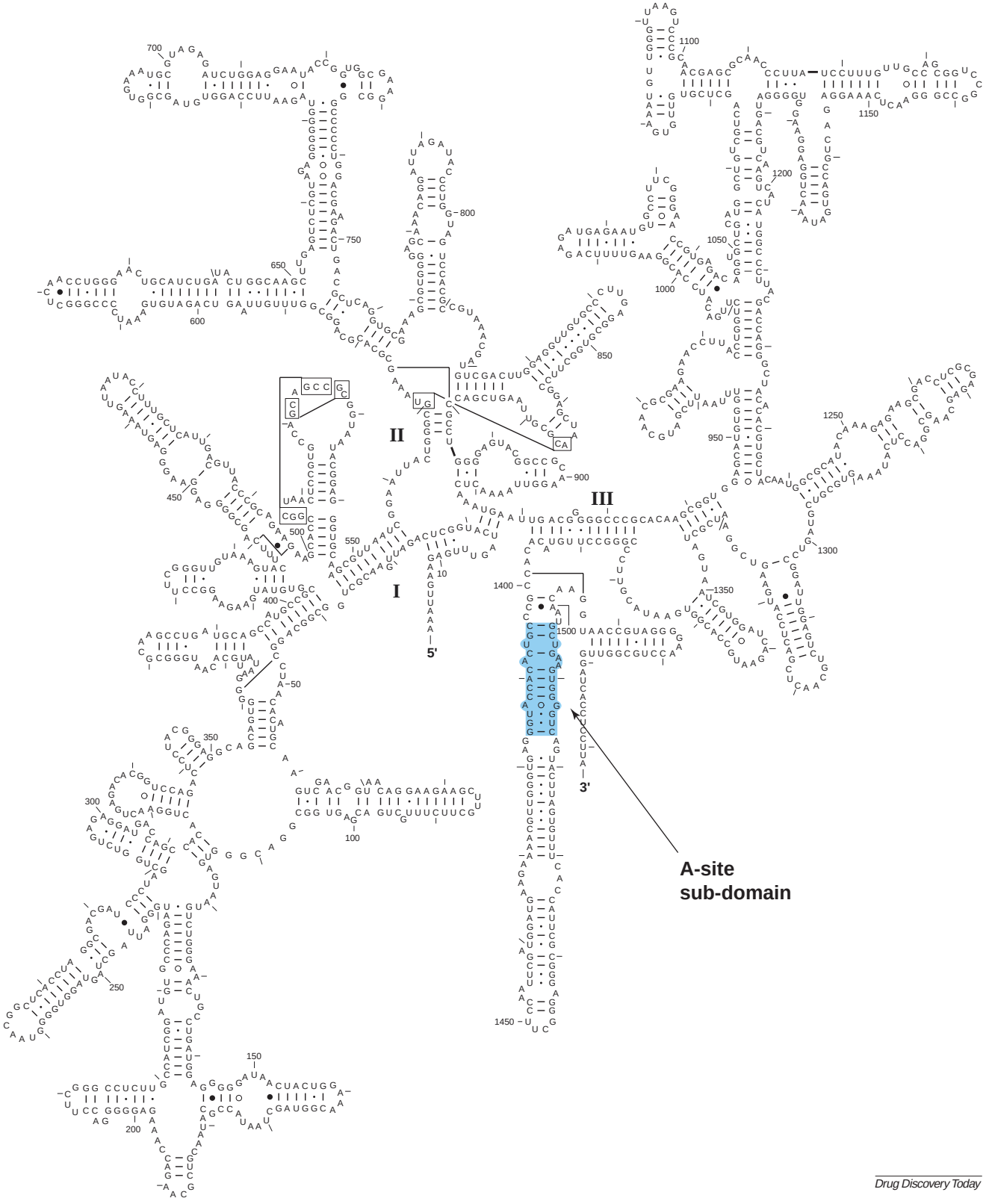

Figure 3. *Functional subdomain of 16S ribosomal RNA from* Escherichia coli[12].

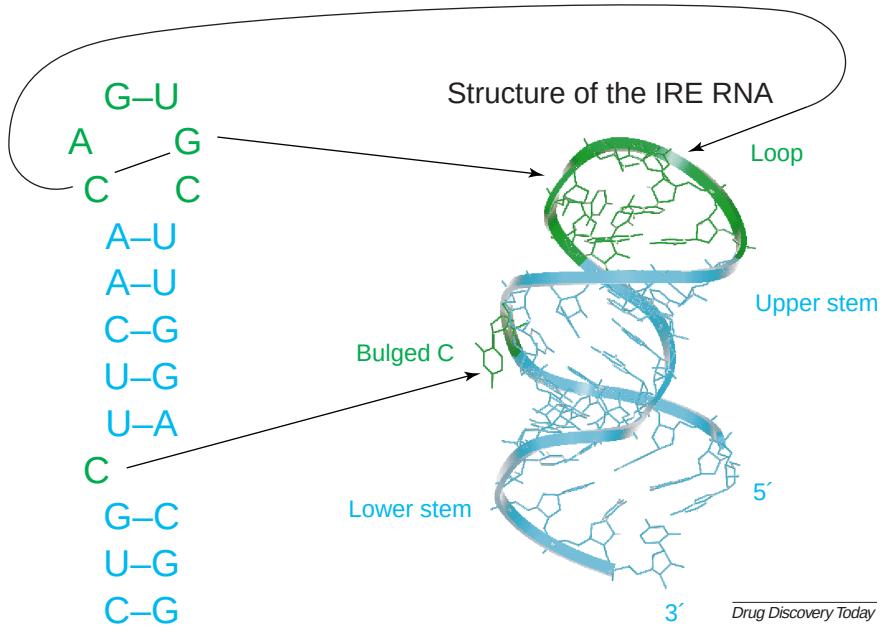

Figure 4. *The iron responsive element, a regulatory element in mRNA (Ref. 16).*

major limitation of classical HTS. Even the largest pharmaceutical companies can only support a finite number of different screens at once, no matter how much screening automation exists.

With RNA as the target, all this changes. The smallest practical unit for drug binding is the functional subdomain[12]. A functional subdomain in RNA is a fragment that, when removed from the larger RNA and studied in isolation, retains its biologically relevant shape and protein-binding properties. The structural biology community has gained significant experience in the identification of functional RNA subdomains to facilitate structural studies using techniques such as NMR spectroscopy. For example, small analogues of the decoding region of 16S rRNA (the A-site; Fig. 3) have been identified that contain only the essential region and have been shown to bind antibiotics in the same fashion as the intact ribosome[5,12–14]. As with any experimental approach that simplifies a more complex system, caution must be exercised to ensure that the subdomain being studied still contains the structural features relevant for drug binding. Experimental results obtained with the subdomain must be confirmed with a more complete system. Undoubtedly, tertiary interactions will be lost when working with a smaller RNA fragment in isolation[15]. Nevertheless, the natural tendency for RNA structure to be driven primarily by secondary features such as stems and loops is a tremendous advantage in drug discovery.

RNA regulatory elements tend to be relatively small structures that are differentiated from each other by bulges, internal loops and hairpin loops. A well-studied example of a mRNA regulatory element is the iron responsive element shown in Fig. 4 (Ref. 16). This RNA structure binds to a specific set of proteins that regulate the translation and stability of mRNAs that encode proteins involved in iron metabolism. A number of other important regulatory elements have been shown to retain their biologically relevant shape and protein-binding properties when removed from their larger RNA context[17].

The size and composition of RNA functional subdomains make them accessible by enzymatic or chemical synthesis and it is hard to overstate the advantage this provides for drug screening. Perhaps the most limiting and expensive step in HTS is the purification of biologically active forms of protein and this step is eliminated for RNA targets. Material for hundreds of different RNA targets can be prepared in a single day using 96-well format synthesis instrumentation[18]. For longer RNAs, *in vitro* enzymatic synthesis can be used[19,20].

With essentially unlimited material for drug screening, new assay formats also need to be considered to maximally exploit this new capability. For example, instead of screening in 96- or 384-well format binding assays, new strategies based on mass spectrometry (MS) have been developed[21]. By using MS instead of classical assay techniques, screening can be accomplished in a massively parallel fashion and a great deal more information can be obtained from an assay[22,23].

Key challenges

Finding the best RNA targets in infectious disease

Bacteria and viruses are excellent targets for small-molecule drugs that bind to RNA. Viruses have the most compact genomes and are forced to use their nucleic acids very efficiently. Moreover, they are the most studied genomes per unit of nucleotide and much of what we know about RNA interactions comes from viruses. RNA viruses, such as influenza, do not use DNA at all and

therefore have to create unique shapes in RNA for all their nucleic acid recognition needs. Many viruses have a large number of isolates that facilitate covariation analysis of sequences, which is currently the most powerful tool for structure prediction[24–26].

Bacteria are also extremely compelling therapeutic targets for small-molecule drugs that bind to RNA. New chemical entities are greatly needed that have a broad spectrum of activity and combat bacterial infection using new mechanisms. Perhaps the biggest challenge in discovering antibacterial drugs that bind to RNA is in identifying vital structures that are common to bacteria and that can be disabled by small-molecule drug binding. RNAs conserve their secondary structure of base pairing more than they conserve their primary sequence. Thus, strategies to use phylogenetic information to identify good structural motifs can be employed.

As mentioned earlier, there are at least three chemical classes of antibiotics that work by binding to bacterial RNA or RNA–protein complexes. These examples from nature provide powerful clues as to how small molecules and targets might be selected. Nature has selected RNA targets in the ribosome – one of the most ancient and conserved targets in bacteria. Since antibacterial drugs need to be potent and have a broad spectrum of activity, these ancient processes, which are fundamental to all bacterial life, represent attractive targets. The closer we get to ancient conserved functions, the more likely we are to find broadly conserved RNA shapes.

Finding the best RNA targets in eukaryotic mRNAs

The cell exerts control over both the timing and the quantity of proteins that are synthesized by direct, specific interactions with mRNA. The processes of RNA maturation, transport, intracellular localization and translation are rich in RNA recognition sites that provide good opportunities for drug binding. Finding these regions is a key element in the process of making drugs that bind to RNA.

Analysis of ESTs reveals that mRNA transcripts are much more heterogeneous than had been anticipated. Many genes have as many as 10–20 alternative transcript forms, which, in some cases, have been associated with a disease phenotype. For example, in cancerous cells, transcription of the *mdm2* gene is initiated at a distinct site that is not used in normal cells[27]. In Bcl-x mRNA, alternatively spliced forms of the transcript result in dramatically different cell behaviour and sensitivity to chemotherapeutic drugs[28].

Alternative 3′-end processing could be the greatest source of alternative transcript forms. Studying 160,000 EST sequences, Gautheret and collaborators have shown that 20–40% of the transcripts have two or more 3′-ends (Fig. 5)[29]. Other investigators have shown that certain classes of mRNAs are alternatively 3′-end processed in a tissue-specific or developmentally specific pattern[30] and, in some cases, this has been correlated with disease. For example, the transcript of the *mss4* gene was recently shown to have alternative 3′-end processing in pancreatic cancer[31]. Alternative 3′-end formation does not change protein composition, but can dramatically influence message stability and regulate translation by including or excluding regulatory sequences in the mRNA transcript.

Alternative transcript forms, despite being transcribed from identical DNA and translated into identical proteins, are full of unique sequences and 3D-shapes that exist only at the level of RNA. A very important consequence of alternative transcript forms for RNA drug targeting is the unique shapes that they create, which can be produced in several ways. Firstly, with alternative transcription initiation or 3′-end formation, there are unique sequences in

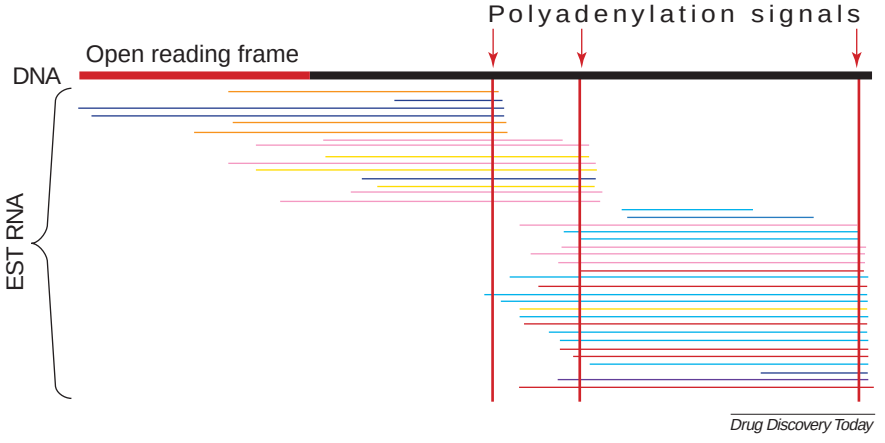

Figure 5. *Example of a 3′-expressed sequence tag (EST) cluster. EST colors correspond to the tissue of origin[29]. In this example, the use of three different polyadenylation signals provides clear evidence of three different mRNA lengths from the same gene.*

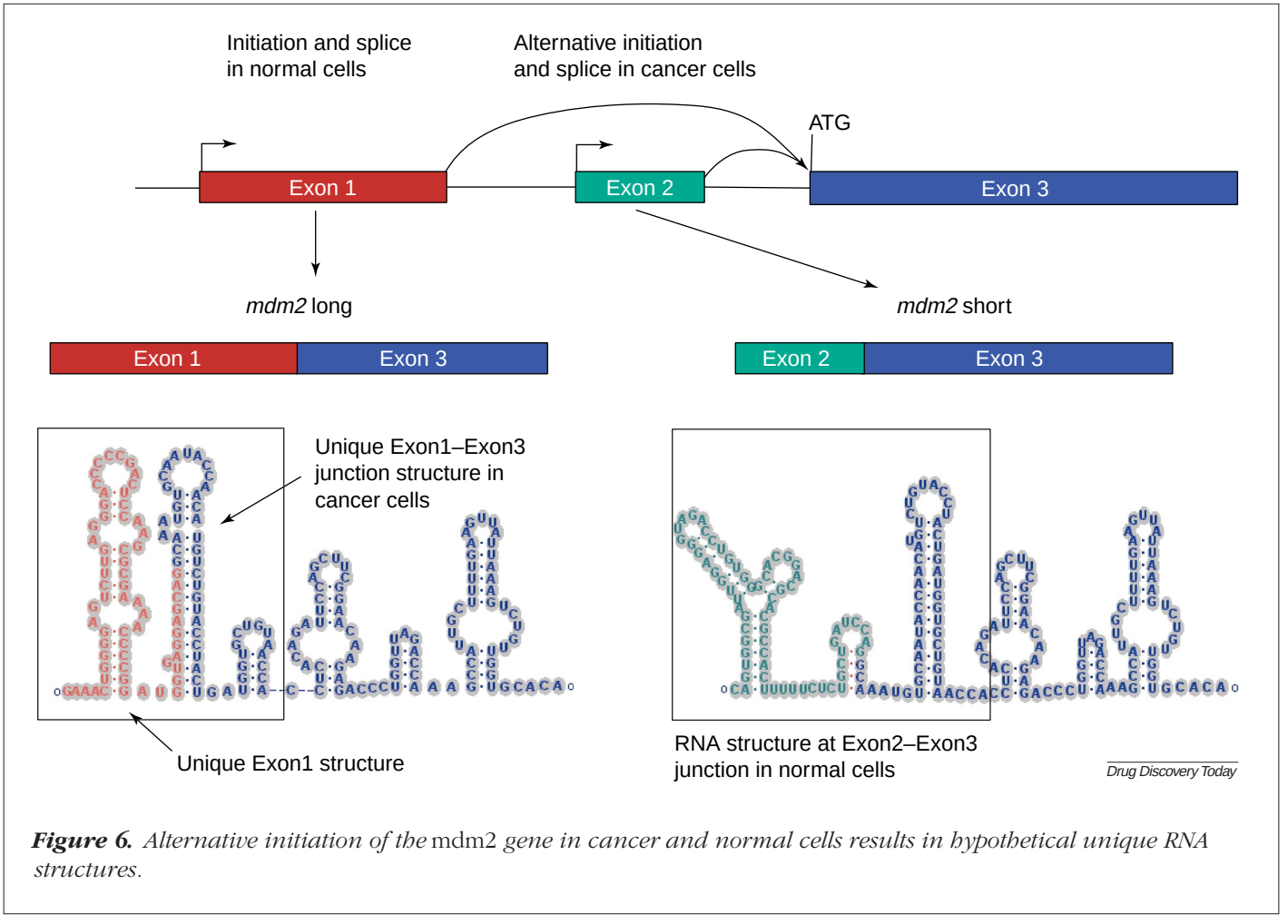

Figure 6. *Alternative initiation of the* mdm2 *gene in cancer and normal cells results in hypothetical unique RNA structures.*

mRNAs that do not appear in the normal mRNA (Fig. 6). These sequences, in turn, will fold into unique structures within themselves and with the adjacent RNA. Secondly, each alternative splicing event produces a unique junction where the adjacent RNA on each side of the junction will rearrange into a new 3D-shape.

It is important to distinguish the concepts of alternative transcript forms from tissue-specific expression of transcripts. Many investigators are pursuing transcripts and proteins that are expressed at different levels in various disease states (i.e. cancer versus normal cells). Indeed, 500 transcripts have been reported to be expressed at significantly different levels in normal cells compared with gastrointestinal tumour cells (15-fold on average)[32]. Tissue-specific transcripts provide a perfectly useful set of molecular targets for small molecules that bind to RNA. However, we believe that the greater opportunity to find useful tissue-specific targets is in alternative transcript forms. The rationale is simple: since there could be between 2 and 20 different forms of every transcript and 10,000–20,000 genes expressed in any given cell, the opportunity to find tissue-specific alternative transcript forms could be much greater than for tissue-specific transcripts.

Chemical approaches to targeting RNA with small molecules

Designing a chemical approach to targeting RNA with small molecules is obviously a key challenge. The objectives are to design compounds with the following properties:

- Sufficient affinity for RNA to produce biological consequences in the cell after binding to the target
- The ability to tailor molecules to match the shape of, and bind specifically to, different RNA structures
- Cell penetration
- Good pharmacokinetic properties
- Acceptable toxicological properties.

The first challenge is to develop a chemical strategy to recognize specific shapes of RNA using small molecules.

Unless this can be achieved, the remaining considerations are irrelevant. There are four sets of data that provide hints on how to do this: natural protein interactions with RNA, natural RNA–RNA interactions, natural product antibiotics that bind to RNA, and man-made RNAs (aptamers) that bind small molecules. Each dataset provides different insights into the problem.

Natural proteins that bind to RNA provide a set of binding recognition rules that fit within the chemical and structural constraints available to proteins. RNA binding strategies for ribosomal proteins were recently summarized by Draper and Reynaldo[33]. The common themes are:

- The α-helix provides a workable scaffold to project hydrogen-bonding to RNA bases in a distorted groove
- β-Sheets are used to display aromatic groups to bind unstacked bases, and additional polar groups hydrogen-bond to the bases to increase specificity
- Extended loops provide additional contacts to the backbone.

Aminoglycosides provide several important lessons in the design of compounds that bind to RNA. The rigid 2-deoxystreptamine framework allows the 4,5-disubstituted compounds paromomycin, neomycin and lividomycin to bind with high affinity to the 16S A-site, whereas the wider 4,6-disubstituted derivatives tobramycin and bekanamycin have poor complementary shapes and bind to the same site with 20–100-fold lower affinity. Properly engineered contacts can provide very high binding affinity for an RNA, as evidenced by the K_D of ~25 nM of neomycin for a 27-mer RNA model of the A site, compared with the K_D of ~10 μM of ribostamycin, which has three of the four sugars of neomycin. However, binding specificity is a balance between nonspecific electrostatic interactions and specific electrostatic, hydrogen-bonding and stacking interactions. The more highly charged neomycin binds to other RNAs with micromolar affinity, whereas the less charged paromomycin binds to other RNAs with 10–100-fold more weaker affinity. The suggestion that the aminoglycoside sugars are simply scaffolds that present hydrogen-bond donors in the right orientation for RNA binding led to attempts to substitute other chemical scaffolds. Wong and coworkers have used the neamine core structure[34,35] as a scaffold for further elaboration. Systematic replacement of the natural sugars with different scaffolds and functional groups will be an important focus for the field of small-molecule RNA recognition in the near future to provide further insight into the roles that specific electrostatic and hydrogen-bonding interactions play in generating binding affinity.

Compared with proteins, the binding sites on RNA are hydrophilic and relatively open. The potential for small-molecule recognition based on shape is enhanced by the deformability of RNA. Hence, binding of molecules to specific RNA targets can be determined by global conformation and the distribution of charged, aromatic and hydrogen-bonding groups off a relatively rigid scaffold. A correctly placed positive charge will be crucial, as long-range electrostatic interactions can be used to steer molecules into a binding pocket with the correct orientation. In structures where nucleobases are exposed, stacking interactions with aromatic functional groups might contribute to the binding interaction. The major groove of RNA provides many sites for specific hydrogen-bonding with a ligand. These include the aromatic N7-nitrogen atoms of adenosine and guanosine, the O4- and O6-oxygen atoms of uridine and guanosine, and the amines of adenosine and cytidine. The rich structural and sequence diversity of RNA suggests that ligands can be created with high affinity and specificity for their target, and that new classes of highly specific therapies derived from exploiting these unique physical properties and cellular functions of RNA could be on the horizon.

Conclusions

Targeting RNA with small molecules opens up a new set of opportunities for the pharmaceutical industry. Perhaps most importantly, drugs that bind to RNA have the potential to produce therapeutic effects that cannot be achieved at the protein level, such as increasing protein expression. Nevertheless, some key challenges will need to be overcome if this potential is to be realized. Although there are no conceptual hurdles, and nature has already provided some examples, new generations of small molecules will be needed that go beyond the natural products. The rules for specific recognition of 3D-RNA shapes using synthetic compounds need to be developed. New methods to identify the best RNA targets will also be needed, and the tough work of advancing new drug candidates that work by this mechanism into preclinical and clinical development lies ahead.

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Correction

Please note the following corrections to the article *Dopaminergic agents for the treatment of cocaine abuse* by Miles Smith, Alexander Hoepping, Kenneth Johnson, Monika Trzcinska and Alan Kozikowski published in *Drug Discovery Today* (1999) issue 7, 322–332. In ten instances, 'DA receptor' (dopamine receptor) was mistakenly written instead of 'DAT' (dopamine transporter). These instances were as follows:

- Under the heading 'Dopamine hypothesis', paragraph 3, line 10 and paragraph 4, last line
- Under the heading 'Points for intervention', paragraph 2, point 3, first line and paragraph 2, point 3, line 4
- Under the heading 'Antagonist or agonist?', paragraph 1, right-hand column, line 13
- Under the heading 'Potential therapeutic agents' under 'Mazindol', lines 3, 9 and 13, and under 'Cocaine analogs', paragraph 2, line 9
- On page IV under 'In this issue', paragraph 3, lines 9–10.

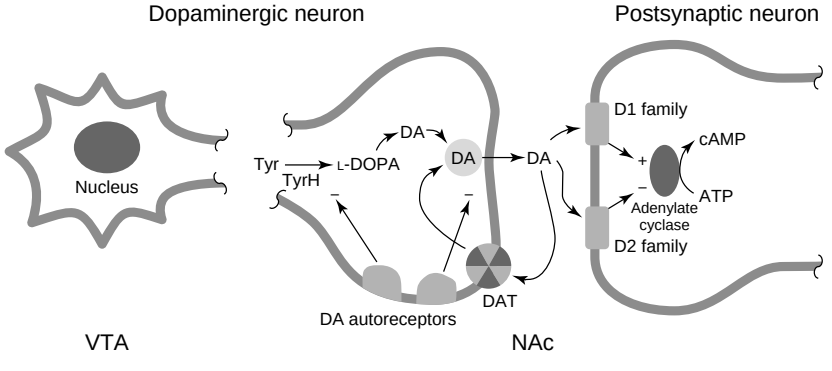

Figure 1. *The dopamine (DA) pathway. This mesolimbic pathway consists of dopaminergic neurons in the ventral tegmental area (VTA) and their projections to forebrain structures, including the nucleus accumbens (NAc). Abbreviations: DAT, dopamine transporter; TYR, tyrosine; TyrH, tyrosine hydroxylase.*

To highlight the importance of the difference between the DA receptor and the DAT, we have republished Fig. 1 from the article. It can clearly be seen that the DA receptors are present on the postsynaptic neuron whilst the DAT is present on the dopaminergic neuron.

Both the authors and the Editor would like to apologize for these inaccuracies and for any misunderstandings these have created for the readers.

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