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REVIEW – CANCER RESEARCH

Novel insights into the role of aptamers in the fight against cancer

Yasen Maimaitiyiming[1] · De Fei Hong[2] · Chang Yang[1] · Hua Naranmandura[1,3]

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Abstract

Purpose Aptamers are a class of single-stranded nucleic acid (DNA or RNA) oligonucleotides that are screened in vitro by a technique called systematic evolution of ligands by exponential enrichment (SELEX). They have stable three-dimensional structures that can bind to various targets with high affinity and specificity. Due to distinct properties such as easy synthesis, high stability, small size, low toxicity and immunogenicity, they have been largely studied as anticancer agents/tools. Consequently, aptamers are starting to play important roles in disease prevention, diagnosis and therapy. This review focuses on studies that evaluated the effect of aptamers on various aspects of cancer therapy. It also provides novel and unique insights into the role of aptamers on the fight against cancer.

Methods We reviewed literatures about the role of aptamers against cancer from PUBMED databases in this article.

Results Here, we summarized the role of aptamers on the fight against cancer in a unique point of view. Meanwhile, we presented novel ideas such as aptamer–pool–drug conjugates for the treatment of refractory cancers.

Conclusions Aptamers and antibodies should form a "coalition" against cancers to maximize their advantages and minimize disadvantages.

Keywords Aptamer · Antibody · Cancer cell heterogeneity and plasticity · Targeted therapy · Immunotherapy · SELEX

Introduction

Cancer is one of the most life-threatening diseases (Bray et al. 2018), which is characterized by the aberrant cell growth along with the potential of metastasis or proliferation to distant tissues and/or organs (Cosphiadi et al. 2018). Common features of cancer cells include resistance to cell death and senescence, sustained proliferation, abnormal metabolism, promoted angiogenesis, self-renewal, activated invasion, metastasis and so on (Cosphiadi et al. 2018). According to the CLOBOCAN 2018 estimates of cancer incidence, there would be over 18.1 million new cancer cases and 9.6 million cancer deaths in 2018 (Bray et al. 2018). This would be a great burden for cancer patients and social healthcare systems all around the world. Thus, it is of great importance to find out effective ways to cope with cancer.

Over the last century, many scientists have conducted research on cancer biology and therapy (Perlmutter et al. 2013). Although some cancers have been successfully cured, there is still a strong need for new therapeutic agents or approaches to cure refractory cancers as well as improve the existing treatment efficacy (Mody et al. 2018). Chemotherapy and radiotherapy are the most common therapeutic approaches for cancer apart from surgery. But the adverse effects of the chemotherapeutics and radiation may damage normal cells and lead to serious consequences like the collapse of immune system, which will in turn cause other cancers or serious infections (Kerns et al. 2014; Menon et al. 2018). Thus, clinicians and researchers have enhanced their focus on immunotherapy and targeted therapy to decrease and even circumvent adverse effects of potent drugs as well as radiation (Lehman et al. 2017).

It has been reported that cancer cells abnormally express a specific type of molecules (known as tumor-associated antigens, TAAs) on their cell membrane, which can be

✉ Hua Naranmandura
narenman@zju.edu.cn

[1] Department of Pharmacology, School of Medicine, Zhejiang University, Hangzhou, China

[2] The Affiliated Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China

[3] Department of Toxicology, School of Medicine and Public Health, Zhejiang University, Hangzhou 310058, Zhejiang, China

recognized by the individual immune system (Weinstein and Case 2008; Qin et al. 2014; Liu et al. 2015). Cancer immunotherapy is a promising approach to eliminate cancer cells (Mellman et al. 2011), and it is commonly categorized into active and passive two types (Brody and Holtzman 2008). For instance, active immunotherapy is attained through stimulating the generation of TAA-specific antibodies and thereby increases intrinsic immune response which results in induction of antibody dependent cell-mediated cytotoxicity that leads to cancer cell death (Chodon et al. 2015). While, passive immunotherapy includes the application of external monoclonal antibodies, lymphocytes and cytokines to enhance the existing anti-tumor response (Karagiannis et al. 2012). Currently, immunotherapy has become the standard treatment approach for several types of cancer (Korneev et al. 2017). However, due to lack of discovery of unique and potential TAAs, target specific antibodies and immune regulatory agents turn into factors that restrict broader application of cancer immunotherapy (Kono 2014; Jia et al. 2017).

Targeted therapy is a preeminent approach to block the growth or induce the death of cancer cells by precise delivery of chemotherapeutics to specific target sites so as to decrease and/or eliminate toxic effects of chemotherapeutic agents to normal tissues and cells (Lipowska-Bhalla et al. 2012; Hainsworth et al. 2018). In particular, conjugation of the drugs with target specific affinity molecules (e.g., antibody, nanoparticles, aptamers and peptides) is the major approach to attain targeted therapy. Since the anticancer drugs could be specifically delivered into cancer cells or solid tumors by affinity molecules, the adverse effects as well as administration dose will be significantly decreased (Baudino 2015). Thus, targeted therapy is a promising treatment approach that is practicable with the help of cancer cell marker-specific affinity molecules and proper drugs through physical or chemical linking (Juilleratjeanneret and Schmitt 2010).

As the most studied affinity molecules, monoclonal antibodies have already been used for cancer treatment in clinic (Capdevila et al. 2009). Currently, several immunotherapeutic antibodies and antibody-mediated targeted delivery agents have been approved by FDA and available in the market (Moja et al. 2006; Demko et al. 2008; Lemery et al. 2010; Tandan et al. 2017). Antibody is commonly generated by the host immune system (e.g., B lymphocytes) to capture the specific antigens entering the body (Houdebine 2011). Molecular level recognition of antigens by the immune system results in selective production of antibodies that are able to bind with specific antigens and lead to their eradication from the circulation.

However, with the increasing demand on affinity molecules, antibodies have also shown some limitations such as the long time span, notable inter-batch variability and auto-inflammatory response in vivo (Beck et al. 2010; Houdebine 2011; Friedman et al. 2016). On the other hand, the advent of oligonucleotide aptamers is gradually filling in this gap. Aptamers are a group of novel and promising recognition units. They are short single-stranded DNA (ssDNA) or RNA molecules (also called chemical antibody) that can specifically bind to target proteins, peptides or other small molecules with high affinity (Tuerk and Gold 1990). In fact, the ability of aptamers to selectively bind to different targets is based on their distinct three-dimensional structures, which allow them to form stable and specific complexes with varying targets (Bouvier-Müller and Ducongé 2018). Due to these superior properties, they are more and more being acknowledged by both the basic and clinical researchers.

Aptamers can be easily obtained by experimental and computational techniques. In general, aptamers are commonly screened in vitro from a large (10^{13-16}) oligonucleotide (i.e., ssDNA or RNA) pool by a technique called systematic evolution of ligands by exponential enrichment (SELEX), which contains iterative rounds of selection and amplification steps (Bouvier-Müller and Ducongé 2018), as shown in Fig. 1. Although many modified SELEX methods have been reported, the classical SELEX-based approach is still the core technique. In fact, many specific aptamers have been successfully screened by SELEX approach and applied on diverse fields (Zhou et al. 2017; Bouvier-Müller and Ducongé 2018). Therefore, aptamers are considered to be potential candidates in the cancer treatment.

What make aptamers so attractive?

It has been more than 28 years since the concept of SELEX was presented by Tuerk and Gold (1990). First aptamer-based drug Macugen (RNA aptamer) was approved by FDA in 2004 for the treatment of age-related macular degeneration (AMD) (Vinores 2006). To date, a number of aptamer-based drugs have been evaluated in clinical trials (Table 1). Comparing with antibodies, aptamers possess some unique properties as follows: (1) aptamers are faster to acquire and more economical to produce (chemically synthesizing in vitro during very short time) (Yang et al. 2019). (2) Aptamers have less immunogenicity which make them safer for in vivo applications such as diagnosis, imaging and target-specific carrier molecules (Zhou et al. 2017). (3) The smaller size of oligonucleotides determined their faster tissue penetration and cellular internalization, which make them feasible candidates for targeted drug delivery (Cheng et al. 2013; Bouvier-Müller and Ducongé 2018). (4) It is facile to modify aptamers which in term determined their important applications in fluorescence-related detection and imaging techniques, as well as detection of trace amount of proteins or other substances in diverse conditions (Zeng et al. 2014a, b). (5) Their targets vary from small

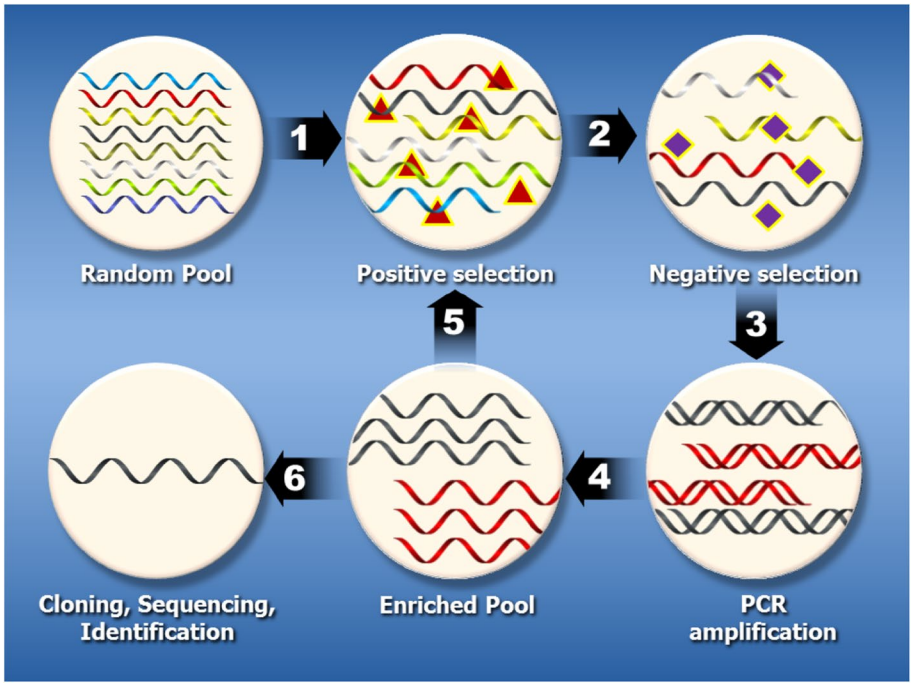

Fig. 1 Illustration of the typical SELEX. General steps of SELEX approach. 1: Preparation of random pool and incubation with the target; 2: elution of target bound sequences and proceeding of negative selection; 3: PCR amplification of the nonbinding pool to negative cells; 4: preparation of single-stranded oligonucleotide pool; 5: beginning of the next round selection if the pool is not enriched well; 6: cloning and sequencing of last enriched pool and identification of optimal aptamer sequence

Table 1 Aptamers evaluated in clinical trials

Name	Nucleotide	Modification	Target	Application	Phase	References
Macugen	28 nt RNA	Nuclease stabilization, PEGylation	$VEGF_{165}$	AMD	Approved	Vinores (2006)
EYE001	27 nt RNA	Nuclease stabilization, PEGylation	$VEGF_{165}$	AMD	Phase III	Eyetech Study Group (2002)
E10030	29 nt DNA	Nuclease stabilization, PEGylation	PDGF	AMD	Phase III	Jaffe et al. (2017)
REG1	34 nt RNA	Nuclease stabilization, PEGylation	Factor IXa	Anticoagulation, ACS	Phase II	Povsic et al. (2014), Lincoff et al. (2016)
AS1411	26 nt DNA	None	Nucleolin	MRCC, AML	Phase II	Bates et al. (2009), Mongelard and Bouvet (2010)
ARC1779	40 nt RNA	Nuclease stabilization, PEGylation	vWF	Thrombosis, AMI	Phase II	Spiel et al. (2009)
Nu172	26 nt DNA	Nuclease stabilization	Thrombin	Anticoagulation	Phase II	Buff et al. (2009)
ARC1905	39 nt RNA	Nuclease stabilization, PEGylation	C5	AMD	Phase II	Leung and Landa (2013)
NOX-A12	45 nt L-RNA	PEGylation	SDF-1	CLL, RMM	Phase II	Vater and Klussmann (2015)
NOX-E36	40 nt L-RNA	PEGylation	MCP-1	T2DM, DN	Phase II	Vater and Klussmann (2015)
NOX-H94	44 nt L-RNA	PEGylation	Hepcidin	Anemia	Phase I	Van Eijk et al. (2014), Vater and Klussmann (2015)
ARC19499	33 nt RNA	Nuclease stabilization, PEGylation	TFPI	Hemophilia	Phase I	Gissel et al. (2012)

Common methods of nuclease stabilization include the following: (1) backbone modifications such as 2′-fluoro (2′F), 2′-amino (2′NH2) or 2′-O-methyl (2′OMe) ribose groups. (2) Substitution of phosphate linkages (PO) with sulfur-containing phosphorothioate linkages (PS). (3) Capping 3′ end with an inverted dT residue as well as conjugation of PEG to the 5′ end. (4) Application of locked nucleic acids such as L-RNA

VEGF vascular endothelial growth factor, *PEG* polyethylene glycol, *AMD* age-related macular degeneration, *ACS* acute coronary syndrome, *MRCC* metastatic renal cell carcinoma, *AML* acute myeloid leukemia, *AMI* acute myocardial infarction, *Vwf* Willebrand factor, *C5* complement component 5, *PDGF* platelet-derived growth factor, *CLL* chronic lymphocytic leukemia, *RMM* relapsed multiple myeloma, *T2DM* type 2 diabetes mellitus, *DN* diabetic nephropathy, *SDF-1* stromal cell-derived factor 1, *MCP-1* monocyte chemoattractant protein 1, *TFPI* tissue factor pathway inhibitor

inorganic molecules to organic complexes or even whole cells, and aptamers can be generated without any knowledge of target molecule. This also makes them promising tools for the discovery of unknown biomarkers (Chang et al. 2013). (6) Aptamers are stable in harsh conditions (such as high temperature) which yield a much higher shelf life, and they can tolerate transportation and reserve without any special requirements for cooling, eliminating the need for a continuous cooling equipment (Chang et al. 2013; Bouvier-Müller and Ducongé 2018).

Additionally, it is not necessary to purify the target molecules for selection of aptamers. As a result, aptamers can be selected in the original biological conditions of various targets (Chang et al. 2013). Cheng et al. (2013) have selected a group of aptamers that could penetrate into the mouse brain. They intravenously injected the aptamer pool from the tail, after a fixed time they took out the mouse brain and recycled the aptamers which could pass blood–brain barrier (BBB) and enter the brain. Finally, they successfully enriched and selected the aptamers with superior ability of brain penetration by this in vivo selection method. Optimistically, difficulties to deliver chemotherapeutics into brain are expected to be solved by such group of aptamers.

Protein-based SELEX and cell-based SELEX are the most common selection methods of aptamers (Elle et al. 2015; Maimaitiyiming et al. 2019). For instance, circulating tumor cells (CTCs) are one type of cancer-related cells appeared in human blood during cancer progression. However, it is very challenging to identify their presence or even discover proper biomarkers due to the extremely low amount of them in the blood circulation (Plaks et al. 2015). Both cell-based and protein-based SELEX approaches were applied to obtain CTC targeting aptamers that could specifically recognize and identify the CTC-like cells from a mixture of different cell populations (Song et al. 2013; Li et al. 2018). Thus, aptamers might open a new era in CTC detection and early diagnosis of cancer. Besides, new and smart SELEX methods like Hybrid (combination of protein and cell) SELEX have also been widely used to screen highly specific aptamers (Bayat et al. 2018). CD30 protein is highly expressed in the membrane of Hodgkins lymphoma and anaplastic large cell lymphoma (ALCL) cells and deemed as an important target for therapy (Ramos et al. 2017). A serum-stabilized ssDNA aptamer that binds to CD30 with high affinity was generated via a hybrid SELEX method (Korneev et al. 2017). And the multivalent form of this aptamer was able to induce ALCL cell apoptosis by disturbing CD30 signaling (Parekh et al. 2013). This implies that aptamers might exert important roles in signaling pathway regulation.

Moreover, the selection of aptamers can be automatized. This is because of the iterative repeating nature of SELEX. Currently, in a very short time, one can select tens of aptamers in a highly parallel, fully automated procedure, obtaining aptamers to varying targets which could work in the predesigned biological conditions, with specificities alike to monoclonal antibodies (Cox et al. 2002). Hünniger et al. (2014) came up with an idea to automatically generate aptamers that was called "Just in Time-Selection". They fixed targets (proteins or other molecules) at the surface of magnetic beads, and then inserted beads into an oligonucleotide pool. After incubation for 15–40 min, the target specific aptamers bound with the beads, and these beads were further isolated by magnetic force just as "fishing". Then, the target binding aptamers were separated and gone through semi-automatic PCR amplification with the help of magnetic beads again. By this approach, many parallel groups of selection could be automatically conducted, which enable one to simultaneously select aptamers for varying targets. Moreover, there are some other reports about automated SELEX (Zhang et al. 2000; Gopinathan et al. 2017), and these fully or partially automated procedures could shorten the selection procedure and gain more time for concomitant application.

All of the above properties make aptamers promising tools for application in various fields and studies on aptamer-based drugs, drug carriers as well as diagnostic tools have already turned into a research hotspot (Sundaram et al. 2012; Ashrafuzzaman 2014). Zhu et al. (2013) have developed aptamer-tethered DNA nanotrain for target-specific delivery of molecular drugs for cancer treatment. The same group has also presented several different approaches for target-specific delivery of drugs with aptamer-based carriers (Zhu et al. 2012; Li et al. 2016). Anti-PSMA aptamer A10-3.2 oriented lipid nano-bubbles were constructed for the diagnosis of prostate cancer (Fan et al. 2016). Satisfactory results were obtained after testing this diagnostic on mice. Hence, aptamers are feasible and promising agents/tools.

As abovementioned, obstructions of immunotherapy and targeted therapy lie in lack of appropriate immune regulators, biomarkers and target-specific affinity molecules. Many high-mortality rate cancers could be successfully cured if they are detected at an early phase (Di Gioia et al. 2015). However, a high examining fee and scarcity of appropriate probes are major obstacles to obtain that. Fortunately, aptamers are like "civilianized version of antibodies" which is going to fill in the gap generated by disadvantages of antibodies. In general, aptamers can be applied for clinical treatment after nuclease stabilization and polyethylene glycol (PEG) conjugation (Table 1). Thus, it is reasonable and necessary to make good use of aptamers in the fight against cancer.

Aptamers and immunotherapy

Immunotherapy is considered as one of the most promising tactics for treating refractory cancers. Notably, the major characteristic of cancer is the aberrant growth of cancer

cells, and these cancer cells abnormally express membrane proteins termed as TAAs (Weinstein and Case 2008). Fortunately, the intrinsic immune system could generate specific antibodies to capture these types of cancer cells, which could induce cancer cell death (Qin et al. 2014). However, most of the cancer patients' immunity is weakened and unable to produce TAA-specific antibodies (Liu et al. 2015). Therefore, application of immune-stimulating agents such as administration of cytokines, lymphocytes and other immune modulators as well as enhancement of cancer antigenicity become major immunotherapeutic approaches (Weiner et al. 2010; Lee et al. 2015).

Due to the unique advantages, immunotherapy has been accepted as the standard treatment method for some relapsed or refractory cancers. Several immunotherapeutic antibodies against a variety of cancers have been approved by FDA (Moja et al. 2006; Demko et al. 2008; Weiner et al. 2010). Since it is attained through enhancement of intrinsic immune system, there would be little adverse effects (Xu 2014; Lehman et al. 2017). However, the major challenges of cancer immunotherapy still lie in low immunogenicity of cancer cells, and scarcity of immune regulators to enhance the intrinsic immune response (Lutz et al. 2014; Jia et al. 2017). Moreover, clinical application of monoclonal antibodies may also lead to some unanticipated adverse effects such as hepatic toxicity and auto-inflammatory responses like fatal cytokine storm (Attarwala 2010; Khedri et al. 2015; Friedman et al. 2016; Gianfranco et al. 2013). Being a newly emerged affinity molecule, aptamers are showing great potential in cancer immunotherapy (Khedri et al. 2015; Ganji et al. 2016). Consequently, aptamers can be used to cope with the major challenges in cancer immunotherapy as mentioned above.

Cancer-targeting aptamers generated by cell-based SLELX can be used for the selective recognition and elimination of tumorigenic cells. More importantly, cell-based SELEX could also be applied to discover new biomarkers of cancer cells that might also include TAAs (Chang et al. 2013). Regarding screening of aptamers by cell-based SELEX, it includes many rounds of positive (cancer cells) and negative (normal cells) selection (Fig. 1). Tumor cell-specific aptamers (targeting cell surface membrane proteins) could be obtained by applying proper positive and negative cells. Then, the cancer cell-specific aptamer can be conjugated with biotin to identify the unknown biomarkers through incubating with tumor cell membrane lysates and pulling down by streptavidin labeled affinity beads, as shown in Fig. 2. An aptamer targeting primary cultured tumor endothelial cells was identified by cell-based SELEX (Ara et al. 2012). Later on, troponin T was discovered as a new marker of endothelial cells with the help of this aptamer (Ara et al. 2014). Recently, nasopharyngeal carcinoma (NPC)-specific biomarker CD109 was identified by aptamer S3 obtained through cell-based SELEX using NPC cell line as positive cells and normal nasopharyngeal (NP) cell as negative cells (Jia et al. 2016).

As abovementioned, sparsity of activators and modulators of immune response against TAAs are another restricting factor of cancer immunotherapy. Opportunely, some studies have reported that aptamers can block or activate immune receptors and cytokines which modulate intrinsic immune responses against cancers (Khedri et al. 2015; Ganji et al. 2016). Currently, the aptamers with immunotherapeutic

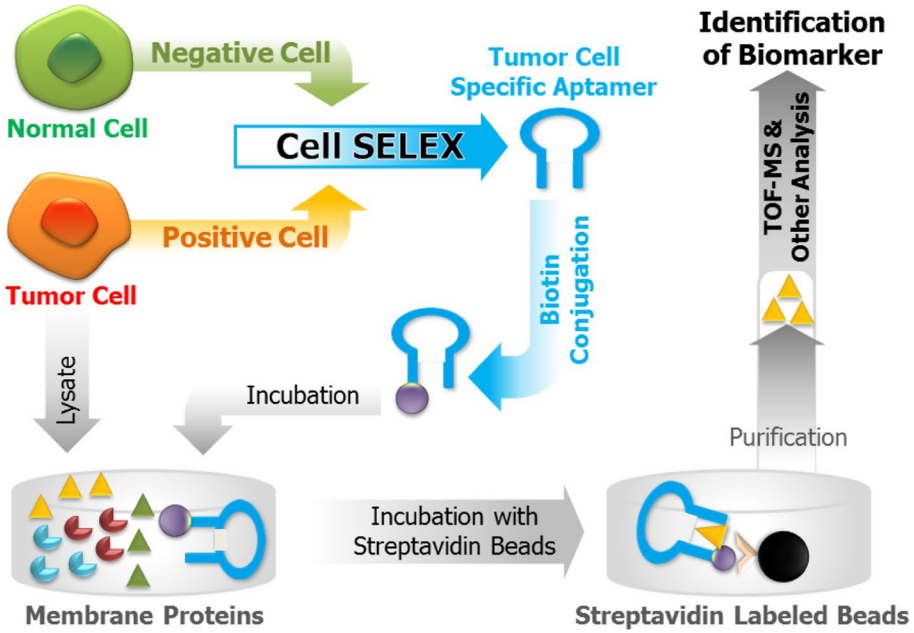

Fig. 2 Flow chart of aptamer-mediated biomarker identification. At first, cancer cell-specific aptamer is generated by cell SELEX. Then, the aptamer is labeled with biotin and incubated with tumor cell membrane protein lysate. Next, the aptamer–biomarker complex is pulled down by streptavidin labeled affinity beads. Finally, the pulled down biomarker is isolated, purified and analyzed by TOF-MS and other approaches to reveal its identity

value are roughly categorized into three groups according to their varying targets, which are immune checkpoints, cytokines and immune receptors (Soldevilla et al. 2016a).

In 2003, high-affinity RNA aptamers against cytotoxic T cell antigen-4 (CTLA-4) were obtained by protein-based SELEX and they showed strong target-specific binding affinity both in vitro and in vivo (Santulli-Marotto et al. 2003). Further, the tetravalent form of aptamers has exhibited enhanced binding activity and in both cases, the aptamers exhibited adequate immune stimulating effects. Since then, many reports sprang up about the favorable effects of aptamers in cancer immunotherapy. Anti-membrane-bound molecules programmed death 1 (PD-1) therapies are frequently used to treat different types of cancers (Swaika et al. 2015), which belongs to the immune checkpoint (Alsaab et al. 2017; Dermani et al. 2019). Importantly, interaction of PD-1 and its ligand PD-L1 assists tumor cells in escaping from the immune system by inhibiting interleukin-2 (IL-2) secretion from primary T cells, finally causing immune suppression (Swaika et al. 2015). Interestingly, the aptamer MP7 was screened from a random DNA library using recombinant chimeric protein containing mouse PD-1 extracellular domain (Prodeus et al. 2015). An in vivo experiment showed that this aptamer could block mouse PD-1 and PD-L1 interaction and abolish suppression of IL-2 secretion and T cell exhaustion.

In fact, aptamers can tightly bind with targets in a specific manner similar with antibodies via structural elements and might affect cell growth (Mi et al. 2005). Two slow off-rate modified aptamers (SOMAmers) carrying hydrophobic base modifications were selected by protein-based SELEX using biotinylated recombinant human interleukin-6 (IL-6) which could inhibit IL-6 signaling pathway (Gupta et al. 2014). Both SOMAmers significantly prohibited IL-6 signaling by hindering the interaction of IL-6 with its ligand and repressed the proliferation of tumor cells in vitro with same effect as tocilizumab (monoclonal antibody drug).

Pastor et al. (2013) screened two RNA aptamers against murine recombinant CD28 protein, one of them could interfere with the binding between CD28 and its ligand B7. This binding positively adjusted immune response and resulted in increased activity of antigen-presenting dendritic cells. Furthermore, MRP1-CD28 bivalent aptamer was engineered to stimulate immune response against refractory melanoma. Consequently, growth of melanoma xenograft on mice was reduced after treatment with this bispecific aptamer (Soldevilla et al. 2016b).

Additionally, aptamers as cargos could also load and deliver drugs or siRNAs into target cells to regulate the immune response. For example, signal transducer and activator of transcription 3 (STAT3) siRNA was precisely delivered into regulatory T cells, exhausted $CD8^+$ T cells and T cell lymphoma cells by cytotoxic T cell antigen-4 (CTLA-4) targeting aptamer mediated delivery and resulted in inhibition of STAT3 activation (Herrmann et al. 2014). Further, this complex ($CTLA4^{apt}$–STAT3 siRNA) was used to treat malignant CTLA-4 positive T-cell lymphoma-bearing mice and it significantly decreased tumor size, indicating that aptamer-mediated siRNA delivery is a promising approach of cancer immunotherapy (Herrmann et al. 2014).

There are yet many other aptamers with immune modulatory capacities (Khedri et al. 2015; Soldevilla et al. 2016a). With their superior properties such as easy synthesis, small size, fast penetration and low immunogenicity, it is likely that immune response modulating aptamers will become important therapeutics or adjuvants to treat cancers. Furthermore, implementation of aptamer-mediated immunotherapy in clinic might increase cost effectiveness of cancer treatment and make it more accessible as well as affordable for cancer patients.

Aptamers and cancer targeted therapy

The fight between humans and cancer has lasted for hundreds of years (Shalapour and Karin 2015). However, many types of cancers still remain without an effective therapeutic approach due to the lack of appropriate biomarkers and molecular targets (Wang and Huang 2017). Even though some cancers can be successfully treated with regular approaches, disease-free survival is very low owing to the relapse of the cancer (Zhu et al. 2014). Moreover, some cancer cells always manage to escape therapeutic agents and form secondary tumors which include many complicated molecular processes (Meacham and Morrison 2013; Roesch 2014). These types of secondary tumors are frequently resistant to the therapeutic agents applied in primary tumors and easily lead to relapse of the disease (Torres-Collado and Jazirehi 2018). Collectively, these features are posing great challenges to the successful treatment and disease-free survival of cancer patients.

To cope with such cancers, scientists are bringing new approaches such as precision medicine (Carrasco-Ramiro et al. 2017). Targeted therapy is one of the major modalities of treatment for cancer, and the essence of precision medicine. Target-specific delivery of potent chemotherapeutic agents could specifically inhibit cell growth or induce cell death on tumor sites without causing much damage to the normal peripheral cells, tissues and organs (Lee et al. 2018). Over the last decades, great achievements have been attained in antibody-based targeted therapeutic agents (Capdevila et al. 2009; Lemery et al. 2010). However, development of antibodies is costly, time consuming and often elicit strong immune responses that might result in loss of their efficacy (Attarwala 2010; Beck et al. 2010; Friedman et al. 2016). Comparatively, aptamers are much more economic, facile

to synthesize and holding the same properties as antibodies. Moreover, aptamer selection process is generally faster than that of monoclonal antibody and allows for optimization of binding affinity by successive rounds of evolutionary screening as well as modification (Zhou et al. 2017; Bouvier-Müller and Ducongé 2018).

Notably, most of the membrane protein-targeting aptamers are immediately internalized after target recognition, which make them more preferable candidates for targeted therapy (Xiao et al. 2008). In fact, aptamers can play dual characters in cancer targeted therapy. On one hand, aptamer–drug conjugates (ApDCs) are promising targeted drug delivery systems for reducing toxicity and increasing the efficacy of anticancer drugs (Xu et al. 2013; Liu et al. 2014; Zhou et al. 2017). On the other hand, they could be applied in the identification of biomarkers and/or potential molecular targets for tumors (Cheng et al. 2013) (Fig. 2). For example, estrogen receptor (ER) α is expressed in most breast cancers, and tamoxifen (anti-estrogen drug) has been widely applied for breast cancer treatment (Cui et al. 2012). Unfortunately, around 50% of all ERα-positive tumors have developed tamoxifen resistance. And it is found that the ER coactivator mediator subunit 1 (MED1) plays a critical role in breast cancer for tamoxifen resistance through cross-talk with HER2 (Cui et al. 2012). Accordingly, HER-2-specific multifunctional RNA aptamer nanoparticles were developed to overcome tamoxifen resistance in breast cancer therapy (Zhang et al. 2016). As anticipated, the complex (pRNA–HER2apt–siMED1) specially recognized the HER2-overexpressing human breast cancer cells and internalized, then released siRNA(siMED1) to silence the MED1 gene, and finally resulted in inhibition of the human breast cancer cell growth. Likewise, a similar result was also obtained from in vivo experiments, that pRNA–HER2apt–siMED1 complex efficiently targeted and penetrated into HER2-overexpressing tumors and suppressed the tumor growth (Zhang et al. 2016).

Similarly, Savla et al. (2011) developed a pH-responsive quantum dot-mucin1 aptamer–doxorubicin (QD–MUC1–Dox) conjugate for targeted delivery of Dox to multidrug-resistant ovarian cancer. This conjugate was stable at blood circulation and it can release Dox at acidic conditions in lysosome inside the cells. Confocal microscopy and in vivo studies showed that this complex preferentially accumulated in multidrug-resistant cancer cells and exhibited higher toxicity than free Dox (Savla et al. 2011).

Heterogeneity and plasticity of tumor cells are major obstacles of cancer targeted therapy (Meacham and Morrison 2013; Roesch 2014). The cells inside a single tumor blast differ greatly (e.g., expression pattern of proteins and so on). As a result, some portion of cells could escape the impairment of regular targeted therapies. It may be the reason behind the relapse of cancers (Merlos-Suárez et al. 2011; Zhu et al. 2014). However, monoclonal antibody-based targeted therapeutics generally target only one marker of cancer cells that might lead to antigen escape and loss of its efficacy. Fortunately, application of selected aptamer or aptamer pool that is generated by cell-based SELEX methods in the targeted therapy might be an efficient approach to overcome relapse in these types of tumors.

Here, we present the schematic representation of developing heterogeneous tumor-specific aptamer pool drug conjugates (ApPDCs) for targeted therapy of heterogeneous tumors (Fig. 3). Heterogeneous tumor cell-specific aptamer pools can be generated by cell-based SELEX in an extremely short period. Then, the enriched aptamer pool could be conjugated with potent drugs to generate ApPDCs that target different markers of cancer cells. Hence, there is a higher chance of success on targeted delivery of drugs or cargos to all parts of the cancer blast.

However, the toxicity of ApPDCs to normal tissues and cells may also be increased due to multi-targeting. Before generating ApPDCs, the selected aptamer pool should be labeled with fluorescence group and tested in vivo and in vitro to detect the enrichment of the pool on tumor cells and other tissues or organs. If the aptamer pool is highly accumulated in normal organs or tissues other than the tumor, then it should not be further used to construct ApPDCs. If the aptamer pool could specifically accumulate in the tumor, then ApPDCs should be evaluated in vivo. Notably, the content of the drug within ApPDCs should be strictly controlled like that of antibody drug conjugates (Savla et al. 2011; Baudino 2015), so as to prevent the toxicity of chemotherapeutics to normal tissues/organs. In a word, it is necessary to evaluate and balance the efficacy and toxicity of ApDCs in cancer treatment.

Collectively, ApPDCs can be used to tackle the constantly changing nature of tumor cells due to the short time span of development. The unique property of ApPDCs enables them to specifically target all of the heterogeneous tumor cells and get rid of them. Thus, it is likely that aptamers have more advantages than antibodies in targeted therapy. In the future therapy of heterogeneous tumors, aptamers might exert more important roles.

Construction of aptamer–aptamer or aptamer–antibody conjugates to increase target binding affinity

The binding affinity of antibodies or aptamers to their specific target is one of the most important indices to assess their quality for further application (Vu et al. 2017). Currently, the low binding affinity is a prominent limitation of some aptamers and antibodies which bring restrictions to put them into practice. Thereby, investigators are struggling to

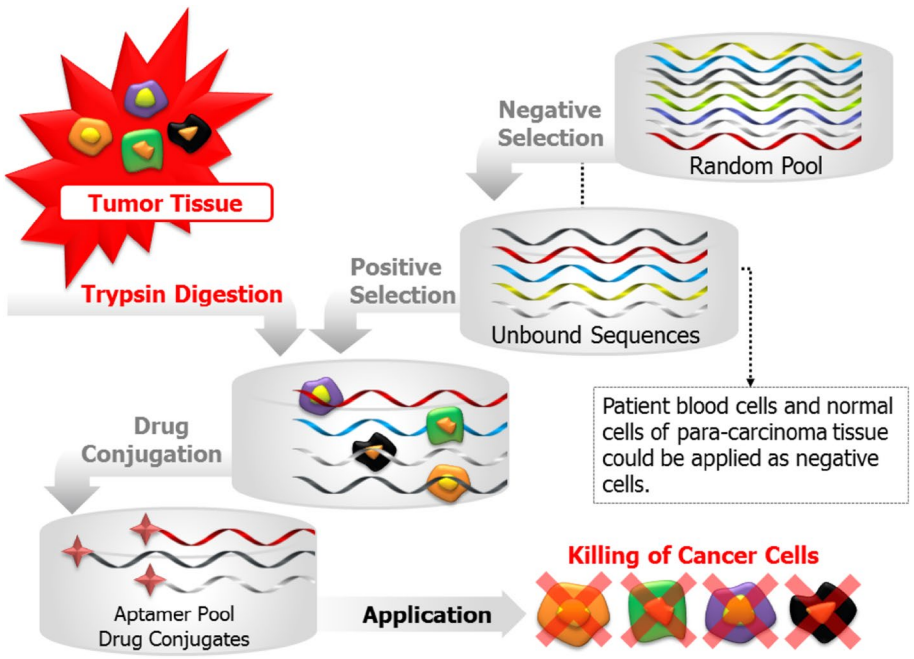

Fig. 3 Demonstration of heterogeneous tumor-specific aptamer pool enrichment and development of (aptamer pool)-drug conjugates (ApPDCs). Initially, random ssDNA pool is incubated with patient blood or normal para-carcinoma tissue cells to get rid of the nonspecific binding sequences (refer to Fig. 1). Then, tumor tissue is digested and allowed to recover for few hours to obtain heterogeneous cancer cells. Next, aptamers specific for heterogeneous cells are generated by a single step or other types of fast selection methods. Subsequently, (aptamer pool)-drug conjugates (ApPDCs) are generated and applied for targeted therapy of malignant and heterogeneous tumors

find out solutions to increase their binding affinity. Accordingly, dimerization is deemed as a feasible way to increase their binding affinity (Kanwar et al. 2011; Huang et al. 2017). However, it seems that dimerization of antibodies not only makes their size bigger, but also changes the three-dimensional structures of antibodies. Comparatively, the conjugation between aptamers or aptamers with antibodies is a feasible approach due to the unique properties of aptamers (Fig. 4a). There is a report that the pincer (conjugate of aptamer with antibody) showed 100 times stronger binding affinity to thrombin than that of the antibody alone (Kang and Hah 2014). Aptamer–antibody conjugates (ApACs) could also significantly decrease the off-target rates of both aptamers and antibodies (Hah and Kang 2017). This implies that the conjugation of aptamer with antibody might be an efficient way to increase binding affinity of antibody.

Besides, aptamer–antibody conjugates (ApACs) might also be used as drug carriers owing to their superior characteristics such as high binding affinity and low off-target rate (Kanwar et al. 2011; Kang and Hah 2014). Since it is the combination of two types of affinity molecules with a spacer, its payload of drugs will be dramatically increased.

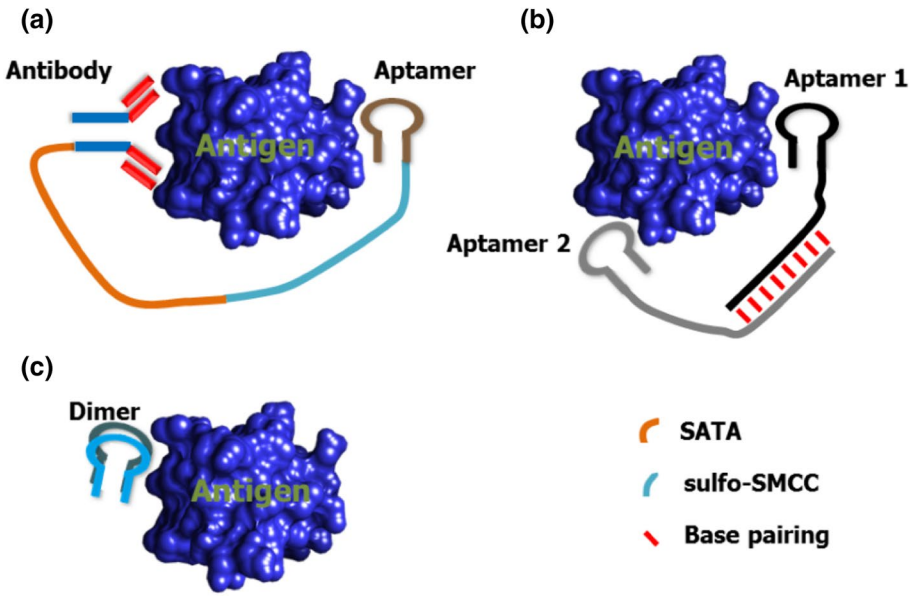

Fig. 4 Schematic representation of aptamer–antibody and aptamer–aptamer conjugates, aptamer dimers as well as their binding to antigen. **a** Aptamer–antibody conjugates could be prepared as follows: Sulfosuccinimidyl 4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate (sulfo-SMCC) is connected to amine-functionalized aptamer and further conjugated with *N*-succinimidyl-*S*-acetylthioacetate (SATA)-functionalized antibody. **b** Aptamer–aptamer conjugates could be easily constructed by complementary base pairing between pre-designed extra bases. **c** Dimers (or polymers) could be directly synthesized as a single oligonucleotide sequence in vitro

Furthermore, it has been reported that activities (e.g., transportation and internalization) of ApACs are almost the same with that of antibodies in vitro and in vivo (Ohk et al. 2010; Heo et al. 2016). Based on the above information, it merits further investigation of aptamer–antibody–drug conjugates (ApADCs) in the treatment of cancer. Apparently, ApADCs might become an important approach in the field of cancer targeted therapy that could improve the clinical outcome of cancer patients.

Notably, although many aptamers have been reported to show similar properties with antibodies, some of them have exhibited low binding affinity (Hasegawa et al. 2016). Fortunately, dimerization of aptamers has been proven as a splendid method to overcome this puzzle. For example, Hasegawa et al. (2008) reported that the binding affinity of aptamers significantly increased through dimerization. Two different aptamers against the thrombin were conjugated and showed at least tenfold increased binding affinity than any of the precursors (Hasegawa et al. 2008). Undoubtedly, this type of dimerization/conjugation is not only able to increase the binding affinity of aptamers but also promotes target specificity. Another study also showed that homo/hetero dimerization could increase binding affinity of the dimer as compared with precursors (Poniková et al. 2011). Moreover, generation of multivalent aptamers by conjugating aptamers that recognize different epitopes is also proven to be effective in increasing the binding affinity of aptamers (Santulli-Marotto et al. 2003; Hasegawa et al. 2016). Conjugation or dimerization of aptamers could be easily managed as shown in Fig. 4b, c.

Additionally, dimers or conjugates of aptamers are deemed to be fine tools for target-specific delivery of chemotherapeutics to malignant tumors. Boyacioglu et al. (2013) screened a DNA aptamer against prostate-specific membrane antigen (PSMA) applying ssDNA pool containing fixed sequences to facilitate Dox binding. Subsequently, they developed dimeric–aptamer complexes for targeted drug delivery with high capacity by pH-sensitive covalent linkages. This complex showed adequate stability in physiological conditions and specifically internalized into PSMA positive C4-2 cells with negligible uptake into PSMA negative PC3 cells (Boyacioglu et al. 2013). Importantly, they also observed that Dox was specifically released from the complex in a target-dependent manner. Thus, aptamer-mediated dimerization or conjugation is a promising approach to overcome the shortcoming of affinity molecules (i.e., aptamers, antibodies etc.) for the clinical application.

On the other hand, the successful construction of aptamer–drug conjugates (ApDCs) is not only based on finding a high-affinity and specific aptamer, but also the selection and application of proper payload and the link between the aptamer and payload, which directly affects the efficacy of ApDCs on eliminating cancer. For instance, ApDCs include physical conjugates and chemical conjugates. Dox is the most studied payload, since it could physically interact with GC/CG sequences in hairpin structures of aptamers or double-strand regions of dimeric aptamers (Savla et al. 2011; Boyacioglu et al. 2013; Xu et al. 2013; Yang et al. 2019). Moreover, other therapeutics such as chemotherapeutic nucleoside analogue and si/shRNAs could be directly incorporated into the aptamer sequence (Herrmann et al. 2014; Kruspe et al. 2014).

Chemical conjugations include the linkage of amino- or thiol-modified aptamers to payloads, or payload inclusive linker molecules containing carboxylic acid or maleimide (Kruspe et al. 2014). Cancer chemotherapeutics (e.g., cisplatin, docetaxel and daunorubicin) encapsulated nanoparticles, natural toxins (e.g., gelonin, ricin A chain and Pseudomonas exotoxin), synthetic toxic molecules such as monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF) could also be used as payload (Sundaram et al. 2012; Ashrafuzzaman 2014; Kruspe et al. 2014; Kelly et al. 2016; Kratschmer and Levy 2018). Common linkers for ApDCs include hexa (ethylene glycol), hydrazine, succinimidyl 3-(2-pyridyldithio) propionate (SPDP) and sulfosuccinimidyl 4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate (sulfo-SMCC) (Heo et al. 2016; Kelly et al. 2016; Hah and Kang 2017; Kratschmer and Levy 2018). The linker molecule should be selected according to the aptamer internalization pathway and subcellular localization of ApDCs to promote efficient release of the payload from ApDCs and its anticancer activity.

Aptamers might refine current pattern of cancer diagnosis

Currently, novel discoveries and technologies in medical science are growing fast (Stefan and Seleiro 2016). Although many high-mortality cancers have been successfully cured, the current clinical therapy and early diagnosis are still harboring some limitations (Mcconigley et al. 2011; Grigera et al. 2013). For example, common diagnostics and therapeutics of cancers are mainly based on the antibody-related techniques. Since the discovery, production, processing, transportation and storage of antibody-related medical supplies are of high cost, the antibody-based therapeutics and diagnostics are expensive and difficult to maintain. Therefore, only the advanced medical centers could provide this type of diagnostics and therapeutics (Wilkes et al. 2006). Accordingly, there is an urgent need to change the pattern and cost of current diagnosis and therapy.

In fact, aptamers have many unique properties as abovementioned. Zeng et al. (2014a, b) have developed an aptamer reporter system, which could be activated by cancer cell for single step analysis of CTCs. They installed fluorescence

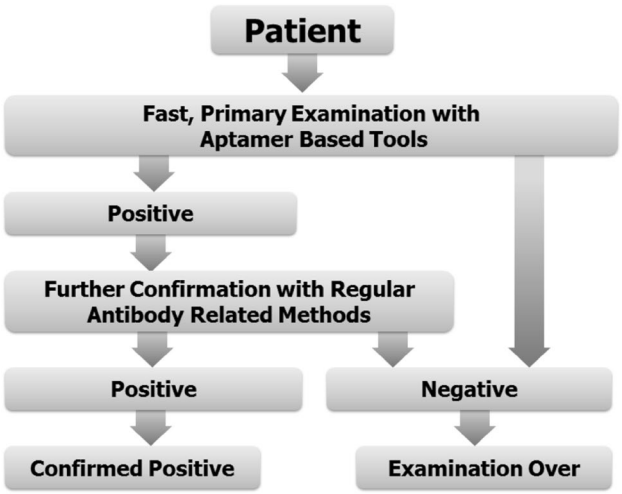

Fig. 5 Flow chart of future antibody and aptamer-based diagnosis of cancer. Since aptamer-based diagnosis is feasible in remote hospitals or community medical service centers, patients could go through a fast, primary examination with aptamer-based diagnostics. If the result is negative, then the examination is over. While if the result is positive, it could be further confirmed by antibody-based diagnostics

and quencher molecules at 3′ and 5′ ends of the aptamer. Fluorescence is quenched in a general condition due to the close location of two molecules. Once the aptamer is internalized into cells, it can be rapidly digested in lysosome and turn on the fluorescence signal that make CTCs detectable (Zeng et al. 2014a, b). Likewise, many redundant steps of traditional diagnostic technics could be omitted such as the consecutive application of primary and fluorescence labeled secondary antibodies and long incubation time before final detection.

More importantly, aptamers are much economic than other affinity molecules. Thus, the high cost of diagnosis and therapeutic drugs or approaches might be decreased by aptamer-based diagnostics and drugs in future. Here, we present a novel pattern on diagnosis (Fig. 5). By this way, not only the cost of diagnosis will be decreased dramatically but also many cancers or other diseases could be discovered at an early phase which means better prognosis of many patients (Di Gioia et al. 2015).

Aptamer-based diagnostic tools enable the people living in rural places get better access to diagnosis of tumors and other diseases much conveniently and economically. Therefore, the economic burden of individuals as well as social health care system will also be notably decreased. The connection and coordination between lower grade and higher grade medical centers will also be facilitated. Thus, it is reasonable that the application of aptamer-based diagnostics along with antibody-based counterparts might refine the current pattern of diagnosis.

Concluding remarks

Cancer is the common threat of humanity. To decrease and eliminate the mortality caused by cancer has become the top priority of medical researchers all around the world. All the best resources and approaches are being applied to cancer research and therapy. Affinity molecules are one of the best tools used in diagnosis and treatment of cancer (Souriau and Hudson 2005; Chandola et al. 2016). The authentic affinity molecule antibody has been successfully applied in clinical treatment of a variety of cancers (Moja et al. 2006; Demko et al. 2008; Lemery et al. 2010; Vmd et al. 2012; Tandan et al. 2017). Meanwhile, their disadvantages are also gradually emerging with the expanding application (Attarwala 2010). Luckily, the newly arising affinity molecule aptamers are not only showing similar affinity toward their targets, but also exhibiting many advantages over the antibodies.

The search of term “aptamer” on PubMed hits more than 8000 results, but the original articles related to the selection of aptamers are very limited (Baird 2010). Thus, the broader scale of aptamer selection should be inspired to discover novel aptamers and excavate much more potential of them. On the fight against cancer, antibody is the veteran, and aptamer is the new recruit. This is not the right time to completely replace one with the other, aptamers and antibodies should form a “coalition” against cancers to maximize their advantages and minimize disadvantages.

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Author contributions HN conceived and designed the study. YM is the major contributor in collecting, analyzing literature and writing of the manuscript. DFH and CY aided in the process of collecting and analyzing literature. All authors read and approved the final manuscript.

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Compliance with ethical standards

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Ethical approval This study does not contain any animal or human participants.

Informed consent Not applicable.

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