Aptamers (Aps), as short single-strand nucleic acids (DNA or RNA), can bind to their specific molecular targets with the high affinity and specificity through their unique three or two dimensional (3D/2D) structures. Aps are considered as great alternatives to the antibodies, in large part because of offering flexible conformations, high stability, ease of modifications, low/no immunogenicity, and cost-effective synthesis.1-3 Aps can act as the therapeutic agents per se, or as the targeting tools for enhancing the effects of various remedies and agents. Nowadays, a number of Aps with the ability of binding to the specific cancer molecular markers (CMMs) have been selected using the systematic evolution of ligands by exponential enrichment (SELEX) process and synthesized artificially. Aps with specificity to the tumor-associated proteins have widely been applied in the molecular diagnosis and therapy of cancer.1

Further, the exclusive features of Aps make them robust tools for enhancing the effects of various remedies and
establishment of different therapeutic systems, including Ap chimera, bispecific Ap and Ap-decorated multimodal nanosystems as shown in Fig. 1.

Noteworthy features of Ap-based multifunctional systems (the so-called aptamedicine) have been the driving force of many researches, resulting in the development of various therapeutic modalities against various malignancies. It is envisioned that Ap-based advanced pharmaceuticals could be translated into potential clinical applications against various detrimental diseases, including different types of cancers. In fact, the specific conformation of Ap allows them to act as the protein antagonist, which may inhibit the interaction of the target protein with other molecular entities. Some Ap were shown to possess the anticancer ability and reduce the proliferation of cancer cells by the suppression of specific target proteins. To date, several Ap have been developed against important clinical targets, including platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) (Table 1). Of these, pegaptanib (Macugen®), which is an RNA Ap specific to VEGF, is the first nucleic acid Ap approved by the U.S. FDA in 2004 and used for the neovascular age-related macular degeneration (nAMD) disease. Further, other Ap have been examined in different phases of clinical trials for diagnosis and treatment of cancer. For examples, it has recently been demonstrated that the Sgc8 single-stranded DNA Ap has a high accumulation in the PTK7-positive tumors and is currently in the early-phase I clinical trial (ID: NCT03385148) to evaluate its diagnostic value in colorectal cancer. Also, PEGylated NOX-A12 (Olaptesed pegol), specifically bind to the chemokine (C-X-C motif) ligand 12 (CXCL12). It is in the phase IIa in multiple myeloma which validates its safety profile without any additional toxicity.

Aps-based drug delivery systems (DDSs) have recently been developed for the targeted therapy of various malignancies. These advanced systems can specifically target the intended cells through specific affinity of Ap to designated oncomarkers, and therefore, reduce the nonspecific cytotoxic impacts of chemotherapy agents that can non-specifically affect both cancerous and healthy cells/tissues. Various Ap-based nanosystems/multifunctional theranostics have successfully been designed for targeted delivery of a wide variety of anticancer drugs/gens owing to the surface functionalization of nanoscaled DDSs with Ap. Additionally, modification of Ap with various chemical groups allows them to be further conjugated with other molecules (Ap-X), including chemotherapy agents, other Ap, siRNAs/miRNAs, antisense oligonucleotides (ASOs), Abs, toxins, ribozymes, DNAzymes, peptides, and imaging agents (so-called Ap chimera). In these hybrid systems (i.e. Ap-X nanoconjugates), the chimerization of an Ap with another Ap produces bispecific Ap, which can be further functionalized to engineer new multifunctional Ap-based structures. In Ap-drug nanoconjugates, some anthracyclines drugs such as doxorubicin (DOX) can be non-covalently intercalated to the GC rich double-strand region of Aps without affecting the Ap conformation. The small size of the Ap-drug nanoconjugates facilitates its penetration into the tumor mass and accumulation in the tumor microenvironment (TME).

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**Fig. 1.** Schematic representation of various aptamer (Ap)-based therapeutic systems.
Aptamers for cancer therapy in clinical trials

<table>
<thead>
<tr>
<th>Aptamer drug</th>
<th>Target</th>
<th>Disease</th>
<th>Type of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegaptanib (Macugen&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>VEGF</td>
<td>Age-related macular degeneration Retinal vein occlusion Diabetic macular edema</td>
<td>Phase IV, recruiting (NCT01573572)</td>
</tr>
<tr>
<td>68Ga-Sgc8</td>
<td>PTK7</td>
<td>Colorectal cancer</td>
<td>Early-phase I (NCT03385148)</td>
</tr>
<tr>
<td>AS1411 (AGRO-100)</td>
<td>NF-kB, BCL-2</td>
<td>AML Advanced solid tumors Metastatic renal cell carcinoma</td>
<td>Phase II completed (NCT01034410)</td>
</tr>
<tr>
<td>NOX-A12 (Speigelmer&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>CXCL12</td>
<td>Multiple myelomas Chronic lymphocytic Leukemia metastatic colorectal cancer</td>
<td>Phase II, completed (NCT01521533) Phase II, completed (NCT01486797) Phase I (NCT03168139)</td>
</tr>
<tr>
<td>ARC1779</td>
<td>C5</td>
<td>Intracranial embolism cerebral Thromboembolism carotid stenosis</td>
<td>Phase II, terminated (NCT00742612)</td>
</tr>
<tr>
<td>NOX-E36</td>
<td>Chemokine (C-C motif) ligand 2</td>
<td>Type 2 diabetes mellitus Mellitus albuminuria</td>
<td>Phase II, completed (NCT01547897)</td>
</tr>
<tr>
<td>E10030</td>
<td>PDGF</td>
<td>Macular degeneration</td>
<td>Phase I, completed (NCT005691400)</td>
</tr>
<tr>
<td>ARC19499</td>
<td>TFPI</td>
<td>Hemophilia</td>
<td>Phase I, terminated (NCT01191372)</td>
</tr>
<tr>
<td>REG1</td>
<td>Coronary artery disease</td>
<td></td>
<td>Phase 2, completed (NCT00715455)</td>
</tr>
</tbody>
</table>


antisense chimera systems have been developed in order to specifically suppress the overexpressed genes involved in the initiation, progression, and chemoresistance of malignancy.19-22 Bispecific Aps have been reported to provide enhanced clinical anticancer outcomes.23 Engineering bispecific Aps with antigustumor immunity impacts, through the activation of immune system effector cells (e.g., natural killer cells, dendritic cells, and effector T lymphocytes) is deemed to result in an Ap-mediated antitumor immunity.24 This can be achieved by recruiting immune system effector cells to the target tumor cells through bispecific Aps, which can concurrently bind to the specific receptors on the surface of tumor and the immune system effector cells.25 Moreover, designing appropriate bi/multivalent Aps specific to the T cell receptors can lead to the co-stimulation of T cells and enhanced tumor immunogenicity.26,27 This latter approach may revolutionize the cell therapy strategies.

Bispecific Aps, which can synchronously bind to the different type of CMMs, are deemed to provide promising strategy to overcome the tumor complexity and heterogeneity. It should be noted that the tumor heterogeneity is often referred to as the differences between same types of tumors in different patients and between cancer cells within a particular tumor. Such hallmarks, together with other traits of cancer cells (e.g., genetics and epigenetics changes) might reduce the therapeutic impacts of anticancer agents and hence result in the different responses, even in the same patients.28 In this context, the coherency of drugs/genes to such structures provides a powerful therapeutic platform which can be further evolved towards "personalized nanomedicines" by means of bispecific Ap-based therapeutics. It appears that the personalized medicine, informed by a molecular understanding of the disease, might provide a great opportunity for much more effective preventive and therapeutic interventions. Personalized medicine uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease.29 With the progress in cancer genomics (in particular oncogenomics), epigenetics and metabolomics using high-throughput sequencing methods, it seems that such specific bi/multi-functional Ap structures targeting different CMMs provide the maximal therapeutic impacts in an individual patient.

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There is none to be declared.

**Competing interests**
No competing interests to be disclosed.

**Authors contribution**
SV, ME, JB and YO conceptualized the study. SV and ME drafted the manuscript. JB reviewed the manuscript. YO finalized the manuscript.

**References**