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Screened peptides from one-bead one-compound technique extend half-life of peptide drugs in circulation through binding to albumin

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ABSTRACT

Peptide drugs are known for their high biological safety. However, compared with small molecule drugs, peptide drugs are easily oxidized and hydrolyzed as well as short in half-life. Herein, inspired by the long circulation of albumin in blood, we screened albumin binding peptides (ABPs) from a one-bead one-compound (OBOC) peptide library to increase the half-life of peptide drugs. Beads displaying random peptides were screened using fluorescent labeled human serum albumin. Fluorescent beads with specific binding to albumin were isolated for sequencing. The selected ABPs can effectively bind to albumin, thus possessing the long circulation of albumin. The dissociation constant (K_D) of ABPs to albumin is up to 1×10^{-8} mol/L. Once one of ABPs (ABP2) was coupled to triptorelin, the circulation half-life of triptorelin in mice was significantly prolonged to 263.50 h much longer than that of triptorelin alone (179.07 h). In addition, the combination therapy using ABP-conjugated triptorelin and doxorubicin (DOX) can effectively inhibit the proliferation of tumor cells in mice. The OBOC screening strategy and resulting ABPs showed great potential for enhancing the delivery efficiency of peptide drugs.

Peptides are increasingly being considered as promising drugs due to their high biological activity and biocompatibility [1–4]. However, the short half-life of peptide drugs in blood circulation caused by the poor plasma stability and rapid renal clearance limits their clinical application [5–8]. Several methods have been employed to prolong the half-life of peptide drugs in clinic. For example, polyethylene glycol (PEG) has been used to modify peptides, such as PEG modifying interferon [9,10]. Biodegradable polymers have also been widely and successfully applied as scaffold materials for microsphere drug delivery systems of peptide drugs, such as poly(lactic-*co*-glycolic acid) (PLGA) microsphere sustained-release carriers [11]. However, PEG is not always the preferred choice for injection due to concerns about safety and tolerance [12,13]. In addition, the quality of polymeric microspheres can be difficult to control. Therefore, there remains a great need for new materials and solutions to prolong the half-life of peptide drugs [14,15].

Nature provides a lot of ideas and solutions for developing advanced materials [16–18]. For instance, albumin, which is abundant in blood and has a long circulating half-life of 21 days in the body, has emerged as a promising carrier candidate [19,20]. Antibodies, peptides and fatty acids could be conjugated with peptide drugs, binding to albumin to increase the half-life of peptide drugs [21,22]. However, the development of antibodies is expensive and difficult, while fatty acids have low affinity for albumin and poor solubility [22–24]. Albumin binding peptides are promising for prolonging the half-life of peptide drugs [25,26].

The one-bead one-compound (OBOC) peptide library method allows for the screening of millions of random peptides on polymer beads [27–31]. Each bead has a unique but unknown peptide sequence that can be identified later. The OBOC peptide library was first proposed by Kit S. Lam *et al.* in 1991 [2]. Since then, it has been widely used to develop peptide ligands for targeting various proteins [32–35].

Herein, we proposed a feasible method to discover a series of albumin binding peptides (ABPs) using a high-throughput OBOC screening technique. We extracted the "brightest" beads for peptide sequencing, which were incubated with fluorescence-labeled

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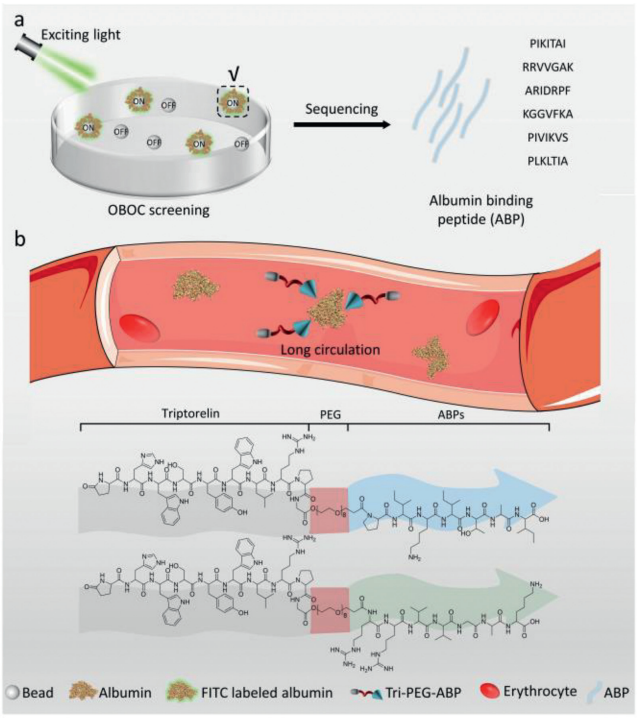
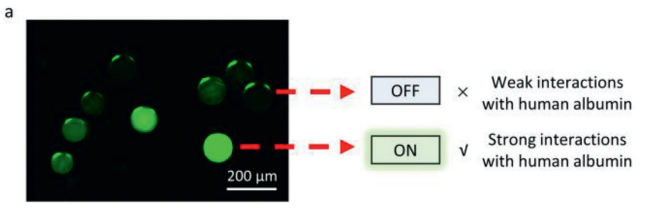


Fig. 1. Schematic diagram of OBOC screening strategy for human serum ABPs, inspired by the long-circulating properties of human serum albumin. (a) Peptide beads with fluorescence were identified and selected after co-incubation of OBOC peptide library with fluorescently labeled native proteins. The sequences of ABPs on these positive peptide beads were sequenced by mass spectrometry. (b) Schematic diagram of the drug conjugate combining ABPs with the peptide drug triptorelin for efficient delivery in mice through binding albumin.



b

	Sequence	K_D (mol/L)	GRAVY[1]	Isoelectric point[2]
ABP1	PIKITAI	1.0×10^{-8}	1.3	9.40
ABP2	RRVVGAK	3.4×10^{-8}	-0.44	12.18
ABP3	ARIDRPF	2.8×10^{-5}	-0.71	10.09
ABP4	KGGVFKA	3.4×10^{-5}	0.03	10.44
ABP5	PIVIKVS	5.8×10^{-6}	1.59	9.38
ABP6	PLKLTIA	1.3×10^{-8}	1.1	9.40

[1]The grand average of hydropathicity (GRAVY) for each peptide was obtained using the ProtParam program (available at https://web.expasy.org/protparam/).
[2]The isoelectric point for each peptide was obtained using NovoPro program (available at https://www.novopro.cn/tools/protein).

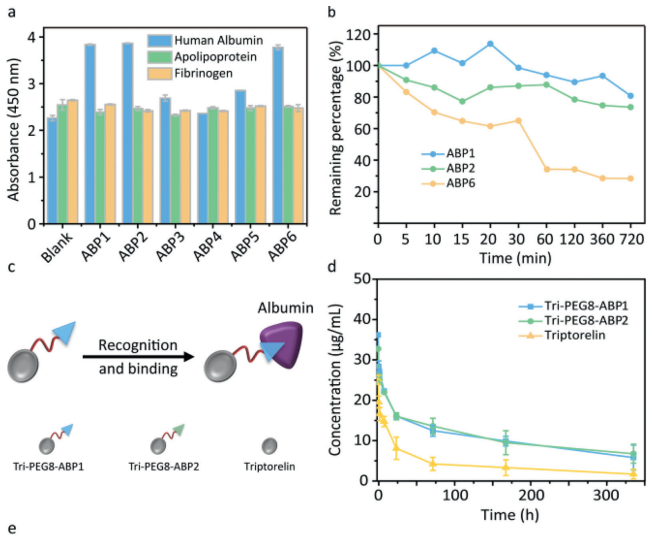
Fig. 2. (a) Typical structure illumination microscopy (SIM) image of the OBOC library incubated with fluorescence-labeled albumin (green). The fluorescent beads contain peptides that have strong interactions with human serum albumin. (b) The ABPs sequences from OBOC screening and K_D to albumin, grand average of hydropathy (GRAVY) and isoelectric point values.

albumin. A series of ABPs were successfully obtained, which had high and specific binding capability to albumin with the highest binding affinity of 1.0×10^{-8} mol/L. The specific binding to albumin can ingeniously take advantage of the long half-life of albumin and effectively improve the half-life of peptide drugs in serum (Fig. 1a). Finally, the practicability of ABPs was verified by chemical coupling of ABPs with triptorelin. It was found that triptorelin modified with ABPs showed significantly prolonged half-life up to 263.50 h in blood of mice, which is longer than that of triptorelin (179.07 h) (Fig. 1b). In addition, the combination of ABP modified triptorelin and doxorubicin (DOX) could enhance the antitumor effect in mice. This study provides a high-throughput screening method to identify a series of ABPs for efficient delivery of peptide drugs *in vivo*. Animal conservation and euthanasia were carried out under the approval of the Laboratory Animal Conservation Administrative Group of the National Center for Nanoscience and Technology.

Since the ideal length of a peptide sequence with a specific function is typically between 5 and 10 amino acids, we selected a 7-mer peptide library for screening ABPs. We prepared this library with all standard amino acids except cysteine *via* standard solid-phase peptide synthesis (Fig. S1 in Supporting information). Albumin covalently labeled with the fluorescent dye fluorescein isothiocyanate (FITC, green) was used as screening target. 100,000 beads from the 7-mer linear OBOC peptide library were incubated with FITC labeled albumin (100 μg/mL) in phosphate-buffered saline (PBS) for 12 h. Strongly fluorescent beads were then picked up at 488 nm under a fluorescent microscope for sequencing (Fig. 2a). The resulting sequences were recognized as ABPs, including PIKITAI (ABP1), RRVVGAK (ABP2), ARIDRPF (ABP3), KGGVFKA (ABP4), PIVIKVS (ABP5), and PLKLTIA (ABP6). It was found that there are more than one basic amino acid in one ABP and totally 6 Lys and 4 Arg in all six ABPs. Therefore, all these ABPs displayed positive charges at pH 7 with high isoelectronic points from 9.38 to 12.18. Typically, there are at least three hydrophobic amino acids in each of these 6 ABPs, including 2 Phe, 2 Leu, 5 Val, 7 Ile, 5 Ala in all. These results indicated that the hydrophobic and positively charged sequences are the basic characteristics for ABPs.

In order to verify the reliability of our screening method, surface plasmon resonance imaging (SPRi) was conducted on the 6 screened ABPs, which were synthesized in soluble form with a carboxylic acid at the C-terminal (Fig. S2 in Supporting information). It can be seen from Fig. 2b that ABPs have small K_D values, indicating that the OBOC method was very reliable in targeting peptide screening. Especially, ABP1, ABP2 and ABP6 with K_D value of about 10^{-8} mol/L displayed strong binding ability to human serum albumin (Fig. S3 in Supporting information). The binding specificity to albumin of ABPs plays an important role in drug delivery with controllable side effects. We further explored this specific binding ability through enzyme-linked immunosorbent assay (ELISA) experiment. Fibrinogen and apolipoprotein, as important plasma proteins, were selected as controls. These proteins, including fibrinogen, apolipoprotein and albumin, were coated on 96-wells plate, and further incubated with ABPs before washing with PBS and measured by a multimode microplate detection system at a test wavelength of 450 nm (Fig. 3a). The results showed that ABP1, ABP2 and ABP6 displayed strong absorbance, indicating strong binding ability with albumin, which was consistent with SPRi experimental results. The absorbance was weak for ABP1, ABP2 and ABP6 when bound to fibrinogen and apolipoprotein, which was similar to that in the blank control. These results verified the reliability of our OBOC peptide library for the screening of ABPs, and revealed that ABP1, ABP2 and ABP6 were promising binding peptides for albumin with high specificity.

The stability of ABP1, ABP2 and ABP6 in plasma was evaluated because biomedical applications require high plasma stability. ABPs were incubated with mouse plasma at 37 °C and their residual levels were quantified over time using high performance liquid chro-



e

	Tri-PEG8-ABP1	Tri-PEG8-ABP2	Triptorelin
$t_{1/2}\alpha$ (h)	4.32	5.36	6.91
$t_{1/2}\beta$ (h)	231.77	263.50	179.07
AUC (μg mL^{-1} h^{-1})	3534.70	3628.37	1341.33
CL (mL/h)	0.06	0.06	0.15
V_d (mL)	18.92	20.96	38.53

Fig. 3. (a) ELISA experimental results for monitoring the interaction between ABPs and human serum albumin, fibrinogen and apolipoprotein. (b) The remaining peptides of ABP1, ABP2 and ABP6 incubated with mouse plasma at different time interval by HPLC. (c) Molecular schematic diagrams of the experimental group and the control group. (d) Time-dependent curves of blood drug concentration of Tri-PEG8-ABP1, Tri-PEG8-ABP2 and triptorelin in mice. Data are presented as mean ± standard deviation (s.d.), $n = 3$ independent experiments. (e) Pharmacokinetic parameters of Tri-PEG8-ABP1, Tri-PEG8-ABP2 and triptorelin by fitting a two-compartmental model from concentration-time curves.

matography (HPLC). As shown in Fig. 3b, it was found that more than 70% of ABP1 and ABP2 remained in mouse plasma after 12 h, indicating good stability. This may be due to their binding to albumin, protecting them from degradation by plasma enzymes and enhancing their plasma stability. The ABP1 and ABP2, with high binding affinity and plasma stability, were selected for further *in vivo* study.

Breast cancer is the most common malignant tumor among women, and triple negative breast cancer (TNBC) is a unique subtype [36,37]. Due to the lack of effective drugs, the prognosis of TNBC is poor. Some reports indicate that triptorelin can effectively treat TNBC by reducing cytokines, such as S100A4 and CYR61 and inhibiting the growth and metastasis of breast cancer *in vivo* [38–41]. Triptorelin is a synthetic decapeptide, a natural gonadotropin releasing hormone (GnRH) analog, and an anti-tumor peptide drug. Compared with natural GnRH, triptorelin has a much longer half-life, but still falls short of the clinical demand [42,43].

Triptorelin was selected as a model peptide drug to validate whether ABPs could increase its half-life. The triptorelin was chemically coupled with ABP1 and ABP2, respectively, with PEG8 as a linker to form Tri-PEG8-ABP1 and Tri-PEG8-ABP2. The PEG8 linker spatially isolated the triptorelin and ABPs, avoiding the interference on the biological activity of triptorelin (Fig. 3c, and Figs. S4 and S5 in Supporting information). Female BALB/c mice were utilized for measuring half-life of Tri-PEG8-ABP1 and Tri-PEG8-ABP2 in blood *in vivo*. The biocompatibility of Tri-PEG8-ABP1 and Tri-PEG8-ABP2 was firstly tested by cell counting kit-8 (CCK-8) assay prior to the *in vivo* experiment, which displayed highly biocompatible to human umbilical vein endothelial cell (HUVECs) and MDA-MB-231 cells (about 100% survival rate at 200 μmol/L, Fig. S6 in Supporting information).

The *in vivo* half-life of Tri-PEG8-ABP1 and Tri-PEG8-ABP2 was measured in mice. Three groups of mice ($n = 3$) were i.v. injected with Tri-PEG8-ABP1, Tri-PEG8-ABP2 and triptorelin, respectively. The blood was collected by using retro-orbital bleeding method and the concentrations of Tri-PEG8-ABP1, Tri-PEG8-ABP2 and triptorelin in the blood were determined by HPLC (Fig. 3d and Fig. S7 in Supporting information). The results showed that the concentrations of Tri-PEG8-ABP1 and Tri-PEG8-ABP2 in the blood at 72 h were 12.5 μg/mL ($^{***}P < 0.001$, compared with triptorelin) and 13.6 μg/mL ($^{***}P < 0.001$, compared with triptorelin), which were significantly higher than that of triptorelin (4.2 μg/mL).

The pharmacokinetic parameters of Tri-PEG8-ABP1, Tri-PEG8-ABP2 and triptorelin from the two compartment model (Fig. 3e) showed that distribution half-lives ($t_{1/2}\ \alpha$) of Tri-PEG8-ABP1 (4.32 h) and Tri-PEG8-ABP2 (5.36 h) were shorter than that of triptorelin (6.91 h). In contrast, eliminate half-lives ($t_{1/2}\ \beta$) of Tri-PEG8-ABP1, Tri-PEG8-ABP2 and triptorelin are 231.77, 263.50 and 179.07 h, respectively. The significantly prolonged eliminate half-life of Tri-PEG8-ABP1 and Tri-PEG8-ABP2 comparing with triptorelin indicated that the ABPs based albumin binding strategy is effective. The area under the cure (AUC) values of Tri-PEG8-ABP1 and Tri-PEG8-ABP2 were 2.6 and 2.7 times higher than that of triptorelin. Clearance rate (CL) is an important pharmacokinetic parameter about drug elimination in the body. The CL of Tri-PEG8-ABP1, Tri-PEG8-ABP2 and triptorelin are 0.06, 0.06 and 0.15 mL/h, respectively. The elimination of Tri-PEG8-ABP1 and Tri-PEG8-ABP2 were markedly slower than triptorelin. The apparent volume of distribution (V_d) value can be used to predict the drug distribution and binding *in vivo* [44]. Tri-PEG8-ABP1 and Tri-PEG8-ABP2 may bind to albumin, most of them would maintain within the intravascular compartment with small V_d 18.92 and 20.96 mL, respectively. Triptorelin may be mainly distributed in extravascular binding or storage in fat or other tissues with a large V_d of 38.53 mL. All these experimental results revealed that the introduction of ABPs effectively prolonged the circulating half-life of triptorelin in the mouse blood, leading to high distribution in blood with a slow clearance rate [45,46].

We finally evaluated the anti-tumor effect of combination therapy of Tri-PEG8-ABPs and DOX (Fig. 4a). The implanted subcutaneous with TNBC MDA-MB-231 tumor-bearing mice were prepared and randomly divided into four groups ($n = 4$), which were intravenously injected with PBS, Tri-PEG8-ABP1 + DOX, Tri-PEG8-ABP2 + DOX and DOX every other day in the first 2 weeks. The tumor volume and weight of mice in each group were measured every other day in 4 weeks (Fig. 4b). The tumors in the PBS group showed rapid growth over time, and the average tumor volume at the end was up to 983.8 mm^3. The average tumor volume of Tri-PEG8-ABP1 + DOX, Tri-PEG8-ABP2 + DOX and DOX groups was 361.4, 400.2 and 513.5 mm^3, respectively, which was significantly smaller than that of PBS group ($^{***}P < 0.001$, compared with DOX) (Fig. 4c). Tri-PEG8-ABP1 + DOX showed the most effective inhibition of tumor growth, where the tumor volume of Tri-PEG8-ABP1 + DOX group was significantly different from that of DOX group on day 28 ($^{*}P < 0.05$). The specific binding of ABPs to albumin effectively prolonged the half-life of triptorelin, leading to an effective therapy of Tri-PEG8-ABP1 + DOX. There was no significant difference in weight between the experimental groups and the PBS group (Fig. 4d). We collected the serum and main organs of mice after treatment by PBS, Tri-PEG8-ABP1 + DOX, Tri-PEG8-ABP2 + DOX and DOX to assess the potential risk of side effects *in vivo*. The hematoxylin and eosin (H&E) staining images of the main organs showed no obvious pathological changes (Fig. S8 in Supporting information). In addition, blood biochemical analysis showed that the liver function indicators (including

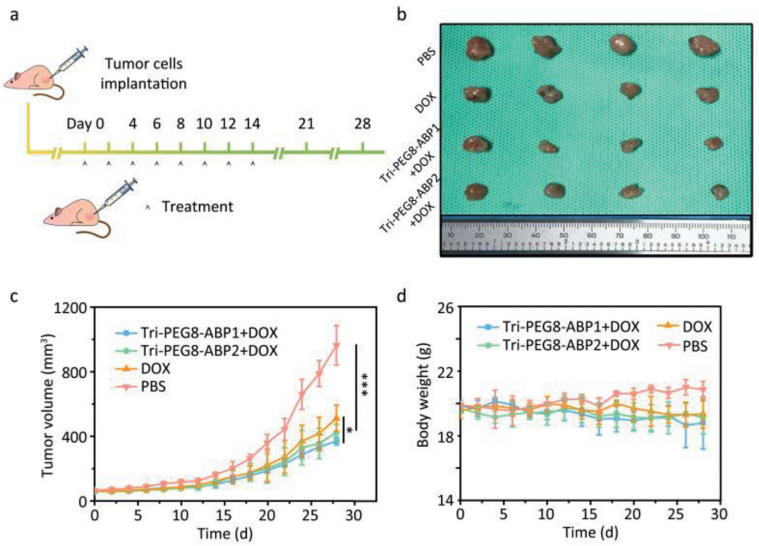


Fig. 4. Antitumor effects of Tri-PEG8-ABP1 and Tri-PEG8-ABP2. (a) Schematic diagram of the preparation and treatment of MDA-MB-231 tumor-bearing mice treatment by PBS, Tri-PEG8-ABP1 + DOX, Tri-PEG8-ABP2 + DOX and DOX. (b) Photograph of tumors from four groups of PBS, Tri-PEG8-ABP1 + DOX, Tri-PEG8-ABP2 + DOX and DOX on day 28, respectively. (c) The MDA-MB-231 tumor volume growth curves after intravenous injection of different formulations of PBS, Tri-PEG8-ABP1 + DOX, Tri-PEG8-ABP2 + DOX and DOX. (d) Changes in body weight of mice over time. Data are presented as mean ± s.d., $n = 3$ independent experiments. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ (two-tailed Student's *t*-test).

alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) of PBS, Tri-PEG8-ABP1 + DOX, Tri-PEG8-ABP2 + DOX and DOX groups had no significant differences (Fig. S9 in Supporting information), indicating that Tri-PEG8-ABPs did not cause liver cell damage or affect protein synthesis. Similarly, data of blood urea nitrogen (BUN) and continuous erythropoietin receptor activator (CREA) indicated that Tri-PEG8-ABPs did not harm the kidneys of mice [47]. The above results verified that Tri-PEG8-ABPs had good biocompatibility and inherent advantages of biosafety.

In this study, we utilized a rapid and high-throughput OBOC strategy to screen for albumin binding properties. The FITC labeled albumin was used to screen 100,000 random heptapeptide beads. We successfully identified and subsequently verified 6 ABPs, one of which displayed low K_D value to 10^{-8} mol/L. ABPs were able to significantly extend the half-life of blood circulation of triptorelin through coupling with it. The $t_{1/2}$ β of Tri-PEG8-ABP2 was up to 263.50 h (10 days) in mice, which was 1.47 times longer than that of triptorelin (179.07 h), a first-line hormonal therapy against tumor as a GnRH agonist. In addition, the combination of ABPs and DOX was able to effectively inhibit tumor proliferation in MDA-MB-231 tumor bearing mice.

Our screening strategy has successfully screened peptides that can specifically bind to human serum albumin. Each ABP was found to contain more than one basic amino acid and three hydrophobic amino acids, indicating that the hydrophobic and positively charged sequences are the basic characteristics for ABPs. This strategy based on OBOC peptide library screening can provide more peptides for drug delivery.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108530.

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