Therapeutic Aptamers: Evolving to Find their Clinical Niche

Shahid M. Nimjee[1,*], **Bruce A. Sullenger**[2]

[1]Department of Neurological Surgery, Wexner Medical Center, The Ohio State University, Columbus, OH, USA

[2]Department of Surgery, Duke University Medical Center, Durham, NC, USA

Abstract

Background: The discovery that short oligonucleotides, termed aptamers, can fold into three-dimensional structures that allow them to selectively bind and inhibit the activity of pathogenic proteins is now over 25 years old. The invention of the SELEX methodology heralded in an era in which such nucleic acid-based ligands could be generated against a wide variety of therapeutic targets.

Results: A large number of aptamers have now been identified by combinatorial chemistry methods in the laboratory and moreover, an increasing number have been discovered in nature. The affinities and activities of such aptamers have often been compared to that of antibodies, yet only a few of these agents have made it into clinical studies compared to a large and increasing number of therapeutic antibodies. One therapeutic aptamer targeting VEGF has made it to market, while 3 others have advanced as far as phase III clinical trials.

Conclusion: In this manuscript, we hope the reader appreciates that the success of aptamers becoming a class of drugs is less about nucleic acid biochemistry and more about target validation and overall drug chemistry.

Keywords

Aptamer; DNA; RNA; therapeutic; clinical trial; ligonucleotides

1. INTRODUCTION

Observations in the 1980s that viruses had evolved nucleic acid ligands, subsequently termed aptamers [1], to modulate the activities of viral and cellular proteins essential for their replication [2], or to interfere with cellular proteins involved in antiviral responses [3], led translational researchers to investigate whether such ligands could be employed for therapeutic applications. The first two studies demonstrating that such nucleic acid aptamers can inhibit the activities of therapeutically relevant proteins were published in 1990 [4, 5]. Sullenger and colleagues demonstrated that an RNA aptamer derived from the Human

*Address correspondence to this author at the Department of Neurological Surgery, Wexner Medical Center, The Ohio State University, Columbus, OH, USA; Tel: 6143660499; shahid.nimjee@osumc.edu.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

Immunodeficiency Virus (HIV) RNA genome, a stem-loop structured RNA ligand called Transactivation response element (TAR), Fig. (1) could act as a decoy and squelch the activity of the viral Trans-activator of transcription (tat) protein and potently inhibit HIV replication in CD4+ T-cells [4]. Bielinska *et al.* demonstrated that a DNA aptamer derived from the DNA binding site of the transcription factor NF-kappa B could limit NF-kappa B activation of gene expression from the Interleukin-2 (IL-2) and HIV promoters in B and T cells [5]. These results suggested that RNA and DNA aptamers derived from nature represent novel therapeutic agents to control the activities of clinically relevant nucleic acid-binding proteins. During the intervening 25 years, numerous naturally occurring aptamers have been discovered that selectively bind to many clinically relevant nucleic acid-binding proteins as well as cellular metabolites [6, 7]. A few of these naturally derived aptamers have been evaluated in clinical studies as potential treatments for maladies ranging from cardiovascular to infectious diseases.

In 1990, two additional seminal publications demonstrated that RNA aptamers could also be generated in the laboratory using combinatorial chemistry methods (Fig. 2) [1, 8]. In these studies, large libraries of artificially created randomized RNA molecules were screened in the test tube for those molecules in the library that could be ligands and bind T4 DNA polymerase [8] or an organic dye [1] with high affinity. The term aptamer, which has been adopted by the field to mean nucleic acid ligand, was coined by Ellington and Szostak [1] and the *in vitro* selection process to identify them in the laboratory was termed SELEX (systematic evolution of ligands by exponential enrichment) by Tuerk and Gold [8]. The invention of the SELEX process fundamentally changed the aptamer field because it offered the possibility of generating aptamers to target proteins, or other types molecules, that are not known to interact with nucleic acid ligands in nature. Moreover, since the SELEX process is performed in the test tube, one is not limited to using naturally occurring nucleotides in the RNA or DNA libraries, which allows for modifications of aptamers to make them more amenable to drug development. Since 1990, thousands of aptamers have been generated by the SELEX methodology or derivatives of it to a vast array of target proteins most of which do not have natural aptamers that bind them [9–11]. Thus, the invention of SELEX by Tuerk and Gold [8] and Ellington and Szostak [1] in 1990 suggested that the concept of therapeutic aptamers first described by Sullenger *et al.* [4] and Bielinska *et al.* [5] that same year might become more broadly useful than initially envisioned. As detailed below, this prediction has been proven correct. The FDA has approved one *in vitro* selected aptamer, while three others have made their way into large phase 3 clinical trials.

2. TRANSLATION OF APTAMERS FOUND IN NATURE INTO THE CLINIC

To date, fourteen aptamers have been translated from the laboratory to the clinic (Table 1). Of these, five were evolved in nature. The first two aptamers to be evaluated in clinical trials were derived from nature: an RNA-based RRE (rev response element) decoy aptamer targeting the HIV rev protein [12] and a DNA decoy aptamer targeting the E2F transcription factor family [13]. Results from phase I clinical trials using both of these aptamers were published in 1999 by Kohn and colleagues (RRE decoy aptamer) [12] and Mann and colleagues (E2F decoy aptamer) [13]. Thus in nine years, the concept of inhibiting the activity of a therapeutically relevant protein with a nucleic acid ligand was translated into

first in human studies. Results from clinical studies on these two aptamers as well as clinical studies using a second RNA decoy aptamer and two additional DNA decoy aptamers all of which target intracellular nucleic acid-binding proteins are briefly described below.

Two RNA aptamers taken from nature [12, 14] have been translated into clinical studies and both target viral RNA binding proteins, rev and tat, essential for HIV replication (Fig. 1). Kohn and colleagues introduced an aptamer derived from the HIV rev Response Element (RRE) into hematopoietic cells of HIV infected children in an effort to inhibit the viral rev protein and virus replication [12]. Because this aptamer is comprised of normal RNA and the rev protein is an intracellular protein, a MoMLV-based retroviral vector was utilized to transfer an expression cassette for the RRE decoy aptamer into CD34+ bone marrow-derived stem cells in an effort to continuously produce the aptamer inside the treated cells. No evidence of adverse events was noted in the treated pediatric patients but the levels of aptamer containing cells in the peripheral blood of treated patients were found to be very modest one year following treatment [12]. The investigators concluded that gene therapy using RNA aptamers to inhibit HIV replication is possible but that improved gene transfer strategies need to be developed for the strategy to be effective. Since this initial study in 1999, significant advances have been made in the field of gene therapy including the development of lentivirus-based vectors. DiGiusto and colleagues utilized such improved gene transfer technology to deliver an expression cassette for an aptamer derived from HIV TAR RNA (Fig. 1), in conjunction with two other anti-HIV RNAs - a short hairpin RNA and a ribozyme, to stem cells from patients with AIDS-related lymphoma [14]. In four patients, persistent therapeutic RNA expression in multiple cell lineages has been observed for years following transplant with no unexpected toxicities. However, the level of gene transfer was observed to be too low to evaluate clinical efficacy. Therefore current efforts are focused upon developing optimal gene transfer and expression cassettes for the evaluation of such decoy RNA aptamers or other short RNA therapeutic agents [15]. Thus, though it took nearly 20 years, the concept of using a TAR decoy aptamer to inhibit HIV replication [4] has been successfully translated into human studies [14]. Evaluation of additional gene transfer strategies and longer-term follow up for the patients treated in this trial are now needed to better assess the utility of this therapeutic approach for treating HIV infected patients by providing a reservoir of HIV-resistant hematopoietic cells in the treated individuals. Three DNA decoy aptamers derived from normal human genomic DNA have also been evaluated in clinical studies. The first to be translated from the lab to the clinic was an aptamer that targets the E2F family of transcription factors. This aptamer was derived from the double-stranded DNA binding site for E2F1 and is bound by the entire family of E2F transcription factors [16]. Since the E2F family regulates cell cycle progression, Mann and colleagues evaluated the ability of the E2F decoy aptamer termed Edifoligide, to limit cell proliferation and vein graft intimal hyperplasia [13]. Vein grafts were pre-treated with Edifoligide *ex vivo* before being implanted during graft bypass surgery. Phase I and II clinical studies suggested that aptamer-treated grafts had a lower incidence of graft stenosis and occlusion [13]. However, in two large randomized phase III clinical trials (Table 1), no improvements were observed in primary or secondary outcomes related to graft patency, stenosis and occlusion in coronary or peripheral vein grafts with Edifoligide treatment [17, 18]. This limited

clinical efficacy is believed to be a consequence of inefficient delivery of the DNA aptamer into cells in the various layers of the vein grafts.

Subsequently, clinical studies have been initiated to begin to evaluate a DNA decoy aptamer targeting nuclear factor kappa-B (NF-KB) for treatment of patients with atopic dermatitis and restenosis following percutaneous coronary intervention [19] while a DNA decoy aptamer to Signal Transducer and Activator of Transcription-3 (STAT3) for treatment of cancer patients (Table 1). In a phase 0 clinical trial, Sen and colleagues demonstrated that direct intratumoral delivery of the STAT3 DNA Decoy Aptamer into 30 patients with head and neck cancer led to a decrease in STAT3 target gene expression in the patients' tumors [20]. Current studies are underway to enhance the systemic delivery and tumor uptake of such STAT3 DNA Decoy aptamers including generating cyclic decoys and appending the STAT3 aptamer to cytosine guanine dinucleotide (CpG) DNA motifs to facilitate cancer cell internalization, as efficient intracellular delivery of these DNA decoy aptamers will most likely be essential for therapeutic efficacy [21].

The major challenge with the development of aptamers derived from nature has been and continues to be that their protein targets are intracellular. Thus, as with si/miRNA, ribozyme, antisense oligonucleotide, and Clustered Regulatory Interspaced Short Palindromic Repeats (CRISPR)-based therapeutics, efficient delivery of such natural aptamers into cells is critical. If improvements in gene transfer technology continue to occur, the delivery of expression cassettes for RNA aptamers that target intracellular proteins will attract increasing therapeutic interest as is suggested by the TAR decoy aptamer clinical studies underway. Given the increasing appreciation for the regulatory functions that intracellular RNA binding proteins play in human biology and disease, RNA decoy aptamers may prove very useful for the treatment of a wide range of clinical applications once this delivery challenge is overcome. Similarly, for short double-stranded DNA decoy aptamers, improvements in the delivery of synthetic oligonucleotides into cells are required for such DNA aptamers to fulfill their potential to inhibit the activities of the numerous therapeutically-relevant nucleic acid-binding proteins inside the cells of patients. In this regard, aptamers that bind cell surface receptors may prove to be effective targeting and intracellular delivery agents for other aptamers that recognize intracellular proteins [22].

3. CLINICAL STUDIES WITH APTAMERS DERIVED IN THE LABORATORY

The 1990 discovery by Tuerk and Gold [8] and Ellington and Szostak [1] that aptamers could be isolated from large libraries of randomized RNA or DNA by SELEX in the test tube, immediately changed the aptamer field in two fundamental ways (Fig. 2). First, it allowed scientists to isolate aptamers against protein targets that do not naturally bind nucleic acids including extracellular proteins [9, 10]. Second, it allowed for unnatural nucleotide chemistries to be incorporated into aptamers to increase their stability in biological fluids [11, 23–26]. Because of these properties, taken together with the challenge of delivering oligonucleotides into cells, eight of the nine aptamers generated in the laboratory that have been evaluated in the clinic target extracellular factors and are highly modified oligonucleotides (Table 1). Thus, they do not have to enter cells to exert their therapeutic effects.

4. DELIVERY INTO THE EYE

Groundbreaking work from investigators at NeXstar Pharmaceuticals led to the first aptamer that was generated by SELEX, to enter clinical studies [27]. This aptamer, which targets Vascular Endothelial Growth Factor$_{165}$ (VEGF$_{165}$) [28] is called pegaptanib sodium or Macugen. It is currently the only aptamer approved by the FDA. Following intravitreal injection, pegaptanib inhibits VEGF$_{165}$ activity and reduces neovascularization and slows vision loss in patients with age-related macular degeneration (AMD, Fig. 3) [29–31]. The initial phase I safety clinical trial for pegaptanib was published in 2002 [29], with phase II and definitive phase III clinical studies published in 2003 and 2004, respectively (Table 1) [30, 31]. Thus, in 12 years, *in vitro* generated aptamers were translated from concept to first in human studies and by 14 years, through definitive clinical studies. The phase III clinical results led the FDA to approve pegaptanib or Macugen for the treatment of AMD in 2004, which was a major milestone for the aptamer field. In 2006, however, the FDA approved an Fab derivative of the anti-VEGF antibody bevacizumab called ranibizumab or Lucentis, for the treatment of AMD as well. Clinical studies demonstrated that Lucentis not only slows the loss of vision in AMD patients but actually improves it following intravitreal injection [32]. It has been speculated that the improved clinical results with ranibizumab are due to pegaptanib being specific for the VEGF$_{165}$ isoform, whereas ranibizumab binds to and inhibits VEGF$_{165}$ and shorter isoforms of VEGF [27, 33]. Thus, the enhanced specificity of the VEGF aptamer may limit its clinical efficacy relative to a less specific VEGF inhibitor. Regardless, the clinical approval of Macugen demonstrated that an aptamer could address an unmet medical need and also validated neovascularization factors as important targets for the treatment of AMD.

With the initial success of aptamer-based therapy to treat eye pathology, two other aptamers, E10030 (Fovista) and Zimura entered clinical trials for the treatment age-related macular degeneration (Table 1) [27]. Fovista targets Platelet-Derived Growth Factor (PDGF) while Zimura targets Complement Factor 5 (C5). Encouraging phase IIb clinical trial results using Fovista in combination with protein-based VEGF inhibitors to treat AMD have been reported that indicate that the combination may be superior to treatment with VEGF inhibitors alone [27]. Unfortunately, phase III clinical studies conducted by Ophthotech demonstrated no improved clinical benefit of combining Fovista with Ranibizumab (an anti-VEGF antibody) compared to Ranibizumab alone [34]. Ophthotech is conducting ongoing clinical trials to evaluate Zimura in a form of AMD called Geographic Atrophy (GA). It remains to be seen if aptamer-based therapeutics will once again become front line treatment for a common ocular disease such as AMD. The fact that direct delivery into the eye (Fig. 3) limits the amount of aptamer required for therapeutic efficacy and also eliminates any challenges associated with systemic delivery makes the development of additional therapeutic aptamers for ocular or other diseases associated with well-defined, self-contained, and easily accessible tissues particularly attractive.

5. SYSTEMIC DELIVERY

The first aptamer to be evaluated in humans following systemic administration is an aptamer that targets coagulation factor IXa. This aptamer, originally identified in our laboratory [35],

was licensed to Regado Biosciences for clinical development. A fully optimized version of the aptamer, termed RB006 or pegnivacogin, is formulated with a 40 kDa polyethylene glycol (PEG) to increase the aptamer's circulating half-life (Table 1). In a phase I clinical study, intravenous administration of RB006 was shown to be a rapid onset and dose-dependent anticoagulant in healthy volunteers with a median duration of effect of up to 30 hours [36]. Because we had observed that potent inhibition of factor IXa activity with the aptamer could result in increased bleeding in animals [37], we invented a strategy to rapidly reverse the activity of aptamers using antidote oligonucleotides [35, 37, 38]. Administration of such an antidote oligonucleotide termed RB007 to patients who had been given the RB006 aptamer resulted in rapid and durable neutralization of the pharmacodynamics effect of the aptamer within 1 to 5 minutes of antidote administration [36]. This result was particularly significant for the aptamer therapeutics field because it highlighted a distinguishing feature of aptamer-based medicines compared to antibody-based drugs; aptamer activity can be rapidly controlled with antidotes making them potentially safer therapeutic agents for clinical applications where target inhibition can result in severe and potentially life-threatening side effects such as bleeding in the case of anticoagulant therapy. A subsequent phase I study of pegnivacogin demonstrated that aptamers can also be administered by subcutaneous injection with a resulting calculated mean residence time of nearly 10 days [39].

To begin to evaluate the potential advantage of being able to rapidly reverse the activity of pegnivacogin, Povsic and colleagues performed a phase IIb clinical study comparing pegnivacogin and its antidote to heparin in patients with Acute Coronary Syndrome (ACS) undergoing cardiac catheterization (Fig. 4) [40]. Results from this study indicate that intravenous administration of the factor IXa aptamer was able to rapidly and adequately anticoagulate patients to allow for cardiac catheterization and reduce ischemic events compared to heparin treatment. Moreover, administration of the antidote rapidly restored normal hemostasis and resulted in numerically fewer patients experiencing significant bleeding compared to heparin treated patients [40]. Results from this phase IIb study indicated that an adequately powered phase III clinical trial of pegnivacogin and its antidote in patients who require rapid onset anticoagulation was warranted.

A phase III study designed to enroll 13,200 patients undergoing Percutaneous Coronary Intervention (PCI) was initiated to compare pegnivacogin to bivalarudin for anticoagulation in this common clinical setting. After enrolling 25% of the intended patients (3,232 patients randomized 1:1 between bivalarudin and RB006), the trial was halted because 10 patients experienced severe allergic reactions immediately after receiving the pegylated aptamer [41]. Subsequent analyses demonstrated that all of these patients had high levels of pre-existing antibodies against PEG [42, 43] but did not have any antibodies that recognized the RNA aptamer portion of the drug. Clinical results from this truncated study did demonstrate that the factor IXa aptamer was able to rapidly and adequately anticoagulate over 1,600 patients to perform PCI and limit ischemic events as well as the standard of care. However, because the trial was stopped early, it was not possible to determine if the aptamer could limit thrombotic events more effectively than bivalarudin. Nevertheless, the study demonstrated that RNA aptamer-antidote pairs represent rapid-onset and rapidly reversible clinical agents that may prove useful for a number of clinical settings [43, 44]. In addition the observed

allergic reactions indicate that alternative, non-PEG, formulations should be considered for improving aptamer PK properties, at least for indications requiring large amounts of rapidly administered drug, or alternatively, the presence of anti-PEG antibodies should be determined prior to treatment and patients with such pre-existing antibodies be excluded to avoid rare allergic events.

A second aptamer, originally developed by Archemix Corporation, has been studied for the treatment of thrombosis. ARC1779, a DNA/RNA aptamer that targets von Willebrand factor has been studied as an anti-thrombotic agent and to treat thrombocytopenia in patients with Thrombotic Thrombocytopenic Purpura (TTP). It is formulated with a 20 kDa PEG. In evaluating its effect in preventing thrombosis, ARC1779 inhibited von Willebrand-dependent platelet activity and in patients undergoing carotid endarterectomy. Aptamer-treated patients had fewer embolic events post-operatively compared to placebo controls [45, 46]. In treating patients with TTP, ARC1779 revealed a dose-dependent relationship in platelet function inhibition as well as recovery of platelet count in phase II trials [47–50]. Currently, the future clinical development of this interesting vWF aptamer is unclear. However, it was reported that one patient out of 47 experienced a moderately severe hypersensitivity reaction at the injection site following treatment with the pegylated vWF aptamer. It is unclear if this reaction was directed toward the PEG portion of ARC1779 and if this hypersensitivity has hindered its clinical development [45].

Four additional aptamers have been evaluated in the clinic. Three are spiegelmers or L-RNA enantiomers of naturally occurring D-RNA. The chiral configuration of spiegelmer, which means "mirror image" in German, renders them highly resistant to exonuclease degradation [51]. NOXXON Pharma has pioneered the highly innovative development of spiegelmers and moved three of these into clinical trials [52]. The NOX-A12 (olaptesed pegol) spiegelmer targets Stromal Cell-Derived Factor 1 (SDF-1) and is being developed for use in stem cell transplantation. NOX-E36 (emapticap pegol), which targets cytokine Monocyte Chemoattractant Protein 1 (MCP-1), is being evaluated for the treatment of chronic inflammatory disease, type-2 diabetes mellitus, Systemic Lupus Erythmatosis (SLE) and in stem cell transplantation. A recent phase 2 clinical trial with NOX-E36 demonstrated that the Spiegelmer was able to significantly reduce albuminuria in type 2 diabetic patients and reduce HbA1c levels as well [53]. Spiegelmer NOX-H94 (lexaptepid pegol) targets hepcidin and is currently under evaluation for treatment of anemia. All three of these Spiegelmers appear to be well tolerated and are prime candidates for additional clinical studies [52]. Finally, AS1411 is a DNA G-quartet aptamer targeting nucleolin that is being clinically evaluated for the treatment of a number of cancers including acute myeloid leukemia (AML) [54] and metastatic Renal Cell Carcinoma (RCC) [55]. Results from a phase II trial in RCC patients demonstrated that AS1411 has minimal effect on most RCC patients but that rare individuals can experience dramatic and durable responses following therapy [55]. Thus personalize medicine efforts appear to be warranted to determine which subset of RCC patients may significantly benefit from AS1411 therapy.

CONCLUSION

We predict that the next two to three years will determine if *in vitro* generated aptamer-based therapeutics will re-emerge as a valuable therapeutic approach. In particular, C5 aptamer is currently being evaluated in phase II and III clinical studies in a therapeutic niche that seems particularly well suited for aptamer-based drugs, both in intra-ocular indications where local delivery is a major advantage.

However, we also believe that additional advances in the aptamer field will uncover additional clinical niches where aptamers may prove particularly useful. As discussed above, the invention of SELEX [1, 8] and the ability to incorporate modified nucleotides into aptamers were major advances for the therapeutic aptamer field [10, 23–25]. Recent advances in both the SELEX process as well as the chemical repertoire that can be incorporated into aptamers promises to herald a new era for the therapeutic aptamer field. Work by scientists at SomaLogic has recently led to the development of aptamers with additional chemical functionalities such as the addition of a benzyl or other groups at the 5-position of uridine. Selection utilizing such novel libraries has allowed for the generation of aptamers that bind proteins in previously unattainable and potentially very therapeutically useful ways [9, 11]. Hirota and colleagues recently reported that such a modified aptamer against interleukin-6 (IL-6) can inhibit the induction of arthritis in primates [56]. Thus we anticipate that these new classes of therapeutic aptamers will soon be evaluated in first-in-man studies.

Work by several groups including our own has demonstrated that *in vitro* selection methods can be performed to simultaneously identify aptamers against entire proteomes [57, 58] or cell surface targets [59, 60]. Moreover, selection for functions other than binding has now been described such as the identification of modified RNA or DNA molecules that efficiently internalize into cells [61] or even home to tumors *in vivo* [62, 63]. The ability to isolate such RNA or DNA molecules has led to much speculation that they may prove useful for the delivery of therapeutic agents [64, 65]. Initial results from these studies are encouraging in that they clearly demonstrate that these nucleic acid-based delivery agents can enter into cells and localize to the endosomal compartment efficiently. However, additional work remains to be performed to enhance the escape of the delivered therapeutic agents from this intracellular compartment. In addition to delivering cargoes to cells, aptamers have also been described that can deliver signals to cells by recognizing and cross-linking cell surface receptors [66–68]. Aptamers can also be conjugated to antineoplastic drugs that have significant systemic toxicity. These aptamer-conjugated cytotoxic drugs inhibited prostate cancer *in vivo* without systemic toxicity [69]. While beyond the scope of this manuscript, an excellent review on this has recently been published [70].

Thus, aptamer-based agonists can now be envisioned that can function as signaling molecules such as growth factors or cytokines. We anticipate that the flexibility of the *in vitro* selection process, taken together with the vastness of the nucleic acid libraries that can be explored and high through-put sequencing methods, will lead to additional innovative advances to further broaden the horizon of the therapeutic aptamer field in the coming years. Finally, as clinically amenable gene transfer technologies reach the market, we anticipate

that a renaissance in the field of therapeutic RNA aptamers derived from nature will emerge. If any of the aptamers currently being evaluated clinically prove to be useful therapeutics, it would obviously facilitate such innovation by encouraging increased investment and interest in the therapeutic aptamer field in general.

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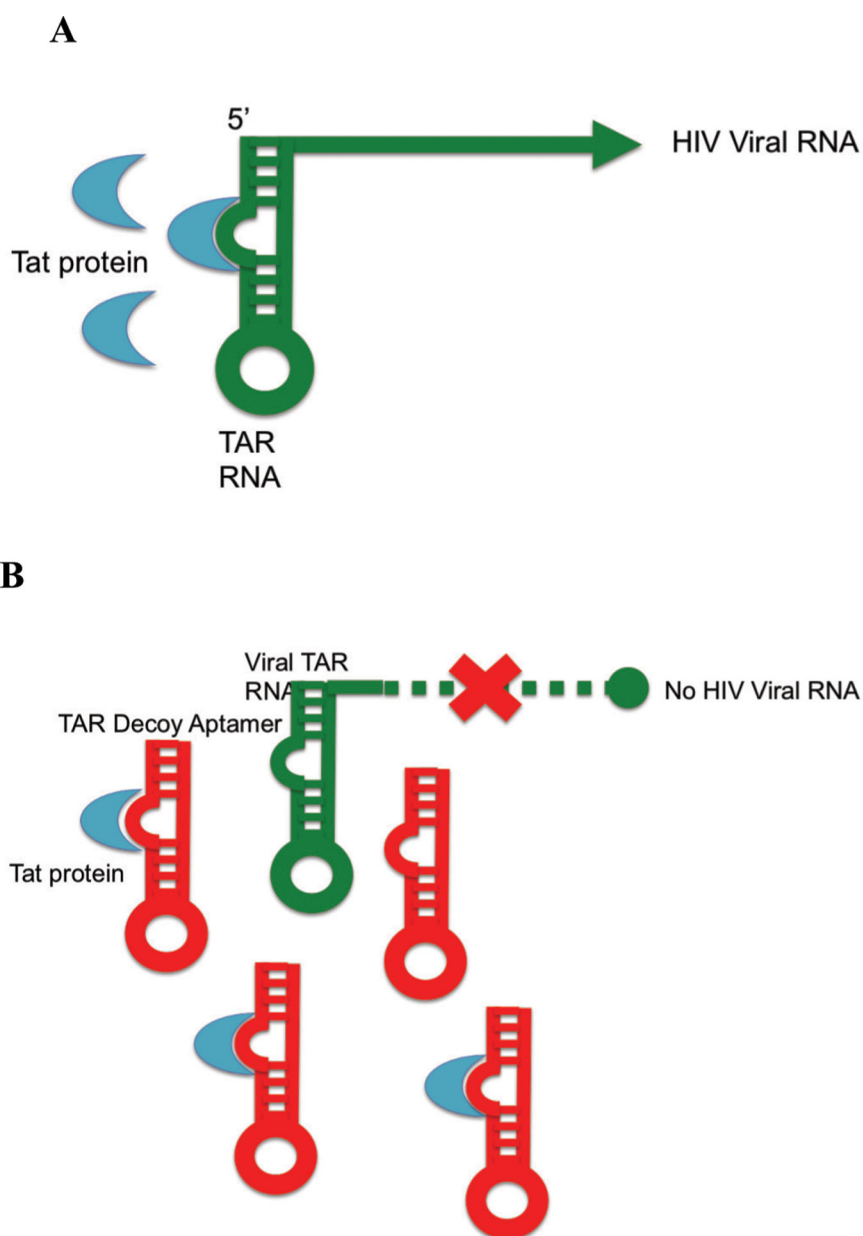
Fig. (1).
A: HIV evolution and use of an RNA aptamer as a decoy. A: HIV evolved an RNA aptamer termed Trans-Activator Response (TAR) element to control its gene expression and replication. The viral trans-activator of transcription (tat) protein binds to TAR at the 5' end of all viral RNAs and together with cellular factors activates viral gene expression and replication. **B:** Inhibition of HIV replication by the first described therapeutic aptamer. TAR decoy RNA aptamers bind the tat protein, preventing them from binding the viral TAR sequence, thereby inhibiting tat-mediated activation of HIV gene expression and replication [4, 14].
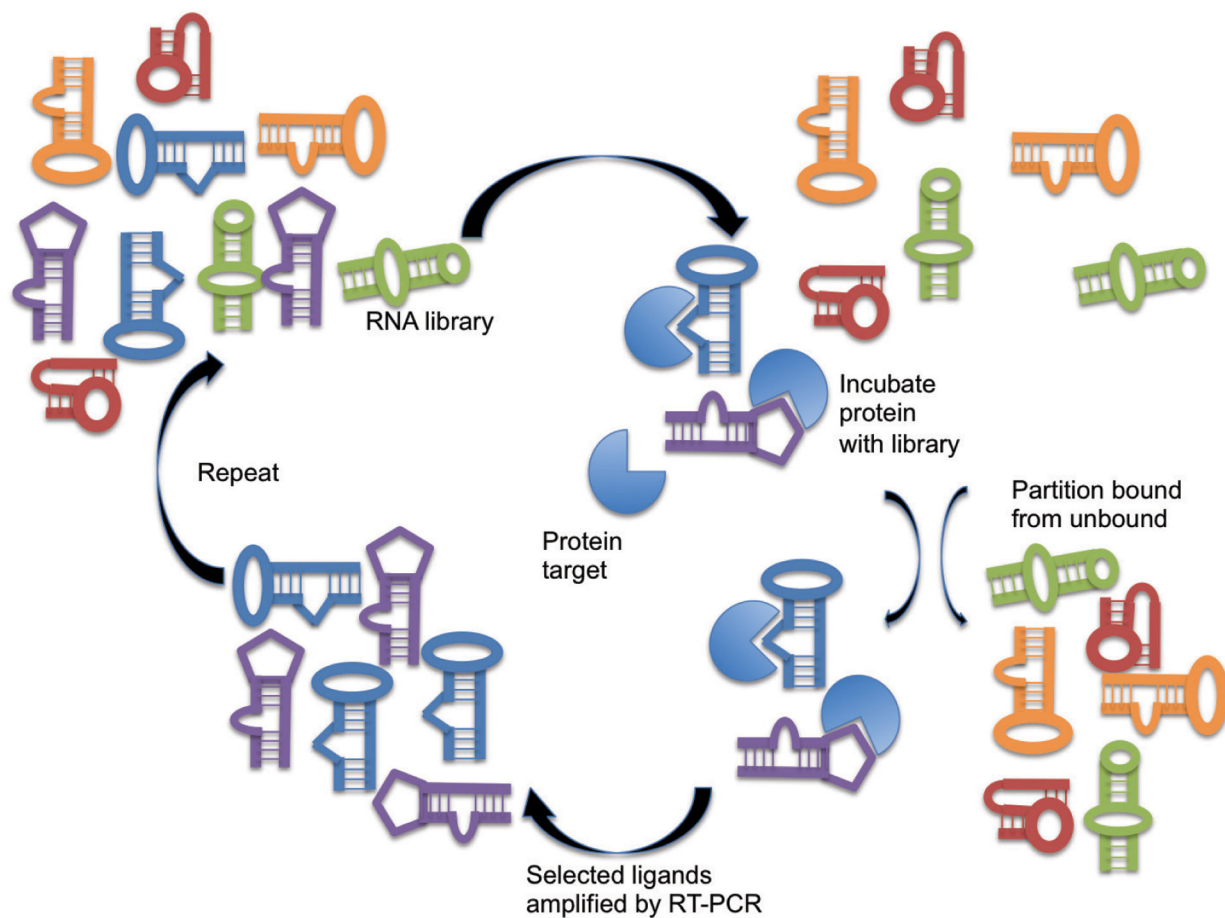
Fig. (2).

In Vitro Evolution of Aptamers *via* SELEX. Systematic Evolution of Ligands by EXponential enrichment (SELEX) is an iterative process that exposes a vast randomized library of RNA/DNA molecules of different structures to a target protein, partitions the RNA/DNA molecules that bind to the target protein from those that do not and amplifies those RNA/DNA molecules by RT-PCR [1].

A

B
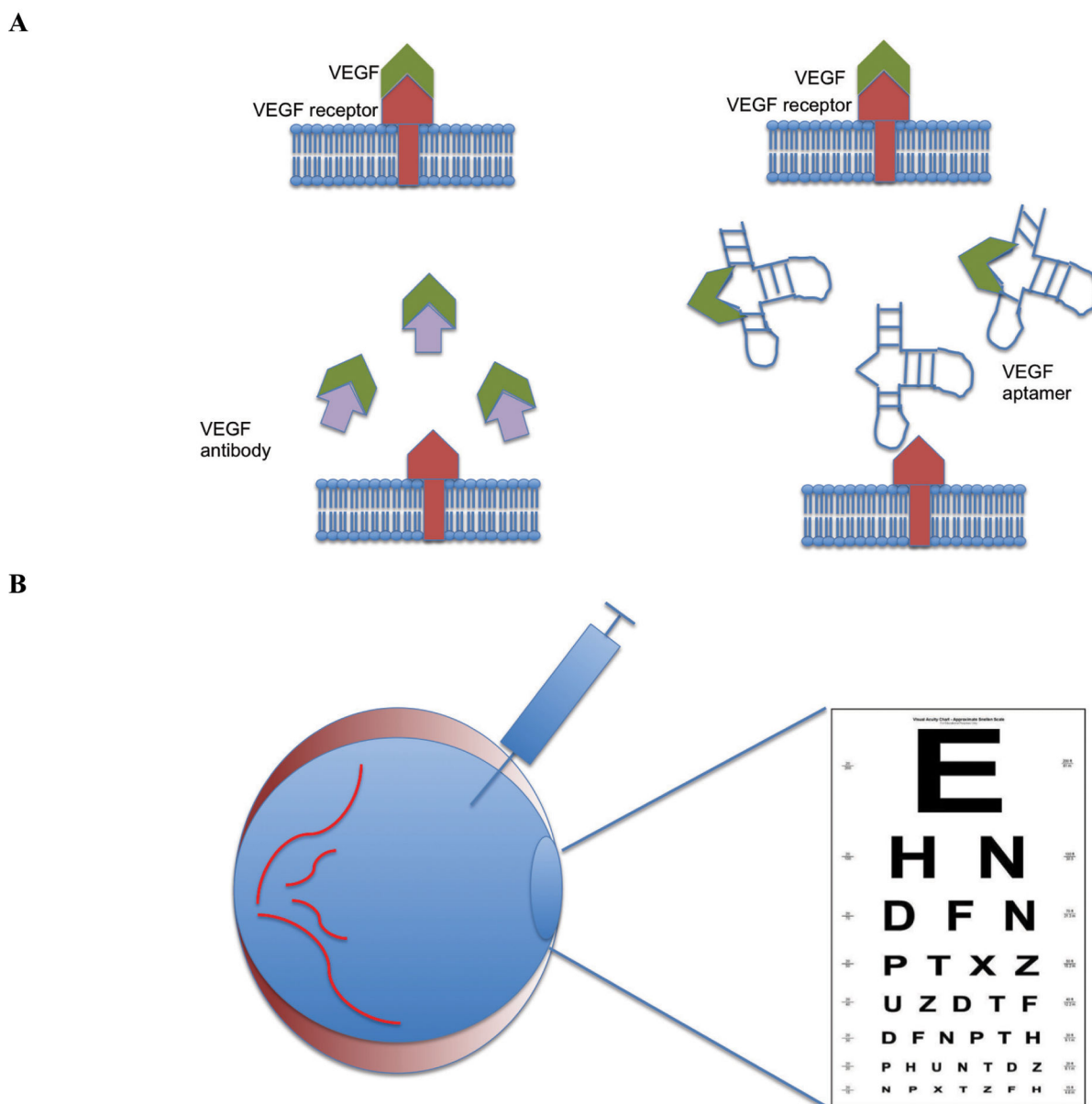
Fig. (3).

Treating Age-Related Macular Degeneration (AMD) with an aptamer. **A**: Macugen or VEGF antibodies target Vascular Endothelial Growth Factor (VEGF) that induces neovascularization and vision loss in AMD. **B**: Aptamer or antibody-based VEGF inhibitors are injected into the vitreous space to bind VEGF in the eye, prevent it from binding to its target receptor and thereby inhibit neovascularization, effectively treating AMD.

Fig. (4).
Aptamer-mediated anticoagulation during percutaneous coronary intervention and antidote-mediated control of factor IXa aptamer function. Utilizing Watson-Crick base-pairing rules, an antidote oligonucleotide (RB007) can be designed to interact with a portion of the factor IXa aptamer (RB006). Upon binding and unwinding the aptamer, the antidote converts the aptamer's structure from a functional one to an inactive conformation thereby reversing the aptamer's ability to inhibit factor IXa activity.

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Table 1.

Aptamers that have been translated into clinical studies.

Aptamer	Company	Target	Origin	DNA/RNA	Indication(s)	Phase(s)	Refs.
Edifoligide (E2F Decoy)	Academic Institution Corgentech	E2F	Nature	DNA	Bypass graft surgery Restenosis	I, II and III	[13,18]
RRE Decoy	Academic Institution	rev	Nature	RNA	Human Immunodeficiency Virus-1 (HIV-1)	I/II	[12]
TAR Decoy	Benitec Biopharma	tat	Nature	RNA	Acquired immunodeficiency syndrome (AIDS)-related lymphoma	I/II	[14]
NF-kappaB Decoy	Academic Institution	Nuclear factor kappa B (NF-kB)	Nature	DNA	Atopic dermatitis Restenosis	I/II	[19]
STAT-3 Decoy	Ophthotech	Signal Transducer and Activator of Transcription (STAT-3)	Nature	DNA	Head and Neck Cancer	0	[20]
Macugen (Pegaptanib)	Nexstar; Ophthotech	VEGF	SELEX	RNA	Age-related macular degeneration	I, II & III Approved	[27, 29, 30]
Fovista (EI0030)	Ophthotech	PDGF	SELEX	DNA/RNA	Age-related macular degeneration	I, II & III	[27]
Zimura	Ophthotech	Complement Factor C5	SELEX	DNA/RNA	Dry age-related macular degeneration	I, II & III	[27]
RB006 (Pegnivacogin)	Regado	Coagulation Factor IXa	SELEX	RNA	Acute Coronary Syndrome, Percutaneous Coronary Intervention	I, II & III	[36,40,41, 43]
ARC1779	Archemix	von Willebrand factor	SELEX	DNA/RNA	Thrombotic microangiopathy; Thrombotic thrombocytopenic purpura (TTP)Acute coronary syndrome; vWD; CEA	I & II	[45,47–50]
NOX-A12 (olaptesed pegol)	Noxxon	Stromal cell-derived factor 1 (SDF-1)	SELEX	RNA	Hematopoietic stem cell transplantation	I & IIa	[52]
NOX-E36 (emapticap pegol),	Noxxon	CCL2 (Monocyte Chemoattractant Protein 1.MCP-1)	SELEX	RNA	Chronic inflammatory diseases; type 2 diabetes mellitus; systemic lupus erythematosis Autologous stem cell transplantation	I & IIa	[52, 53]
NOX-H94 (lexaptepid pegol)	Noxxon	Hepcidin	SELEX	RNA	Anemia of chronic disease; inflammation	I & IIa	[52]
AS1411	Antisoma	Nucleolin	In Vitro Cell Screen	DNA	Acute myeloid leukemia and Metastatic Renal Cell Carcinoma	I & II	[54, 55]