Vandghanooni S., et al., ***BioImpacts,*** 2019, 9(2), 67-70
doi: 10.15171/bi.2019.09
https://bi.tbzmed.ac.ir/

Aptamedicine: a new treatment modality in personalized cancer therapy

Somayeh Vandghanooni[1†], Morteza Eskandani[1†], Jaleh Barar[1,2], Yadollah Omidi[1,2*]

[1] Research Center for Pharmaceutical Nanotechnology, Biomedicine Institute, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Department of Pharmaceutics, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

Article Info

Article Type:
Editorial

Article History:
Received: 5 Sep. 2018
Accepted: 15 Nov. 2018
ePublished: 30 Nov. 2018

Keywords:
Aptamer
Aptamedicine
Nanomedicine
Drug delivery systems
Personalized medicine
Cancer therapy

Summary

Aptamers (Aps) are short single-strand nucleic acids exhibiting unique 3D structure which facilitate their targeting potential against various cancer molecular markers (CMMs). Such features of Aps not only make them as suitable homing agents in targeted drug delivery systems (DDSs) but also candidate them as macromolecules that inhibit the interaction of the target ligand with other proteins. On the other hand, the conjugation of Aps with another therapeutic molecule such as antisense oligonucleotides (ASOs), siRNAs/miRNAs, Aps, toxins, chemotherapeutic agents, DNAzymes/Ribozymes provides hopeful strategy to eradicate the malignancies and overcome the off-target unwanted side effects. Such prominent features of Aps make them a promising treatment modality to overcome the tumor complexity and heterogeneity, which can be consequently applied for personalized therapy of cancer by using bispecific Ap-based therapeutics.

Authors' Biosketch

Dr. Somayeh Vandghanooni received her B.Sc. degree in Biology (2005), M.Sc. degree in Genetics (2007) from the University of Tabriz (Tabriz, Iran) and Ph.D. degree in Medical Nanotechnology (2018) from Tabriz University of Medical Science (Tabriz, Iran) under supervision of Prof. Omidi and Prof. Barar. Her Ph.D. thesis was about engineering of aptamer-targeted drug delivery system for chemo and gene therapy of ovarian cancer. She is now working on the cell-based therapy for cancer.

Dr. Morteza Eskandani obtained his B.Sc. in Zoology (2004) from the University of Golestan, M.Sc. in Biochemistry (2007) from the University of Guilan and Ph.D. degree in Pharmaceutical Nanotechnology (2015) from Tabriz University of Medical Science (Tabriz, Iran). He is an assistant professor at the Research Center for Pharmaceutical Sciences, Tabriz University of Medical Science (Tabriz, Iran). His main research interests are molecular targeting of different types of solid tumors using nanoscaled drug delivery systems.

Professor Jaleh Barar obtained her Ph.D. degree (2004) in Pharmaceutical Cell Biology from Cardiff University, UK. Since then, she has worked at the Faculty of Pharmacy, Tabriz University of Medical Sciences (Iran), and the Perelman School of Medicine at the University of Pennsylvania (USA), teaching and conducting researches on various aspects of molecular pharmaceutics. Her main research interest is cancer drug delivery and targeting through exploitation of advanced novel multifunctional nanosystems for simultaneous diagnosis and therapy in different malignancies.

Professor Yadollah Omidi obtained his Pharm.D. from Tabriz University of Medical Sciences (Iran) and Ph.D. from Cardiff University (UK). He is a Professor of Pharmaceutical and Biomedical Sciences at TUOMS Faculty of Pharmacy, working on the development of advanced multifunctional nanobiosystems used for drug delivery and targeting, biosensing and tissue engineering. He has worked in Cardiff University and the University of Pennsylvania. Since 2004, Prof. Omidi has published over 200 papers and 18 book chapters, supervised and trained over 100 postgraduate students/researchers and founded several educational and research programs and infrastructures nationally. His researches in the field of pharmaceutical nanobiotechnology have been awarded with several national prizes.

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/or no immunogenicity, and cost-effective synthesis.[1,2] Aps can act as the therapeutic agents per se, or as the targeting 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.[3]

Further, the exclusive features of Aps make them robust tools for enhancing the effects of various remedies and

***Corresponding author:** Yadollah Omidi, Email: yomidi@tbzmed.ac.ir
† These authors contributed equally to this work and should be considered as the first co-authors.

establishment of different therapeutic systems, including Ap chimera, bispecific Aps 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 to be translated into potential clinical applications against various detrimental diseases, including different types of cancers. In fact, the specific conformation of Aps allows them to act as the protein antagonist, which may inhibit the interaction of the target protein with other molecular entities. Some Aps were shown to possess the anticancer ability and reduce the proliferation of cancer cells by the suppression of specific target proteins. To date, several Aps have been developed against important clinical targets, including platelet-derived growth factor (PDGF)[4] and vascular endothelial growth factor (VEGF)[5] (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.[6] Further, other Aps 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.[7] 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.[8]

Aps-based drug delivery systems (DDSs) have recently been developed for the targeted therapy of various malignancies.[9-11] These advanced systems can specifically target the intended cells through specific affinity of Aps to designated oncomarkers, and therefore, reduce the nonspecific cytotoxic impacts of chemotherapy agents that can non-specifically affect both cancerous and healthy cells/tissues.[12] Various Ap-based nanosystems/multifunctional theranostics have successfully been designed for targeted delivery of a wide variety of anticancer drugs/genes owing to the surface functionalization of nanoscaled DDSs with Aps.[13] Additionally, modification of Aps with various chemical groups allows them to be further conjugated with other molecules (Ap-X), including chemotherapy agents, other Aps, siRNAs/miRNAs, antisense oligonucleotides (ASOs), Abs, toxins, ribozymes, DNAzymes, peptides, and imaging agents (so-called Ap chimera).[14] In these hybrid systems (i.e. Ap-X nanoconjugates), the chimerization of an Ap with another Ap produces bispecific Aps, which can be further functionalized to engineer new multifunctional Ap-based structures.[15] 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.[16] The small size of the Ap-drug nanoconjugates facilitates its penetration into the tumor mass and accumulation in the tumor microenvironment (TME).[17,18] Ap-siRNA/or

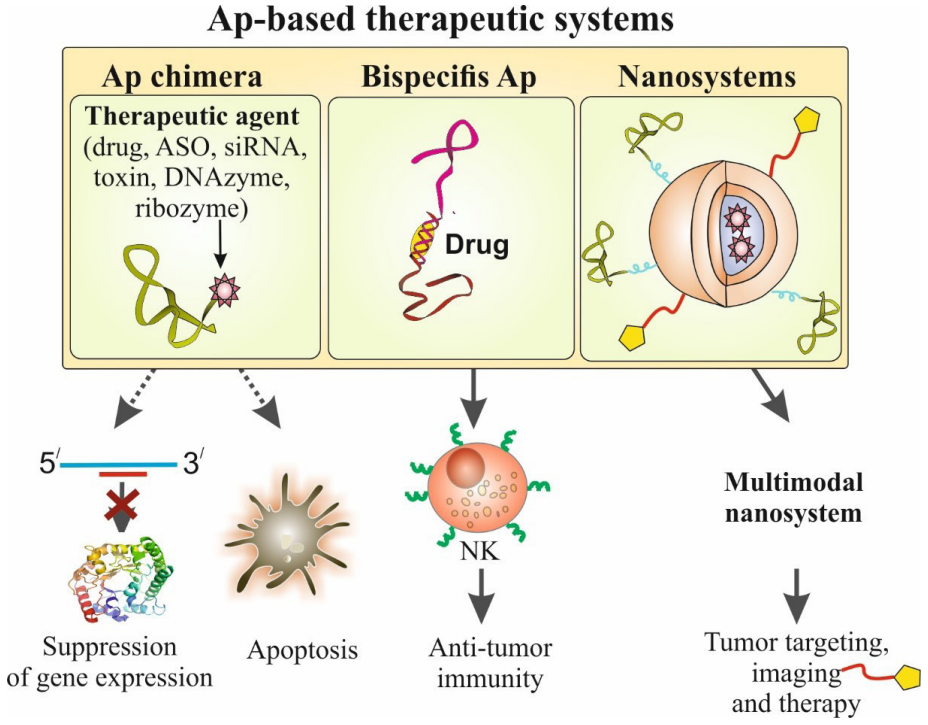

Fig. 1. Schematic representation of various aptamer (Ap)-based therapeutic systems.

Table 1. Aptamers for cancer therapy in clinical trials

Aptamer drug	Target	Disease	Type of study (ClinicalTrials.gov Identifier)
Pegaptanib (Macugen®)	VEGF	Age-related macular degeneration Retinal vein occlusion Diabetic macular edema	Phase IV, recruiting (NCT01573572)
68Ga-Sgc8	PTK7	Colorectal cancer	Early-phase I (NCT03385148)
AS1411 (AGRO-100)	NF-κB, BCL-2	AML Advanced solid tumors Metastatic renal cell carcinoma	Phase II completed (NCT01034410) Phase 1, completed (NCT00881244) Phase 2, unknown (NCT00740441)
NOX-A12 (Speigelmer®)	CXCL12	Multiple myelomas Chronic lymphocytic Leukemia metastatic colorectal cancer	Phase II, completed (NCT01521533) Phase II, completed (NCT01486797) Phase I (NCT03168139)
ARC1779	C5	Intracranial embolism cerebral Thromboembolism carotid stenosis	Phase II, terminated (NCT00742612)
NOX-E36	Chemokine (C-C motif) ligand 2	Type 2 diabetes mellitus *Mellitus albuminuria*	Phase II, completed (NCT01547897)
E10030	PDGF	Macular degeneration	Phase I, completed (NCT005691400
ARC19499	TFPI	Hemophilia	Phase 1, terminated (NCT01191372)
REG1		Coronary artery disease	Phase 2, completed (NCT00715455)

VEGF: Vascular endothelial growth factor, PTK7: Protein tyrosine kinase-7, NF-κB: Nuclear factor kappa light chain enhancer of activated B cells, CXCL12: Chemokine (C-X-C motif) ligand 12, C5: Complement component 5, PDGF: Platelet-derived growth factor, TFPI: Tissue factor pathway inhibitor.

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 antitumor 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 possibility 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 Aps structures targeting different CMMs provide the maximal therapeutic impacts in an individual patient.

Funding sources

This work is a part of a Ph.D. thesis (No: 94/009/155/2) supported by the Research Center for Pharmaceutical Nanotechnology (grant No: 94009), Biomedicine Institute, Tabriz University of Medical Sciences.

Ethical statement

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

1. Morita Y, Leslie M, Kameyama H, Volk DE, Tanaka T. Aptamer Therapeutics in Cancer: Current and Future. *Cancers (Basel)* **2018**; 10. doi:10.3390/cancers10030080
2. Lee JF, Stovall GM, Ellington AD. Aptamer therapeutics advance. *Curr Opin Chem Biol* **2006**; 10: 282-9. doi:10.1016/j.cbpa.2006.03.015
3. Mercier MC, Dontenwill M, Choulier L. Selection of Nucleic Acid Aptamers Targeting Tumor Cell-Surface Protein Biomarkers. *Cancers (Basel)* **2017**; 9. doi:10.3390/cancers9060069
4. Green LS, Jellinek D, Jenison R, Ostman A, Heldin CH, Janjic N. Inhibitory DNA ligands to platelet-derived growth factor B-chain.

Biochemistry **1996**; 35: 14413-24. doi:10.1021/bi961544+
5. Green LS, Jellinek D, Bell C, Beebe LA, Feistner BD, Gill SC, et al. Nuclease-resistant nucleic acid ligands to vascular permeability factor/vascular endothelial growth factor. *Chem Biol* **1995**; 2: 683-95.
6. Zhou B, Wang B. Pegaptanib for the treatment of age-related macular degeneration. *Exp Eye Res* **2006**; 83: 615-9. doi:10.1016/j.exer.2006.02.010
7. Xiao Z, Shangguan D, Cao Z, Fang X, Tan W. Cell-specific internalization study of an aptamer from whole cell selection. *Chemistry* **2008**; 14: 1769-75. doi:10.1002/chem.200701330
8. Ludwig H, Weisel K, Petrucci MT, Leleu X, Cafro AM, Garderet L, et al. Olaptesed pegol, an anti-CXCL12/SDF-1 Spiegelmer, alone and with bortezomib-dexamethasone in relapsed/refractory multiple myeloma: a Phase IIa Study. *Leukemia* **2017**; 31: 997-1000. doi:10.1038/leu.2017.5
9. Guo X, Zhu X, Gao J, Liu D, Dong C, Jin X. PLGA nanoparticles with CD133 aptamers for targeted delivery and sustained release of propranolol to hemangioma. *Nanomedicine (Lond)* **2017**; 12: 2611-24. doi:10.2217/nnm-2017-0130
10. Hanafi-Bojd MY, Moosavian Kalat SA, Taghdisi SM, Ansari L, Abnous K, Malaekeh-Nikouei B. MUC1 aptamer-conjugated mesoporous silica nanoparticles effectively target breast cancer cells. *Drug Dev Ind Pharm* **2018**; 44: 13-8. doi:10.1080/03639045.2017.1371734
11. Jurek PM, Zablocki K, Wasko U, Mazurek MP, Otlewski J, Jelen F. Anti-FGFR1 aptamer-tagged superparamagnetic conjugates for anticancer hyperthermia therapy. *Int J Nanomedicine* **2017**; 12: 2941-50. doi:10.2147/ijn.s125231
12. Vandghanooni S, Eskandani M, Barar J, Omidi Y. AS1411 aptamer-decorated cisplatin-loaded poly (lactic-co-glycolic acid) nanoparticles for targeted therapy of miR-21-inhibited ovarian cancer cells. *Nanomedicine (Lond)* **2018**; 13: 2729-58. doi: 10.2217/nnm-2018-0205
13. Vandghanooni S, Eskandani M, Barar J, Omidi Y. Recent advances in aptamer-armed multimodal theranostic nanosystems for imaging and targeted therapy of cancer. *Eur J Pharm Sci* **2018**; 117: 301-12. doi:10.1016/j.ejps.2018.02.027
14. Kanwar JR, Roy K, Kanwar RK. Chimeric aptamers in cancer cell-targeted drug delivery. *Crit Rev Biochem Mol Biol* **2011**; 46: 459-77. doi:10.3109/10409238.2011.614592
15. Vandghanooni S, Eskandani M, Barar J, Omidi Y. Bispecific therapeutic aptamers for targeted therapy of cancer: a review on cellular perspective. *J Mol Med* **2018**. doi:10.1007/s00109-018-1669-y
16. Bagalkot V, Farokhzad OC, Langer R, Jon S. An aptamer-doxorubicin physical conjugate as a novel targeted drug-delivery platform. *Angew Chem Int Ed Engl* **2006**; 45: 8149-52. doi:10.1002/anie.200602251
17. Barar J. Bioimpacts of nanoparticle size: why it matters? *Bioimpacts* **2015**; 5: 113-5. doi:10.15171/bi.2015.23
18. Omidi Y, Barar J. Targeting tumor microenvironment: crossing tumor interstitial fluid by multifunctional nanomedicines. *Bioimpacts* **2014**; 4: 55-67. doi:10.5681/bi.2014.021
19. Subramanian N, Kanwar JR, Akilandeswari B, Kanwar RK, Khetan V, Krishnakumar S. Chimeric nucleolin aptamer with survivin DNAzyme for cancer cell targeted delivery. *Chem Commun* **2015**; 51: 6940-3. doi:10.1039/c5cc00939a
20. Iaboni M, Russo V, Fontanella R, Roscigno G, Fiore D, Donnarumma E, et al. Aptamer-miRNA-212 Conjugate Sensitizes NSCLC Cells to TRAIL. *Mol Ther Nucleic Acids* **2016**; 5: e289. doi:10.1038/mtna.2016.5
21. Dai F, Zhang Y, Zhu X, Shan N, Chen Y. Anticancer role of MUC1 aptamer-miR-29b chimera in epithelial ovarian carcinoma cells through regulation of PTEN methylation. *Target Oncol* **2012**; 7: 217-25. doi:10.1007/s11523-012-0236-7
22. Zhao N, Pei SN, Qi J, Zeng Z, Iyer SP, Lin P, et al. Oligonucleotide aptamer-drug conjugates for targeted therapy of acute myeloid leukemia. *Biomaterials* **2015**; 67: 42-51. doi:10.1016/j.biomaterials.2015.07.025
23. Gilboa E, McNamara J, 2nd, Pastor F. Use of oligonucleotide aptamer ligands to modulate the function of immune receptors. *Clin Cancer Res* **2013**; 19: 1054-62. doi:10.1158/1078-0432.ccr-12-2067
24. Pastor F. Aptamers: A New Technological Platform in Cancer Immunotherapy. *Pharmaceuticals (Basel)* **2016**; 9. doi:10.3390/ph9040064
25. Boltz A, Piater B, Toleikis L, Guenther R, Kolmar H, Hock B. Bi-specific aptamers mediating tumor cell lysis. *J Biol Chem* **2011**; 286: 21896-905. doi:10.1074/jbc.M111.238261
26. Schrand B, Berezhnoy A, Brenneman R, Williams A, Levay A, Kong LY, et al. Targeting 4-1BB costimulation to the tumor stroma with bispecific aptamer conjugates enhances the therapeutic index of tumor immunotherapy. *Cancer Immunol Res* **2014**; 2: 867-77. doi:10.1158/2326-6066.cir-14-0007
27. Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. *Nat Rev Immunol* **2013**; 13: 227-42. doi:10.1038/nri3405
28. Allison KH, Sledge GW. Heterogeneity and cancer. *Oncology (Williston Park)* **2014**; 28: 772-8.
29. Institute NC. Personalized medicine **2011**; Available from: http://www.cancer.gov/dictionary/?CdrID=561717.