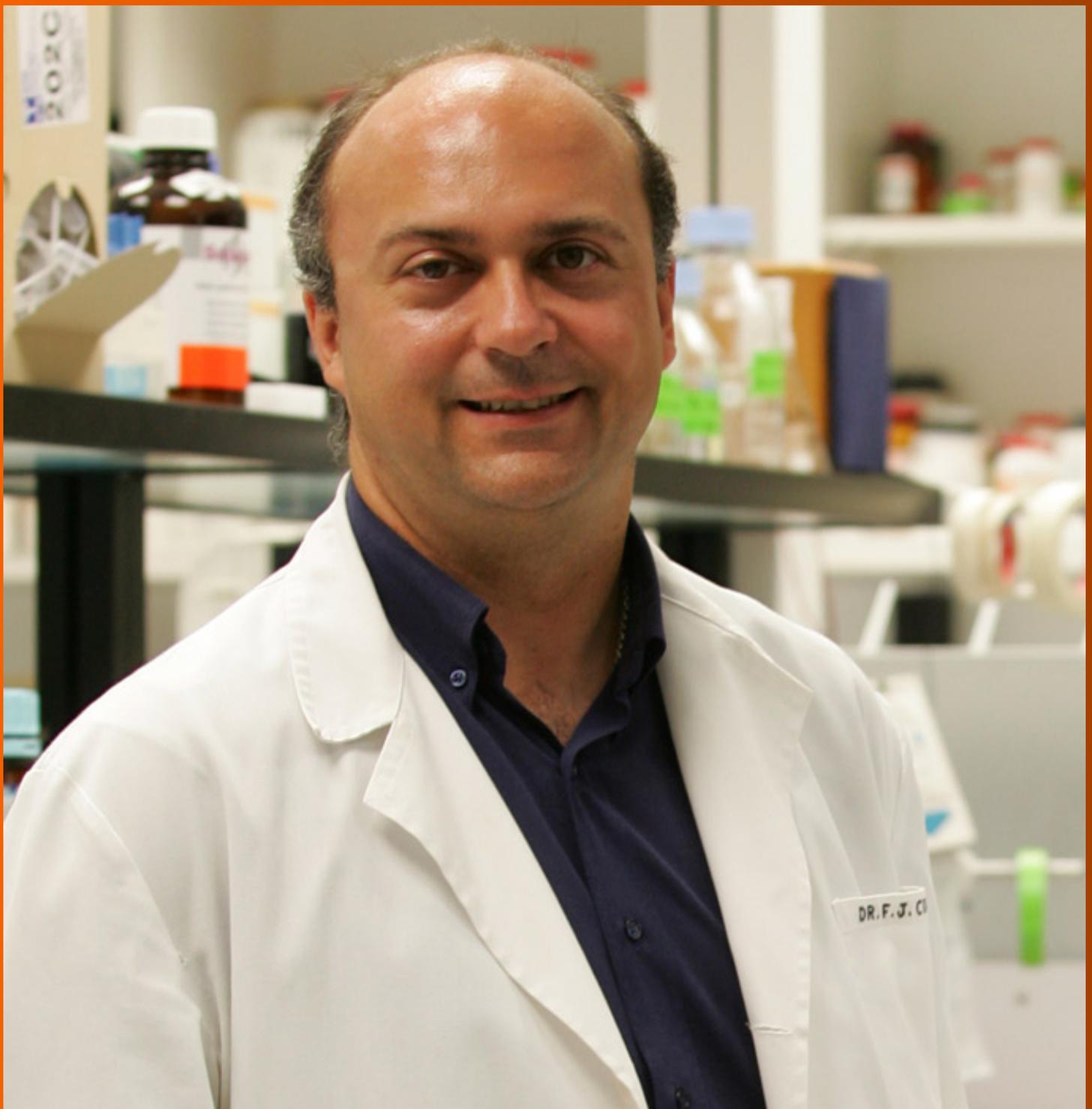


World Journal of *Gastroenterology*

World J Gastroenterol 2019 July 14; 25(26): 3283-3467



OPINION REVIEW

- 3283 Diuretic window hypothesis in cirrhosis: Changing the point of view
Brito-Azevedo A
- 3291 Fluoroquinolones for the treatment of latent *Mycobacterium tuberculosis* infection in liver transplantation
Silva JT, San-Juan R, Fernández-Ruiz M, Aguado JM

REVIEW

- 3299 Reactivation of hepatitis B virus infection in patients with hemo-lymphoproliferative diseases, and its prevention
Sagnelli C, Pisaturo M, Calò F, Martini S, Sagnelli E, Coppola N
- 3313 Current status of endoscopic retrograde cholangiopancreatography in patients with surgically altered anatomy
Krutsri C, Kida M, Yamauchi H, Iwai T, Imaizumi H, Koizumi W

MINIREVIEWS

- 3334 Choledochal cysts: Similarities and differences between Asian and Western countries
Baison GN, Bonds MM, Helton WS, Kozarek RA
- 3344 Gastro-duodenal disease in Africa: Literature review and clinical data from Accra, Ghana
Archampong TN, Asmah RH, Richards CJ, Martin VJ, Bayliss CD, David L, Beleza S, Carrilho C, Botão E
- 3359 Screening of aptamers and their potential application in targeted diagnosis and therapy of liver cancer
Zhang GQ, Zhong LP, Yang N, Zhao YX

ORIGINAL ARTICLE**Basic Study**

- 3370 Drug-eluting fully covered self-expanding metal stent for dissolution of bile duct stones *in vitro*
Huang C, Cai XB, Guo LL, Qi XS, Gao Q, Wan XJ
- 3380 Raddeanin A promotes apoptosis and ameliorates 5-fluorouracil resistance in cholangiocarcinoma cells
Guo SS, Wang Y, Fan QX
- 3392 Identification of differentially expressed genes regulated by methylation in colon cancer based on bioinformatics analysis
Liang Y, Zhang C, Dai DQ

Retrospective Study

- 3408** Histologic features and genomic alterations of primary colorectal adenocarcinoma predict growth patterns of liver metastasis
Wu JB, Sarmiento AL, Fiset PO, Lazaris A, Metrakos P, Petrillo S, Gao ZH

Observational Study

- 3426** International normalized ratio and Model for End-stage Liver Disease score predict short-term outcome in cirrhotic patients after the resolution of hepatic encephalopathy
Hu XP, Gao J

SYSTEMATIC REVIEWS

- 3438** Synchronous resection of esophageal cancer and other organ malignancies: A systematic review
Papaconstantinou D, Tsilimigras DI, Moris D, Michalinos A, Mastoraki A, Mpaili E, Hasemaki N, Bakopoulos A, Filippou D, Schizas D

META-ANALYSIS

- 3450** Genetic testing vs microforceps biopsy in pancreatic cysts: Systematic review and meta-analysis
Faias S, Pereira L, Luís Á, Chaves P, Cravo M

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Andrew Stewart Day, MD, Professor, Paediatrics Department, University of Otago, Christchurch 8041, New Zealand

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. The *WJG* Editorial Board consists of 701 experts in gastroenterology and hepatology from 58 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, etc. The *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2019 edition of Journal Citation Report® cites the 2018 impact factor for *WJG* as 3.411 (5-year impact factor: 3.579), ranking *WJG* as 35th among 84 journals in gastroenterology and hepatology (quartile in category Q2). CiteScore (2018): 3.43.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Liang Zhang*
 Proofing Production Department Director: *Yun-Xiaoqian Wu*

NAME OF JOURNAL <i>World Journal of Gastroenterology</i>
ISSN ISSN 1007-9327 (print) ISSN 2219-2840 (online)
LAUNCH DATE October 1, 1995
FREQUENCY Weekly
EDITORS-IN-CHIEF Subrata Ghosh, Andrzej S. Tarnawski
EDITORIAL BOARD MEMBERS http://www.wjgnet.com/1007-9327/editorialboard.htm
EDITORIAL OFFICE Ze-Mao Gong, Director
PUBLICATION DATE July 14, 2019

COPYRIGHT © 2019 Baishideng Publishing Group Inc
INSTRUCTIONS TO AUTHORS https://www.wjgnet.com/bpg/gerinfo/204
GUIDELINES FOR ETHICS DOCUMENTS https://www.wjgnet.com/bpg/GerInfo/287
GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH https://www.wjgnet.com/bpg/gerinfo/240
PUBLICATION MISCONDUCT https://www.wjgnet.com/bpg/gerinfo/208
ARTICLE PROCESSING CHARGE https://www.wjgnet.com/bpg/gerinfo/242
STEPS FOR SUBMITTING MANUSCRIPTS https://www.wjgnet.com/bpg/GerInfo/239
ONLINE SUBMISSION https://www.f6publishing.com

Screening of aptamers and their potential application in targeted diagnosis and therapy of liver cancer

Guo-Qing Zhang, Li-Ping Zhong, Nuo Yang, Yong-Xiang Zhao

ORCID number: Guo-Qing Zhang (0000-0003-3865-0378); Li-Ping Zhong (0000-0003-1532-4107); Nuo Yang (0000-0003-0606-7313); Yong-Xiang Zhao (0000-0003-1219-0908).

Author contributions: Zhang GQ, Zhong LP, Yang N, and Zhao YX wrote the paper.

Conflict-of-interest statement: All the authors have no conflict of interest related to the manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: May 18, 2019

Peer-review started: May 18, 2019

First decision: May 30, 2019

Revised: June 2, 2019

Accepted: June 8, 2019

Article in press: June 8, 2019

Published online: July 14, 2019

P-Reviewer: Mohamed SY, Tanabe S

S-Editor: Yan JP

L-Editor: Wang TQ

Guo-Qing Zhang, Li-Ping Zhong, Nuo Yang, Yong-Xiang Zhao, National Center for International Research of Biological Targeting Diagnosis and Therapy, Guangxi Key Laboratory of Biological Targeting Diagnosis and Therapy Research, Collaborative Innovation Center for Targeting Tumor Diagnosis and Therapy, Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

Corresponding author: Yong-Xiang Zhao, MD, PhD, Full Professor, National Center for International Research of Biological Targeting Diagnosis and Therapy, Guangxi Key Laboratory of Biological Targeting Diagnosis and Therapy Research, Collaborative Innovation Center for Targeting Tumor Diagnosis and Therapy, Guangxi Medical University, 22 Shuangyong Road, Nanning 530021, Guangxi Zhuang Autonomous Region, China. yongxiang_zhao@126.com

Telephone: +86-15177120015

Fax: +86-771-5317061

Abstract

Aptamers are a class of single oligonucleotide molecules (DNA or RNA) that are screened from random DNA or RNA oligonucleotide chain libraries by the systemic evolution of ligands by exponential enrichment technology. The selected aptamers are capable of specifically binding to different targeting molecules, which is achieved by the three-dimensional structure of aptamers. Aptamers are similar in function to monoclonal antibodies, and therefore, they are also referred to as "chemical antibodies". Due to their high affinity and specificity and low immunogenicity, aptamers are topics of intense interest in today's biological targeting research especially in tumor research. They not only have high potential for clinical advances in tumor targeting detection but also are highly promising as targeted tumor drug carriers for use in tumor therapy. Various experimental studies have shown that aptamer-based diagnostic and therapeutic methods for liver cancer have great potential for application. This paper summarizes the structure, characteristics, and screening methods of aptamers and reviews the recent research progress on nucleic acid aptamers in the targeted diagnosis and treatment of liver cancer.

Key words: Aptamer; Systemic evolution of ligands by exponential enrichment; Liver cancer; Outlook

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: For liver cancer, conventional diagnostic methods have low sensitivity,

E-Editor: Zhang YL



therapeutic drugs have great side effects, and tumor monitoring is difficult, which limit the diagnosis and treatment of liver cancer. However, the diagnosis and treatment of liver cancer based on aptamers have great application prospects. This review describes the screening of aptamers and reviews the recent advances on aptamers in the targeted diagnosis and treatment of liver cancer.

Citation: Zhang GQ, Zhong LP, Yang N, Zhao YX. Screening of aptamers and their potential application in targeted diagnosis and therapy of liver cancer. *World J Gastroenterol* 2019; 25(26): 3359-3369

URL: <https://www.wjgnet.com/1007-9327/full/v25/i26/3359.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v25.i26.3359>

INTRODUCTION

Tumors are one of the leading causes of human death worldwide. With the development of society, the population has increased, and the risk of tumors has also greatly increased. Tumor diagnosis and treatment have become an issue of intense concern. Liver cancer is a common malignant tumor, and its diagnosis and treatment are the research focus of many scholars.

Aptamer refers to a type of single oligonucleotide molecule (DNA or RNA) that is screened and enriched from a library of random single-stranded oligonucleotide sequences constructed *in vitro*, and aptamers can specifically bind to target molecules, such as small molecules, proteins, and even whole cells^[1-3]. In 1990, Ellington *et al*^[4] and Tuerk *et al*^[5] screened for a random oligonucleotide that binds to T4 DNA polymerase with high affinity and specificity and confirmed the ability of this oligonucleotide sequence to bind to the target. The identified oligonucleotide was referred to as an aptamer, and the screening method was named systematic evolution of ligands by exponential enrichment (SELEX). The first aptamer drug, pegaptanib sodium (trade name: Macugen), was approved by the United States Food and Drug Administration in 2004 and is used to treat age-related macular degeneration^[6]. Now, scientists have acquired a variety of aptamers screened using the SELEX technology, which have a special three-dimensional structure that can bind different target molecules^[7,8]. The more detailed explanation for aptamers is given below.

APTAMERS

Structure and function of aptamers

An aptamer is a specific three-dimensional structure formed by the folding of a single-stranded nucleic acid molecule. The binding of an aptamer to the target molecule is achieved by its own special three-dimensional structure, with features such as hairpins, internal loops, bulges, pseudoknots, and G-tetramers^[9]. The factors by which an aptamer binds to the target molecule are the complementary effects of the geometric shape, the interactions of aromatic ring overlap, the electrostatic interactions of the charged groups, the bases of the nucleic acid aptamer, the van der Waals forces, and the hydrogen bonds. Targets that can be bound include small molecules, proteins, cells, and even entire tissues. Proteins are the most numerous targets^[10,11].

DNA and RNA aptamers

Both DNA and RNA aptamers can produce similar specificities and affinities, but each has its own distinct advantages. The primary difference between DNA and RNA lies in the sugar. The GH bond of deoxyribose in DNA has low reactivity and a stable structure, making it better able to resist the action of enzymes. The ribose in RNA is more reactive and less stable than deoxyribose, and double-stranded regions of RNA can stimulate the immune system via the Toll-like receptor. An RNA aptamer obtained from an RNA oligonucleotide chain library using the SELEX method needs to be modified for improved stability^[12].

In the early stages, many researchers were more likely to screen for RNA aptamers because they have more diverse stereoscopic three-dimensional structures than DNA and higher affinity for targets^[13]. However, in-depth studies of aptamers have presented increasing evidence that DNA aptamers are superior to RNA aptamers in

application. For example, DNA aptamers have better structural stability and are easy to screen. Therefore, an increasing number of researchers are now more inclined to explore DNA aptamers, and in 2013, it was reported that more than 85% of aptamers were obtained from DNA oligonucleotide libraries^[14].

SELEX METHOD FOR SCREENING APTAMERS

Basic principles of SELEX technology

The SELEX technology combines multiple fields, such as molecular biology, bioinformatics, and materials science, to develop aptamers for a variety of targets^[15]. A large number (approximately 10^{14-15}) of random DNA or RNA oligonucleotide chains are first synthesized, and then multiple screening and enrichment cycles are performed to select oligonucleotide chains from this library that can bind target molecules with high specificity and high affinity. New base sequences will appear during the screening process, and as the cycle progresses, the specificity and affinity with which the selected oligonucleotide strand binds the target molecule will gradually increase. The final oligonucleotide chain has the highest specificity and affinity for the target molecule and is referred to as the aptamer of the specific target molecule^[16,17].

Establishment of a random oligonucleotide chain library

As a raw material, the oligonucleotide chain for aptamer screening is fixed at both ends and random in the middle. The random sequences can specifically bind to the target molecule, and the fixed sequences can be used for amplification and screening. Screening of DNA or RNA aptamers starts with synthesis of random DNA or RNA oligonucleotide chain libraries.

The first step in building a library is to design fixed sequences at both ends of the oligonucleotide chain, which are usually 20-30 nucleotides in length. The fixed sequences generally contain primer binding sites and restriction endonuclease binding sites required for PCR amplification, while binding sites containing RNA polymerase are needed when preparing RNA aptamers. The transcribed RNA sequences must also be able to bind to reverse transcriptase^[18]. In designing the intermediate sequences, attention should be paid to length. Short chains are easier to design and fabricate and less expensive, but if the sequence is too short, it cannot form secondary structures that specifically and stably bind to target molecules, or there are not enough secondary structures in the library for screening. As the length of the intermediate sequence increases, the capacity of the library increases, but increasing the length of the intermediate sequence beyond a certain threshold will not significantly increase the number of unique stereo structures available for screening. Generally, the length of the intermediate sequence is 30-50 nucleotides, which can theoretically form approximately 10^{14} - 10^{24} random oligonucleotide chains. The stereo structure formed by this number of nucleotides is sufficient to bind a target molecule^[19]. After the sequence design is completed, a large number of DNA oligonucleotide chains with random sequences in the middle can be synthesized with a DNA synthesizer, and a DNA oligonucleotide chain library can be established.

Selection and enrichment of aptamers

After establishment of a DNA oligonucleotide chain library, it is necessary to screen for and enrich oligonucleotide chains that can bind to target molecules with high specificity and affinity. Mature screening techniques include magnetic bead separation^[20], high-speed centrifugation, affinity chromatography^[21], capillary electrophoresis^[22], and nitrocellulose membrane filtration^[23]. For example, studies have shown that a target aptamer can be obtained in only four cycles of capillary electrophoresis SELEX^[24].

On the basis of traditional screening methods, many screening methods have been developed, such as counter SELEX^[25], subtractive SELEX^[26], photo SELEX^[27], and negative SELEX^[28], which can improve the selectivity of aptamers. Blended SELEX^[29], complex targeting SELEX^[30], expression cassette SELEX^[31], and toggle SELEX^[32] can improve the universality of aptamers. In addition, automated SELEX^[33], non-SELEX^[34], and FluMag SELEX^[35] can shorten the screening cycle. Methods for combining different pools, such as tailored SELEX^[36] and genomic SELEX^[37], can increase the likelihood of screening for aptamers of interest. At present, cell-based screening (cell-SELEX) is widely used^[38] (Figure 1).

To shorten the screening process, the following screening methods have been developed. Multiple GO-SELEX employs graphene oxide (GO) for screening. This method is simple, fast, and high throughput, and thus reduces the screening cost and

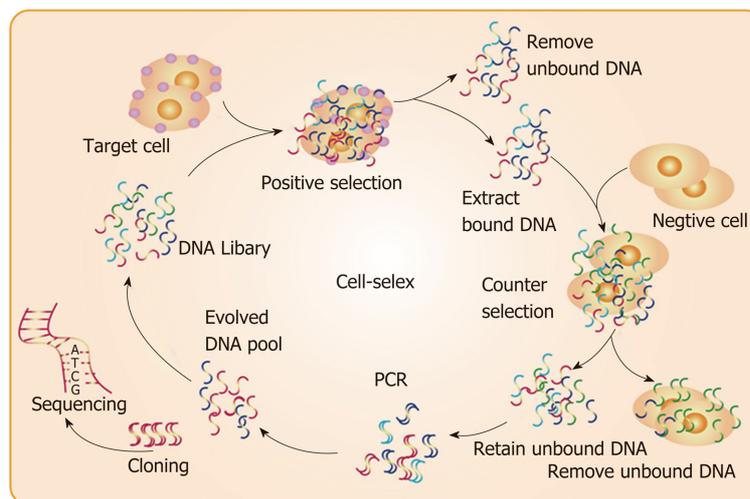


Figure 1 Schematic diagram of cell systemic evolution of ligands by exponential enrichment strategy. The target cells are used to screen and enrich the selection pools, and clonal sequencing is performed to obtain the required aptamers. SELEX: Systemic evolution of ligands by exponential enrichment.

shortens the screening time^[39]. Single-walled carbon nanotube-assisted cell-SELEX (SWCNT-assisted cell-SELEX) requires only six rounds of screening compared with the 15 rounds necessary in standard cell-SELEX and has a high screening efficiency^[40]. On-chip cell-SELEX, which incorporates microfluidic chips into the cell-SELEX process, requires only five rounds of screening, greatly shortening the screening process^[41]. Sequence-constructive SELEX modifies the sequence of aptamers to improve the affinity and specificity for the targets^[42]. Furthermore, Hi-Fi SELEX is a protocol for rapid and efficient DNA aptamer selection^[43].

The general procedures for screening and enrichment of DNA aptamers are as follows: in the first round of screening, target molecules are used to screen DNA oligonucleotide chain libraries and the oligonucleotide chain DNA is amplified *via* PCR; in the second round of screening, the amplified products are rescreened and the DNA is amplified *via* PCR; after 8-16 repeated rounds of screening, flow cytometry and clonal sequencing are performed to obtain the required high specificity and high affinity aptamers^[15]. However, depending on the SELEX method used, the number of screening and enrichment rounds will vary. In most cases, too many rounds will waste consumable reagents without significantly improving the screening rate. However, too few rounds may not identify the best aptamers or impurities. The appropriate number of screening rounds is generally the number at which the affinity does not continue to increase. Because of the low fidelity of the polymerase used in SELEX, each screening enrichment cycle may produce variants, and thus, the screening enrichment cycles actually increase the capacity of oligonucleotide chain libraries. In addition to the effect of screening enrichment, the number of cycles needed for screening enrichment is one of the criteria for evaluating the advantages and disadvantages of screening enrichment methods. Many of the methods mentioned above are optimized in terms of the number of cycles.

Base sequencing, characterization, and molecular structure modification of aptamers

Screening of enriched aptamers requires base sequencing to obtain well-defined base sequences. Then, structural analysis and characterization of these screened aptamers need to be performed, to assess factors such as specificity, affinity, and stability.

The chemical synthesis of aptamers is more stable than antibodies. However, despite their high stability and tolerance to temperature, pH range, and some organic solvents, aptamers can be readily degraded or removed by the kidneys *in vivo*. Because of the limited interaction between natural base pairs and drugs, *in vivo* use requires prolonging the survival time of aptamers under physiological conditions, that is, optimizing the structure of aptamers. Conventional optimization methods include the following: (1) Substituting a natural nucleotide for a nucleotide modified with a group to avoid degradation of the nucleic acid^[44]; (2) Chemically synthesizing a mirror image sequence of the selected aptamers with high plasma and serum stability to enhance the stability of aptamers to make them have significant therapeutic potential^[45]; (3) Modifying aptamers with locked nucleic acids to enhance their ribozyme resistance. Methylene-linked 2'-oxygen and 4'-carbon in carbohydrate

residues have strong ability to hybridize with nucleic acid molecules and are not easily degraded by enzymes^[46]; and (4) Covalently attaching PEG or cholesterol to aptamers, prolonging their residence time in the human body and reducing renal filtration rate^[47,48]. The half-life of survival of aptamers in human physiological environment can be extended from a few minutes to several hours by one or more of the above methods, and aptamers with modifiable properties are superior to antibodies or polypeptides in the diagnosis and treatment of tumor diseases.

CHARACTERISTICS OF APTAMERS AND COMPARISON WITH MONOCLONAL ANTIBODIES

Characteristics of aptamers

Aptamers have many advantages, such as high affinity and specificity, a wide range of action, small size, good stability, low cost, and easy synthesis and screening compared with traditional immunological and chemical recognition molecules, and aptamers have shown broad application prospects in the diagnosis and treatment of diseases^[49].

Comparison of aptamers and monoclonal antibodies

There are some similarities between aptamers and monoclonal antibodies (mAbs). In terms of function, both aptamers and mAbs can bind target molecules with high specificity and affinity. In terms of application, both aptamers and mAbs can be used in medical research and in clinical diagnosis and treatment; therefore, aptamers are known as "chemical antibodies". Compared with mAbs, aptamers do not exhibit immunogenicity or antigenicity and do not cause a related immune response or immune rejection in the human body. This property makes aptamers reusable for the same patient in the diagnosis and treatment of clinical diseases^[50].

APPLICATION OF APTAMERS IN THE TARGETED DIAGNOSIS OF LIVER CANCER

The early stage of tumorigenesis may present no symptoms, leading to tumors in the middle and late stages before symptoms are identified, which hinders the treatment of tumors. However, tumor markers already exist in the early stage of tumorigenesis, which is of great significance for the early diagnosis and treatment of tumors. The main difficulty in the early diagnosis of tumors is the identification of the characteristics of tumors and tumor cells. Tumor markers are important molecules in the diagnosis and treatment of tumors. They can target whole tumors or tumor cells. Fluorescence imaging of tumors and cells can diagnose tumors and monitor their treatment. Due to the high specificity and affinity of aptamers, a goal currently attracting intense interest is to screen for aptamers as tumor markers and apply them to the targeted diagnosis of tumors. Aptamers have become potential probe molecules for targeted diagnosis of liver cancer, and their application *in vitro* and *in vivo* of liver cancer can improve detection specificity and sensitivity^[51] (Figure 2).

Aptamers for *in vitro* detection of liver cancer

In recent years, with the in-depth study of aptamers, increasing numbers of liver cancer detection methods based on aptamers have been developed to provide different *in vitro* detection methods for the diagnosis of liver cancer (Table 1).

The aptamer-nanoparticle system (Apt-NP) formed by the conjugation of liver cancer-related aptamers and nanoparticles, can be used for the diagnosis of liver cancer. Recently, Hu *et al*^[52] labeled HepG2 cells with biotin-conjugated TLS11a aptamer (Bio-TLS11a), and then co-incubated with streptavidin-conjugated fluorescent silica nanoparticles (SA-FSNPs). HepG2 cells were detected *in vitro* by the interaction between biotin and streptavidin. Hu *et al*^[52] pointed out that these SA-FSNPs can specifically and sensitively detect aptamer-labeled HepG2 cells and show no obvious toxic effects, showing the good application prospect of this method for liver cancer cells and other types of cancer cells.

With the deeper research on nano-molecules, more and more nano-molecules have been discovered and used together with aptamers for targeted detection of liver cancer cells. Wang *et al*^[53] established a new method for detecting circulating tumor cells (CTCs) in hepatocellular carcinoma (HCC). They combined the aptamer of the carbohydrate sialic acid Lewis X with a hydroxyapatite/chitosan (HA/CTS) nanofilm to form the CTC-BioTChip platform, which effectively captures and identifies HCC

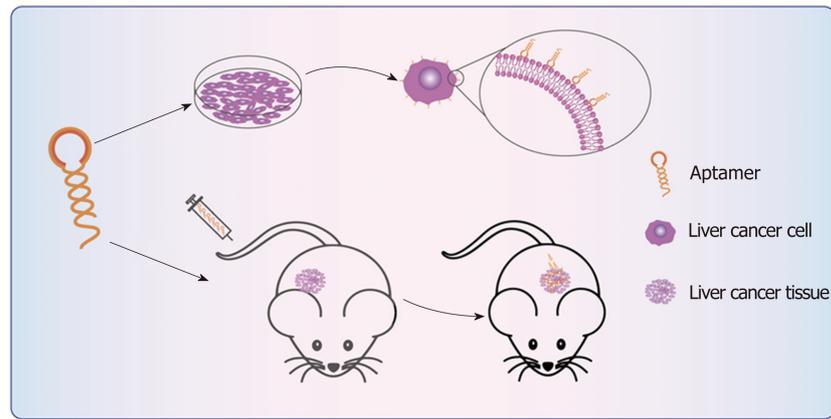


Figure 2 Schematic diagram of aptamer targeting to liver cancer. The aptamers bind to the surface of the liver cancer cells with high specificity and high affinity after incubation with the liver cancer cells. After the aptamers are injected into the mouse model through the tail vein, they specifically bind to the liver cancer tissue site.

CTCs. A small amount of aflatoxin B₁ can cause liver cancer to occur. Joo *et al.*^[54] developed a rapid method for the determination of aflatoxin B₁ (AFB₁) based on GO and fluorescein imide modified AFB₁-specific aptamer. When the aptamer binds to AFB₁, the conformation of the aptamer changes and interacts with GO such that the fluorescence intensity is reduced or even quenched.

In the past few years, the potential role of quantum dots in fluorescence imaging has gradually attracted the attention and research of more scholars. QD-labeled aptamers are also a new strategy for detecting liver cancer cells. It has been found that the SL2-B aptamer labeled with QDs can specifically recognize HepG2 cells and be taken up by HepG2 cells, and the results can be detected by fluorescence microscopy. Moreover, as the incubation time of HepG2 cells with the conjugate increased, it also showed potential antiproliferative activity against HepG2 cells^[55]. This technique of QDs labeling aptamers provides a new strategy for *in vitro* detection and research of liver cancer.

Dickkopf-1 (DKK1) has potential application value for the early diagnosis of HCC. Zhou *et al.*^[56] obtained two kinds of aptamers that recognize DKK1, one is slow-off aptamer, and the experimental results show that it can be used for aptamer-based ELISA assay, while another fast-off aptamer is more suitable for flow cytometry and spot-blot. In addition, the combination of molecular beacons^[57], which have stem-ring structures and contain fluorescent and quenching agents, and fluorescent dyes^[58] with aptamers targeting tumors has also been proven to be useful for detecting or imaging tumors. This provides more potential methods for *in vitro* detection of liver cancer.

Aptamers for *in vivo* imaging of liver cancer

In vivo imaging is still a common method for the clinical diagnosis of tumors. Techniques include magnetic resonance imaging (MRI), ultrasound molecular imaging, computed tomography (CT), and fluorescence molecular tomography, which have been verified in small rodents^[59]. Nowadays, due to the extremely high incidence of liver cancer and the increasingly intensive research on aptamer, the application of various aptamer-based contrast agents, probes, and fluorescent groups to *in vivo* oncology imaging has become the research topic of numerous scholars (Table 2).

MRI is a non-invasive tumor diagnosis technique. To improve the diagnostic efficacy of MRI, Yan *et al.*^[60] obtained an aptamer capable of binding to endoglin (CD105) with high specificity by SELEX. This aptamer is conjugated to paramagnetic and fluorophore on the G5 dendrimer to form a targeted nanoprobe that can be used to detect tiny HCCs. Zhong *et al.*^[61] developed a nanoprobe targeting CD105 for MRI by the use of aptamer-modified magnetic carboxymethyl chitosan, which can improve the early diagnosis of HCC. In addition, Zhao *et al.*^[62] prepared a targeted MRI molecular probe based on ultrasmall superparamagnetic iron oxide (USPIO) mediated by phosphatidylinositol-3 (GPC3) aptamer. The probe was verified in xenograft mice, and the experimental results confirmed the targeted imaging effect of the probe on HCC expressing GPC3.

Various studies have shown that aptamers have great potential advantages in the targeted diagnosis of liver cancer, but this application is still in its infancy. For some malignant tumors with a low expression rate of tumor markers, further exploration is

Table 1 Current literature summary of aptamers for *in vitro* detection of liver cancer

First author	Year	Aptamer	Target	System for detection	Method for detection
Hu <i>et al.</i> ^[51]	2017	TLS11a	HepG2 cells	Bio-TLS11a and SA-FSNPs	Fluorescence Microscopy
Wang <i>et al.</i> ^[52]	2016	sLex-AP	CTCs	CTC-BioT Chip	Fluorescence Microscopy
Joo <i>et al.</i> ^[53]	2017	AFB ₁ -Apt	AFB ₁	FAM modified AFB ₁ -Apt and GO	Fluorescence Microscopy
Kaur <i>et al.</i> ^[54]	2019	SL2-B	HepG2 cells	QDs labeled SL2-B	Fluorescence Microscopy
Zhou <i>et al.</i> ^[55]	2019	Slow-off aptamer (TD10); fast-off aptamer	DKK1 protein	5' amino C6 modified TD10-based ELISA; 5' FAM labeled fast-off aptamer	ELISA (TD10); dot blot and flow cytometry (fast-off aptamer)

still needed^[63].

APPLICATION OF APTAMERS IN TARGETED THERAPY OF LIVER CANCER

In addition to acting as therapeutic agents, aptamers can also be used as targeting agents to conjugate with antitumor drugs, oligonucleotides, or nanocarriers for targeted tumor therapy. A drug delivery system based on aptamers has many advantages. It can not only significantly improve the pharmacokinetic properties of drugs *in vivo*, but also can reduce toxic and side effects to some extent certain due targeting properties. Because aptamers are small (nanosized) molecules, the whole drug delivery system can effectively penetrate all levels of blood vessels into the tumor site^[64].

The traditional methods of liver cancer therapy have poor targeting, inefficient drug delivery, poor efficacy, and severe side effects, which together present great challenges in the therapy of liver cancer. The targeted therapy of liver cancer is now the focus of scientists' research. Currently, aptamers have been widely studied and applied in various fields because of their characteristics. Modified aptamers have been applied to the treatment of liver cancer, improving the efficiency of treatment and greatly reducing the side effects of drug treatment^[65]. Aptamers can be used as therapeutic agents to intervene in the treatment of liver cancer. They can also be conjugated with antineoplastic drugs, oligonucleotides, or nanocarriers for the treatment of tumors, such as chemotherapy, gene therapy, immune therapy, radiotherapy, and phototherapy^[66] (Table 3).

Hu *et al.*^[67] constructed a bispecific system using the hepatoma cells-specific aptamer TLS11a and anti-CD3, which mediates T cell activation, targets cytotoxic T cells to the liver cancer site, and thus enhances the anti-tumor effect. The experimental results show that TLS11a/CD3 can connect hepatoma cells and T cells, avoiding the occurrence of immune escape and mediating the lysis of hepatoma cells and the release of cytokines, and the released cytokines can continue to enhance anti-tumor effects. This aptamer-based bispecific system provides a new technology platform for targeted immunotherapy of liver cancer.

The recombinant adenovirus carrying the PTEN gene (Ad5-PTEN) is an effective anti-tumor agent, but its application is greatly limited due to its poor stability and toxic effects to normal tissues. To overcome the application limitations of Ad5-PTEN, Xiao *et al.*^[68] formed a novel gene delivery system, EPAP, by linking EpDT3, an aptamer that specifically binds to epithelial cell adhesion molecule (EpCAM), to Ad-PTEN. The results show that EPAP is non-toxic to normal cells and tissues, can target and inhibit EpCAM-positive hepatoma cells, enhance anti-tumor activity, and improve the gene therapy efficiency of liver cancer.

Today, mesoporous silica nanoparticles (MSNs) are a potential therapeutic platform for cancer therapy. MSNs are a good nano-drug delivery platform because of its good stability, high load, high biocompatibility, adjustable pore size, and protection against inactivation or degradation of the incorporated drug^[69]. Babaei *et al.*^[70] developed a PEGylated MSN system capable of targeting EpCAM and controlling the release of 5-fluorouracil. First, the authors loaded 5-fluorouracil into mesoporous silica, hybridized with gold nanoparticles to its outer surface, PEGylated, and then conjugated with EpCAM aptamer, and the resulting complex can be used for HCC

Table 2 Current literature summary of aptamers for *in vivo* imaging of liver cancer

First author	Year	Aptamer	Type of tumor	Probe for detection	Method for detection
Yan <i>et al</i> ^[59]	2018	CD105-Apt	Tiny HCC	Conjugated CD105-Apt to paramagnetic and fluorophore on the G5 dendrimer	MRI
Zhong <i>et al</i> ^[60]	2019	mEND	HCC	mEND-Fe O @CMCS	MRI
Zhao <i>et al</i> ^[61]	2018	AP613-1	HCC expressing GPC3	Apt-USPIO	MRI
Babaei <i>et al</i> ^[69]	2017	EpCAM-Apt	HCC	EpCAM-PEG-Au@Si-5-FU NPs	CT

Apt: Aptamer; HCC: Hepatocellular carcinoma; MRI: Magnetic resonance imaging; CT: Computed tomography; USPIO: Ultrasmall superparamagnetic iron oxide.

treatment. This system has potential application prospects in the targeted therapy of early liver cancer. In addition, it can also be used for CT imaging.

Black Phosphorus Quantum Dots (BPQDs) have a unique photocatalytic activity and have potential applications in photodynamic therapy, but the application of BPQD is limited due to the instability of the tumor microenvironment. To solve this problem, Lan *et al*^[71] constructed a nanostructure based on the TLS11a aptamer. Lan *et al*^[71] synthesized BPQDs/Pt hybrid mesoporous silica (BMSF@Pt), and then conjugated the TLS11a aptamer to BMSF@Pt to form Apt-MBMSF@Pt nanostructure. This structure can specifically target to HCC cells, killing HCC cells by self-compensation of oxygen, enhancing photodynamic efficacy, and providing a new method for targeted therapy of HCC.

MiRNA-195 (miR195) is a potent gene drug that inhibits vascular endothelial growth factor (VEGF), and some studies have demonstrated the inhibitory effect of miR195 in HCC^[72]. Liu *et al*^[73] conjugated histidine-modified disulfide cross-linked stearyl polyarginine peptide (H₃R₅) to cell penetrating peptide-modified aptamer, ST21, which is capable of specifically binding to HCC cells. Then, under the action of PEG, miR195 and Fasudil were loaded to the conjugation. Finally, a nano-system, Fasudil-ST21-H₃R₅-PEG_{miR195}, based on ST21-H₃R₅-PEG was constructed. The results showed that Fasudil-ST21-H₃R₅-PEG_{miR195} has a strong ROCK2 blocking effect and VEGF silencing effect, showing a higher anti-tumor effect, and has great application prospects for targeted therapy of HCC.

Liposomes are complex structures composed of cholesterol and phospholipids that can contain hydrophilic and lipophilic drugs and reduce the cytotoxicity of drugs. Liposomes are very effective drug nanocarriers. Cabazitaxel is a broad-spectrum antineoplastic drug, but its clinical adverse reactions hinder its use. Cheng *et al*^[74] modified capsaicin liposomes with a TLS1c aptamer targeting MEAR cells and demonstrated the highly specific targeting ability and strong antitumor effect of this complex on MEAR cells. This drug delivery system is also an effective potential therapeutic strategy. Nanoparticles, polymer micelles, and biomimetic nanocarriers can also be used as drug carriers to construct drug delivery systems, providing potential for the further development of targeted therapy for liver cancer^[75].

CONCLUSION

In conclusion, the diagnosis and treatment of liver cancer developed on the basis of aptamer solve the problems of low diagnostic sensitivity, large side effects of anticancer drugs, and difficulty in tumor monitoring. Various experimental results have confirmed the great potential of these strategies in the clinical application to liver cancer, and provide good scientific evidence for the clinical application of aptamers in liver cancer.

As “chemical antibodies”, aptamers have been considered an important research direction in the targeted diagnosis and treatment of tumors. With the continuous development of aptamers with different targeting sites, the application of aptamers with different targeting sites has become increasingly extensive. Aptamers have been modified and applied to various aspects of targeting research for liver cancer. With the development of different detection methods and treatment methods based on aptamers, aptamers will continue to develop in the clinical application of liver cancer, and finally realize early diagnosis and treatment of liver cancer.

Table 3 Current literature summary on the application of aptamers in targeted therapy for liver cancer

First author	Year	Aptamer	Target	System for therapy	Function
Hu <i>et al</i> ^[66]	2018	TLS11a	H22 cells	TLS11a/CD3	Immunity therapy
Xiao <i>et al</i> ^[67]	2017	EpDT3	EpCAM-positive cells HepG2	EpDT3-PEG-Ad5-PTEN (EPAP)	Gene therapy
Babaei <i>et al</i> ^[69]	2017	EpCAM-Apt	EpCAM-positive cells HepG2	EpCAM-PEG-Au@Si-5-FU NPs	Chemotherapy
Lan <i>et al</i> ^[70]	2019	TLS11a	HepG2 cells	Apt-BMSF@Pt	Phototherapy
Liu <i>et al</i> ^[72]	2016	ST21	SK-Hep-1 cells	Fasudil ^{ST21} -H3R5-PEG _{miR195}	Chemotherapy and gene therapy
Cheng <i>et al</i> ^[73]	2019	TLS1c	MEAR cells	BioTL Cab/lipo	Chemotherapy

REFERENCES

- Gold L, Polisky B, Uhlenbeck O, Yarus M. Diversity of oligonucleotide functions. *Annu Rev Biochem* 1995; **64**: 763-797 [PMID: 7574500 DOI: 10.1146/annurev.bi.64.070195.003555]
- Pestourie C, Tavitian B, Duconge F. Aptamers against extracellular targets for in vivo applications. *Biochimie* 2005; **87**: 921-930 [PMID: 15963620 DOI: 10.1016/j.biochi.2005.04.013]
- Cibiel A, Pestourie C, Duconge F. In vivo uses of aptamers selected against cell surface biomarkers for therapy and molecular imaging. *Biochimie* 2012; **94**: 1595-1606 [PMID: 22738730 DOI: 10.1016/j.biochi.2012.02.025]
- Ellington AD, Szostak JW. In vitro selection of RNA molecules that bind specific ligands. *Nature* 1990; **346**: 818-822 [PMID: 1697402 DOI: 10.1038/346818a0]
- Tuerk C, Gold L. Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase. *Science* 1990; **249**: 505-510 [PMID: 2200121 DOI: 10.1126/science.2200121]
- Ng EW, Shima DT, Calias P, Cunningham ET, Guyer DR, Adamis AP. Pegaptanib, a targeted anti-VEGF aptamer for ocular vascular disease. *Nat Rev Drug Discov* 2006; **5**: 123-132 [PMID: 16518379 DOI: 10.1038/nrd1955]
- Ahmadyousefi Y, Malih S, Mirzaee Y, Saidijam M. Nucleic acid aptamers in diagnosis of colorectal cancer. *Biochimie* 2019; **156**: 1-11 [PMID: 30244135 DOI: 10.1016/j.biochi.2018.09.009]
- Zhou G, Latchoumanin O, Hebbard L, Duan W, Liddle C, George J, Qiao L. Aptamers as targeting ligands and therapeutic molecules for overcoming drug resistance in cancers. *Adv Drug Deliv Rev* 2018; **134**: 107-121 [PMID: 29627370 DOI: 10.1016/j.addr.2018.04.005]
- Perez-Gonzalez C, Lafontaine DA, Penedo JC. Fluorescence-Based Strategies to Investigate the Structure and Dynamics of Aptamer-Ligand Complexes. *Front Chem* 2016; **4**: 33 [PMID: 27536656 DOI: 10.3389/fchem.2016.00033]
- Cai S, Yan J, Xiong H, Liu Y, Peng D, Liu Z. Investigations on the interface of nucleic acid aptamers and binding targets. *Analyst* 2018; **143**: 5317-5338 [PMID: 30357118 DOI: 10.1039/c8an01467a]
- Takahashi M. Aptamers targeting cell surface proteins. *Biochimie* 2018; **145**: 63-72 [PMID: 29198584 DOI: 10.1016/j.biochi.2017.11.019]
- Zhu B, Hernandez A, Tan M, Wollenhaupt J, Tabor S, Richardson CC. Synthesis of 2'-Fluoro RNA by Syn5 RNA polymerase. *Nucleic Acids Res* 2015; **43**: e94 [PMID: 25897116 DOI: 10.1093/nar/gkv367]
- Zhang Y, Lai BS, Juhas M. Recent Advances in Aptamer Discovery and Applications. *Molecules* 2019; **24**: pii: E941 [PMID: 30866536 DOI: 10.3390/molecules24050941]
- Wang T, Chen C, Larcher LM, Barrero RA, Veedu RN. Three decades of nucleic acid aptamer technologies: Lessons learned, progress and opportunities on aptamer development. *Biotechnol Adv* 2019; **37**: 28-50 [PMID: 30408510 DOI: 10.1016/j.biotechadv.2018.11.001]
- Blind M, Blank M. Aptamer Selection Technology and Recent Advances. *Mol Ther Nucleic Acids* 2015; **4**: e223 [PMID: 28110747 DOI: 10.1038/mtna.2014.74]
- Kinghorn AB, Fraser LA, Lang S, Shiu SCC, Tanner JA. Aptamer Bioinformatics. *Int J Mol Sci* 2017; **18**: pii: E2516 [PMID: 29186809 DOI: 10.3390/ijms18122516]
- Bayat P, Nosrati R, Aliboland M, Rafatpanah H, Abnous K, Khedri M, Ramezani M. SELEX methods on the road to protein targeting with nucleic acid aptamers. *Biochimie* 2018; **154**: 132-155 [PMID: 30193856 DOI: 10.1016/j.biochi.2018.09.001]
- Fitzwater T, Polisky B. A SELEX primer. *Methods Enzymol* 1996; **267**: 275-301 [PMID: 8743323 DOI: 10.1016/S0076-6879(96)67019-0]
- Cowperthwaite MC, Ellington AD. Bioinformatic analysis of the contribution of primer sequences to aptamer structures. *J Mol Evol* 2008; **67**: 95-102 [PMID: 18594898 DOI: 10.1007/s00239-008-9130-4]
- Wang L, Wang C, Li H. Selection of DNA aptamers and establishment of an effective aptasensor for highly sensitive detection of cefquinome residues in milk. *Analyst* 2018; **143**: 3202-3208 [PMID: 29872833 DOI: 10.1039/c8an00709h]
- Yang L, Ding P, Luo Y, Wang J, Lv H, Li W, Cao Y, Pei R. Exploration of Catalytic Nucleic Acids on Porphyrin Metalation and Peroxidase Activity by in Vitro Selection of Aptamers for N-Methyl Mesoporphyrin IX. *ACS Comb Sci* 2019; **21**: 83-89 [PMID: 30602113 DOI: 10.1021/acscombsci.8b00129]
- Luo Z, Zhou H, Jiang H, Ou H, Li X, Zhang L. Development of a fraction collection approach in capillary electrophoresis SELEX for aptamer selection. *Analyst* 2015; **140**: 2664-2670 [PMID: 25728760 DOI: 10.1039/c5an00183h]
- Song KM, Lee S, Ban C. Aptamers and their biological applications. *Sensors (Basel)* 2012; **12**: 612-631 [PMID: 22368488 DOI: 10.3390/s120100612]
- Zhuo Z, Yu Y, Wang M, Li J, Zhang Z, Liu J, Wu X, Lu A, Zhang G, Zhang B. Recent Advances in SELEX Technology and Aptamer Applications in Biomedicine. *Int J Mol Sci* 2017; **18**: pii: E2142 [PMID: 29036890 DOI: 10.3390/ijms18102142]
- Jenison RD, Gill SC, Pardi A, Polisky B. High-resolution molecular discrimination by RNA. *Science* 1994; **263**: 1425-1429 [PMID: 7510417 DOI: 10.1126/science.7510417]

- 26 **Li K**, Xiu CL, Gao LM, Shi M, Zhai Y. [Subtractive SELEX using agar beads for screening DNA aptamers with specific affinity to HIV gp41 antigen]. *Nan Fang Yi Ke Da Xue Xue Bao* 2016; **36**: 1592-1598 [PMID: [27998850](#)]
- 27 **Golden MC**, Collins BD, Willis MC, Koch TH. Diagnostic potential of PhotoSELEX-evolved ssDNA aptamers. *J Biotechnol* 2000; **81**: 167-178 [PMID: [10989176](#) DOI: [10.1016/S0168-1656\(00\)00290-X](#)]
- 28 **Ellington AD**, Szostak JW. Selection in vitro of single-stranded DNA molecules that fold into specific ligand-binding structures. *Nature* 1992; **355**: 850-852 [PMID: [1538766](#) DOI: [10.1038/355850a0](#)]
- 29 **Charlton J**, Kirschenheuter GP, Smith D. Highly potent irreversible inhibitors of neutrophil elastase generated by selection from a randomized DNA-valine phosphonate library. *Biochemistry* 1997; **36**: 3018-3026 [PMID: [9062133](#) DOI: [10.1021/bi962669h](#)]
- 30 **Morris KN**, Jensen KB, Julin CM, Weil M, Gold L. High affinity ligands from in vitro selection: Complex targets. *Proc Natl Acad Sci USA* 1998; **95**: 2902-2907 [PMID: [9501188](#) DOI: [10.1073/pnas.95.6.2902](#)]
- 31 **Martell RE**, Nevins JR, Sullenger BA. Optimizing aptamer activity for gene therapy applications using expression cassette SELEX. *Mol Ther* 2002; **6**: 30-34 [PMID: [12095300](#) DOI: [10.1006/mthe.2002.0624](#)]
- 32 **White R**, Rusconi C, Scardino E, Wolberg A, Lawson J, Hoffman M, Sullenger B. Generation of species cross-reactive aptamers using "toggle" SELEX. *Mol Ther* 2001; **4**: 567-573 [PMID: [11735341](#) DOI: [10.1006/mthe.2001.0495](#)]
- 33 **Cox JC**, Hayhurst A, Hesselberth J, Bayer TS, Georgiou G, Ellington AD. Automated selection of aptamers against protein targets translated in vitro: From gene to aptamer. *Nucleic Acids Res* 2002; **30**: e108 [PMID: [12384610](#) DOI: [10.1093/nar/gnf107](#)]
- 34 **Lisi S**, Fiore E, Scarano S, Pascale E, Boehman Y, Ducongé F, Chierici S, Minunni M, Peyrin E, Ravelet C. Non-SELEX isolation of DNA aptamers for the homogeneous-phase fluorescence anisotropy sensing of tau Proteins. *Anal Chim Acta* 2018; **1038**: 173-181 [PMID: [30278900](#) DOI: [10.1016/j.aca.2018.07.029](#)]
- 35 **Stoltenburg R**, Reinemann C, Strehlitz B. FluMag-SELEX as an advantageous method for DNA aptamer selection. *Anal Bioanal Chem* 2005; **383**: 83-91 [PMID: [16052344](#) DOI: [10.1007/s00216-005-3388-9](#)]
- 36 **Vater A**, Jarosch F, Buchner K, Klussmann S. Short bioactive Spiegelmers to migraine-associated calcitonin gene-related peptide rapidly identified by a novel approach: Tailored-SELEX. *Nucleic Acids Res* 2003; **31**: e130 [PMID: [14576330](#) DOI: [10.1093/nar/gng130](#)]
- 37 **Shimada T**, Ogasawara H, Ishihama A. Genomic SELEX Screening of Regulatory Targets of Escherichia coli Transcription Factors. *Methods Mol Biol* 2018; **1837**: 49-69 [PMID: [30109605](#) DOI: [10.1007/978-1-4939-8675-0_4](#)]
- 38 **Chen M**, Yu Y, Jiang F, Zhou J, Li Y, Liang C, Dang L, Lu A, Zhang G. Development of Cell-SELEX Technology and Its Application in Cancer Diagnosis and Therapy. *Int J Mol Sci* 2016; **17**: pii: E2079 [PMID: [27973403](#) DOI: [10.3390/ijms17122079](#)]
- 39 **Lee BH**, Kim SH, Ko Y, Park JC, Ji S, Gu MB. The sensitive detection of ODAM by using sandwich-type biosensors with a cognate pair of aptamers for the early diagnosis of periodontal disease. *Biosens Bioelectron* 2019; **126**: 122-128 [PMID: [30396019](#) DOI: [10.1016/j.bios.2018.10.040](#)]
- 40 **Tan Y**, Guo Q, Xie Q, Wang K, Yuan B, Zhou Y, Liu J, Huang J, He X, Yang X, He C, Zhao X. Single-walled carbon nanotubes (SWCNTs)-assisted cell-systematic evolution of ligands by exponential enrichment (cell-SELEX) for improving screening efficiency. *Anal Chem* 2014; **86**: 9466-9472 [PMID: [25184732](#) DOI: [10.1021/ac502166b](#)]
- 41 **Hung LY**, Wang CH, Hsu KF, Chou CY, Lee GB. An on-chip Cell-SELEX process for automatic selection of high-affinity aptamers specific to different histologically classified ovarian cancer cells. *Lab Chip* 2014; **14**: 4017-4028 [PMID: [25144781](#) DOI: [10.1039/c4lc00587b](#)]
- 42 **Wang CY**, Wu CY, Hung TC, Wong CH, Chen CH. Sequence-constructive SELEX: A new strategy for screening DNA aptamer binding to Globo H. *Biochem Biophys Res Commun* 2014; **452**: 484-489 [PMID: [25159850](#) DOI: [10.1016/j.bbrc.2014.08.086](#)]
- 43 **Ang A**, Ouellet E, Cheung KC, Haynes C. Highly Efficient and Reliable DNA Aptamer Selection Using the Partitioning Capabilities of ddPCR: The Hi-Fi SELEX Method. *Methods Mol Biol* 2018; **1768**: 531-554 [PMID: [29717463](#) DOI: [10.1007/978-1-4939-7778-9_30](#)]
- 44 **Mai G**, Enweronye O, Zumrut HE, Batool S, Van N, Mallikaratchy P. Systematic optimization and modification of a DNA aptamer with 2'-O-methyl RNA analogues. *ChemistrySelect* 2017; **2**: 2335-2340 [PMID: [29226219](#) DOI: [10.1002/slct.201700359](#)]
- 45 **Wang Z**, Xu W, Liu L, Zhu TF. A synthetic molecular system capable of mirror-image genetic replication and transcription. *Nat Chem* 2016; **8**: 698-704 [PMID: [27325097](#) DOI: [10.1038/nchem.2517](#)]
- 46 **Gissberg O**, Zaghoul EM, Lundin KE, Nguyen CH, Landras-Guetta C, Wengel J, Zain R, Smith CI. Delivery, Effect on Cell Viability, and Plasticity of Modified Aptamer Constructs. *Nucleic Acid Ther* 2016; **26**: 183-189 [PMID: [26859550](#) DOI: [10.1089/nat.2015.0592](#)]
- 47 **Haruta K**, Otaki N, Nagamine M, Kayo T, Sasaki A, Hiramoto S, Takahashi M, Hota K, Sato H, Yamazaki H. A Novel PEGylation Method for Improving the Pharmacokinetic Properties of Anti-Interleukin-17A RNA Aptamers. *Nucleic Acid Ther* 2017; **27**: 36-44 [PMID: [27827561](#) DOI: [10.1089/nat.2016.0627](#)]
- 48 **Lee CH**, Lee SH, Kim JH, Noh YH, Noh GJ, Lee SW. Pharmacokinetics of a Cholesterol-conjugated Aptamer Against the Hepatitis C Virus (HCV) NS5B Protein. *Mol Ther Nucleic Acids* 2015; **4**: e254 [PMID: [26440598](#) DOI: [10.1038/mtna.2015.30](#)]
- 49 **Ali MH**, Elsherbiny ME, Emar M. Updates on Aptamer Research. *Int J Mol Sci* 2019; **20**: pii: E2511 [PMID: [31117311](#) DOI: [10.3390/ijms20102511](#)]
- 50 **Xu J**, Liao S, Tian C, Zhang L, Zhai M, Chen C, Tang J, Zeng J. [Screening of nucleic acid aptamer of lung cancer cells based on cell exponential enrichment ligand system evolution and its application in tumor diagnosis and treatment]. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi* 2018; **35**: 964-969 [PMID: [30583324](#) DOI: [10.7507/1001-5515.201806006](#)]
- 51 **Li G**, Zeng J, Liu H, Ding P, Liang J, Nie X, Zhou Z. A fluorometric aptamer nanoprobe for alpha-fetoprotein by exploiting the FRET between 5-carboxyfluorescein and palladium nanoparticles. *Mikrochim Acta* 2019; **186**: 314 [PMID: [31041529](#) DOI: [10.1007/s00604-019-3403-z](#)]
- 52 **Hu Z**, Tan J, Lai Z, Zheng R, Zhong J, Wang Y, Li X, Yang N, Li J, Yang W, Huang Y, Zhao Y, Lu X. Aptamer Combined with Fluorescent Silica Nanoparticles for Detection of Hepatoma Cells. *Nanoscale Res Lett* 2017; **12**: 96 [PMID: [28176286](#) DOI: [10.1186/s11671-017-1890-6](#)]
- 53 **Wang S**, Zhang C, Wang G, Cheng B, Wang Y, Chen F, Chen Y, Feng M, Xiong B. Aptamer-Mediated Transparent-Biocompatible Nanostructured Surfaces for Hepotocellular Circulating Tumor Cells Enrichment. *Theranostics* 2016; **6**: 1877-1886 [PMID: [27570557](#) DOI: [10.7150/thno.15284](#)]
- 54 **Joo M**, Baek SH, Cheon SA, Chun HS, Choi SW, Park TJ. Development of aflatoxin B1 aptasensor based

- on wide-range fluorescence detection using graphene oxide quencher. *Colloids Surf B Biointerfaces* 2017; **154**: 27-32 [PMID: 28285035 DOI: 10.1016/j.colsurfb.2017.03.010]
- 55 **Kaur H.** Aptamer Conjugated Quantum Dots for Imaging Cellular Uptake in Cancer Cells. *J Nanosci Nanotechnol* 2019; **19**: 3798-3803 [PMID: 30764936 DOI: 10.1166/jnn.2019.16735]
- 56 **Zhou Y, Li W, Tseng Y, Zhang J, Liu J.** Developing slow-off dickkopf-1 aptamers for early-diagnosis of hepatocellular carcinoma. *Talanta* 2019; **194**: 422-429 [PMID: 30609553 DOI: 10.1016/j.talanta.2018.10.014]
- 57 **Yu Q, Zhai F, Zhou H, Wang Z.** Aptamer Conformation Switching-Induced Two-Stage Amplification for Fluorescent Detection of Proteins. *Sensors (Basel)* 2018; **19**: pii: E77 [PMID: 30587808 DOI: 10.3390/s19010077]
- 58 **Bayat P, Taghdisi SM, Rafatpanah H, Abnous K, Ramezani M.** In vitro selection of CD70 binding aptamer and its application in a biosensor design for sensitive detection of SKOV-3 ovarian cells. *Talanta* 2019; **194**: 399-405 [PMID: 30609550 DOI: 10.1016/j.talanta.2018.10.063]
- 59 **Bouvier-Müller A, Ducongé F.** Application of aptamers for in vivo molecular imaging and theranostics. *Adv Drug Deliv Rev* 2018; **134**: 94-106 [PMID: 30125606 DOI: 10.1016/j.addr.2018.08.004]
- 60 **Yan H, Gao X, Zhang Y, Chang W, Li J, Li X, Du Q, Li C.** Imaging Tiny Hepatic Tumor Xenografts via Endoglin-Targeted Paramagnetic/Optical Nanoprobe. *ACS Appl Mater Interfaces* 2018; **10**: 17047-17057 [PMID: 29708329 DOI: 10.1021/acsami.8b02648]
- 61 **Zhong L, Zou H, Huang Y, Gong W, He J, Tan J, Lai Z, Li Y, Zhou C, Zhang G, Li G, Yang N, Zhao Y.** Magnetic Endoglin Aptamer Nanoprobe for Targeted Diagnosis of Solid Tumor. *J Biomed Nanotechnol* 2019; **15**: 352-362 [PMID: 30596557 DOI: 10.1166/jbn.2019.2688]
- 62 **Zhao M, Liu Z, Dong L, Zhou H, Yang S, Wu W, Lin J.** A GPC3-specific aptamer-mediated magnetic resonance probe for hepatocellular carcinoma. *Int J Nanomedicine* 2018; **13**: 4433-4443 [PMID: 30122918 DOI: 10.2147/IJN.S168268]
- 63 **Cao H, Fang X, Li H, Li H, Kong J.** Ultrasensitive detection of mucin 1 biomarker by immuno-loop-mediated isothermal amplification. *Talanta* 2017; **164**: 588-592 [PMID: 28107977 DOI: 10.1016/j.talanta.2016.07.018]
- 64 **Bates PJ, Laber DA, Miller DM, Thomas SD, Trent JO.** Discovery and development of the G-rich oligonucleotide AS1411 as a novel treatment for cancer. *Exp Mol Pathol* 2009; **86**: 151-164 [PMID: 19454272 DOI: 10.1016/j.yexmp.2009.01.004]
- 65 **Soldevilla MM, Meraviglia-Crivelli de Caso D, Menon AP, Pastor F.** Aptamer-iRNAs as Therapeutics for Cancer Treatment. *Pharmaceuticals (Basel)* 2018; **11**: pii: E108 [PMID: 30340426 DOI: 10.3390/ph11040108]
- 66 **Zhu G, Chen X.** Aptamer-based targeted therapy. *Adv Drug Deliv Rev* 2018; **134**: 65-78 [PMID: 30125604 DOI: 10.1016/j.addr.2018.08.005]
- 67 **Hu Z, He J, Gong W, Zhou N, Zhou S, Lai Z, Zheng R, Wang Y, Yang X, Yang W, Zhong L, Lu X, Zhao Y.** TLS11a Aptamer/CD3 Antibody Anti-Tumor System for Liver Cancer. *J Biomed Nanotechnol* 2018; **14**: 1645-1653 [PMID: 29958558 DOI: 10.1166/jbn.2018.2619]
- 68 **Xiao S, Liu Z, Deng R, Li C, Fu S, Chen G, Zhang X, Ke F, Ke S, Yu X, Wang S, Zhong Z.** Aptamer-mediated gene therapy enhanced antitumor activity against human hepatocellular carcinoma in vitro and in vivo. *J Control Release* 2017; **258**: 130-145 [PMID: 28522194 DOI: 10.1016/j.jconrel.2017.05.017]
- 69 **Sábio RM, Meneguín AB, Ribeiro TC, Silva RR, Chorilli M.** New insights towards mesoporous silica nanoparticles as a technological platform for chemotherapeutic drugs delivery. *Int J Pharm* 2019; **564**: 379-409 [PMID: 31028801 DOI: 10.1016/j.ijpharm.2019.04.067]
- 70 **Babaei M, Abnous K, Taghdisi SM, Amel Farzad S, Peivandi MT, Ramezani M, Alibolandi M.** Synthesis of theranostic epithelial cell adhesion molecule targeted mesoporous silica nanoparticle with gold gatekeeper for hepatocellular carcinoma. *Nanomedicine (Lond)* 2017; **12**: 1261-1279 [PMID: 28520529 DOI: 10.2217/nmm-2017-0028]
- 71 **Lan S, Lin Z, Zhang D, Zeng Y, Liu X.** Photocatalysis Enhancement for Programmable Killing of Hepatocellular Carcinoma through Self-Compensation Mechanisms Based on Black Phosphorus Quantum-Dot-Hybridized Nanocatalysts. *ACS Appl Mater Interfaces* 2019; **11**: 9804-9813 [PMID: 30773883 DOI: 10.1021/acsami.8b21820]
- 72 **Wang R, Zhao N, Li S, Fang JH, Chen MX, Yang J, Jia WH, Yuan Y, Zhuang SM.** MicroRNA-195 suppresses angiogenesis and metastasis of hepatocellular carcinoma by inhibiting the expression of VEGF, VAV2, and CDC42. *Hepatology* 2013; **58**: 642-653 [PMID: 23468064 DOI: 10.1002/hep.26373]
- 73 **Liu Y, Wu X, Gao Y, Zhang J, Zhang D, Gu S, Zhu G, Liu G, Li X.** Aptamer-functionalized peptide H3CR5C as a novel nanovehicle for codelivery of fasudil and miRNA-195 targeting hepatocellular carcinoma. *Int J Nanomedicine* 2016; **11**: 3891-3905 [PMID: 27574422 DOI: 10.2147/IJN.S108128]
- 74 **Cheng Y, Ou Z, Li Q, Yang J, Hu M, Zhou Y, Zhuang X, Zhang ZJ, Guan S.** Cabazitaxel liposomes with aptamer modification enhance tumor targeting efficacy in nude mice. *Mol Med Rep* 2019; **19**: 490-498 [PMID: 30483775 DOI: 10.3892/mmr.2018.9689]
- 75 **Qu L, Xu J, Tan X, Liu Z, Xu L, Peng R.** Dual-aptamer modification generates a unique interface for highly sensitive and specific electrochemical detection of tumor cells. *ACS Appl Mater Interfaces* 2014; **6**: 7309-7315 [PMID: 24801611 DOI: 10.1021/am5006783]



Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

