Chinese Chemical Letters 37 (2026) 111502

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Selection and characterization of aptamers against CD38 for clinical diagnostics

Di Jiang[a,b], Ling Wang[a,b], Hengyi Lin[b], Xiaoqiu Wu[b], Mingxin Zhang[b], Songxiao Xu[b], Zhenhao Long[b,*], Tao Bing[b,c,d,e,*]

[a] Zhejiang University of Technology, Hangzhou 310014, China
[b] Zhejiang Cancer Hospital, The Key Laboratory of Zhejiang Province for Aptamers and Theranostics, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou 310022, China
[c] Eye Research Center, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Eye Hospital, Wenzhou Medical University, Hangzhou 310018, China
[d] School of Molecular Medicine, Hangzhou Institute for Advanced Study, UCAS, Hangzhou 310024, China
[e] University of Chinese Academy of Sciences, Beijing 100049, China

ARTICLE INFO

Article history:
Received 4 January 2025
Revised 30 April 2025
Accepted 24 June 2025
Available online 25 June 2025

Keywords:
Aptamer
SELEX
Diagnosis
CD38
Flow analysis

ABSTRACT

Multiple myeloma (MM) is a highly aggressive hematologic malignancy characterized by abnormal proliferation of malignant plasma cells. CD38, a transmembrane glycoprotein, is highly expressed on the surface of plasma cells and serves as a critical diagnostic and therapeutic target for MM. However, the masking of CD38 epitopes caused by therapeutic interventions often leads to false-negative results in clinical detection of CD38, compromising diagnostic accuracy and underscoring the urgent need for novel specific molecular tools. Herein, we reported a novel aptamer, CD38jd4a, specifically targeting CD38 with potential clinical applications. A series of high-affinity aptamers specifically binding CD38 were selected and identified through a highly efficient aptamer selection method with CD38 as the target. Among them, aptamer CD38jd4a exhibited the best performance, with a dissociation constant (K_d) value as low as 5.4 ± 0.6 nmol/L. Through siRNA-mediated knockdown experiments, CD38jd4a was further validated to specifically recognize native CD38 expressed on surface of cells. Furthermore, binding epitopes of CD38jd4a were confirmed to be distinct from those recognized by any of current therapeutic antibodies. This unique characteristic enabled the simultaneous application of CD38jd4a with therapeutic antibodies for CD38 detection on CD38-positive Ramos cells by flow cytometry without cross-interference. Importantly, clinical blood sample analysis revealed that CD38jd4a was capable of effectively detecting CD38 despite epitope masking, thereby overcoming limitations of conventional antibody-based detection methods. Given the small molecular size and excellent performance, CD38jd4a is expected to be a robust diagnostic tool for CD38 detection, offering a promising alternative for clinical diagnostics of CD38.

© 2025 Published by Elsevier B.V. on behalf of Chinese Chemical Society and Institute of Materia Medica, Chinese Academy of Medical Sciences.

Multiple myeloma (MM), characterized by abnormal proliferation of clonal plasma cells, is the second most common hematologic malignancy with an increasing global incidence [1]. Although the development of novel therapies such as immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies has significantly improved treatment outcomes in recent years [2], MM remains a highly heterogeneous and challenging disease to cure, and most patients continue to recur with a poor prognosis [3]. CD38, a transmembrane glycoprotein, plays a pivotal role in various physiological processes, including immune response regulation, calcium signaling, and nicotinamide adenine dinucleotide (NAD) metabolism [4]. CD38 is markedly overexpressed in numerous malignancies, particularly in multiple myeloma, making it a critical diagnostic biomarker and a key target for therapeutic intervention [5]. Currently, CD38-targeting monoclonal antibodies, such as Daratumumab [6] and Isatuximab [7], have demonstrated significant therapeutic efficacy in MM by inducing tumor cell apoptosis through immune-mediated mechanisms, including antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) [8].

However, the application of monoclonal antibodies in therapy has also caused new significant challenges for flow cytometry-

* Corresponding authors.
E-mail addresses: longzhenhao@him.cas.cn (Z. Long), bingtao@him.cas.cn (T. Bing).

https://doi.org/10.1016/j.cclet.2025.111502
1001-8417/© 2025 Published by Elsevier B.V. on behalf of Chinese Chemical Society and Institute of Materia Medica, Chinese Academy of Medical Sciences.

based CD38 detection in the assessment of minimal residual disease (MRD) during treatment [9]. Studies have demonstrated that flow cytometry-based CD38 detection on the surface of plasma cells is often disturbed in patients treated with Daratumumab, as the therapeutic antibody competitively binds to CD38 epitopes [10]. This binding mask the target epitopes of conventional antibody-based CD38 detection kits, preventing effective interaction with plasma cells and leading to false-negative results [10]. Notably, this interference can persist for 4–6 months, substantially increasing the likelihood of false-negative MRD tests and potentially compromising clinical decision-making [11]. To address these limitations, researchers explored alternative approaches, including the use of antibodies targeting other marker proteins such as CD319 [12], or employing multi-phenotype antibodies and nanobodies [13] for CD38 detection to minimize the risk of false negatives [14]. However, none of them are optimal due to large molecular size of traditional antibodies (greatly exceeded CD38) [15], high production costs, and lack of stability (traditional antibodies and nanobodies) [16]. These limitations underscore an urgent need for more effective and cost-efficient molecular recognition tools to improve CD38 detection.

Aptamers are single-stranded DNA or RNA oligonucleotides, typically consisting of 15–100 nucleotides and generated by Systematic Evolution of Ligands by Exponential Enrichment (SELEX) [17]. Aptamers are capable of folding into stable three-dimensional structures, such as stem-loops, hairpins, and G-quadruplexes, through which aptamers achieve specific binding to target molecules *via* weak interactions [18]. Aptamers are characterized by their small molecular weight, high stability, and excellent specificity. The small size and structural flexibility allow aptamer to bind smaller targets [19] or hidden epitopes [20] that are inaccessible to antibodies, thereby reducing steric hindrance. These properties make aptamers an ideal alternative to traditional antibodies, particularly in applications where conventional antibodies face limitations [21]. For example, aptamers have shown great potential for application in precision medicine, especially in the areas of diagnostics and targeted therapies [22]. By integrating with biosensors [23] and fluorescence labeling technologies, aptamers can efficiently recognize disease biomarkers and are widely used for early detection and dynamic monitoring of diseases such as cancer [24] and infectious diseases [25]. In tumor-targeted therapy, aptamers can be engineered to deliver chemotherapeutic drugs [26,27] or nucleic acids, thereby achieving precise, efficient, and low-toxicity therapeutic effects [28].

In this study, we performed an aptamer selection against CD38 protein and obtained a high-affinity aptamer, CD38jd4a, specifically targeting CD38. We demonstrated that binding epitopes of CD38jd4a was distinct from that of monoclonal antibody drugs. Importantly, CD38jd4a-based detection was not disturbed by CD38 monoclonal antibody drugs, effectively mitigating the risk of false-negative results in CD38 detection during MRD assessment. As a validation, we demonstrated through flow cytometry that CD38jd4a can be used simultaneously with CD38 monoclonal antibody for the detection CD38-positive cells in blood samples. These findings suggest that CD38jd4a has the potential to address the limitations of existing molecular tools, improve current diagnostic methods, and provide a novel solution for the precise diagnosis and treatment of multiple myeloma.

To obtain aptamers specifically targeting CD38, we performed a protein-SELEX using purified human recombinant extracellular domain of CD38 protein as the target according to previously established protocol [29] with modifications (Fig. 1a). A total of 6 rounds of screening were carried out and the detailed conditions of SELEX process are listed in Table S1 (Supporting information). To obtain high-performance aptamers with potential for clinical application, we employed a complex solution system for screening from the first round, incorporating fetal bovine serum (FBS) and surfactant (Tween 80). In addition, CD38 protein was immobilized on Sepharose beads to facilitate separation of enriched library, more efficiently removing non-specifically bound or weakly bound sequences by using large amounts of wash buffer. To improve the specificity of aptamers against CD38, we introduced a negative selection step starting from the third round, employing epidermal growth factor (EGF) as negative protein to eliminate sequences bound to EGF or beads. The progression of SELEX process was monitored by assessing the binding of enriched libraries to CD38 *via* flow cytometry, measuring changes in fluorescence intensity as an indicator of aptamer binding.

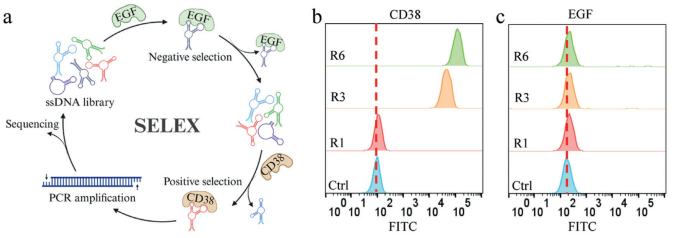


Fig. 1. Selection of aptamers targeting CD38. (a) The schematic diagram of selection. Binding of enriched libraries to target protein CD38 (b) and negative protein EGF (c) by flow cytometry.

As shown in Fig. 1b, the enriched library from the third round exhibited strong binding to CD38, while exhibiting no detectable binding to negative protein EGF (Fig. 1c). The fluorescence intensity of the enriched library binding to CD38 from the sixth round showed no significant improvement compared to the third round (Fig. 1b), indicating that the enrichment of ssDNA sequences specific to CD38 had reached saturation. Notably, the entire SELEX process was surprisingly efficient, with considerable enrichment and relative saturation of CD38-bound sequences in only three selection rounds. This may be attributed to the stringent pressure of SELEX process, which effectively facilitated the rapid enrichment of CD38-specific high-affinity sequences, minimized non-specific binding, and improved the overall efficiency of SELEX. Therefore, the SELEX process was terminated after six rounds of selection.

Subsequently, six sequencing libraries were sequenced according to the previously established protocol [30]. The sequencing data from each enriched library of six rounds were analyzed, and the copy numbers of each sequence were precisely identified by unique molecular identifiers (UMIs). The top 100 sequences from enriched library of the sixth round were ranked based on their relative abundance (Fig. S1 and Table S2 in Supporting information). Recently, we achieved a one-round DNA and RNA aptamer selection of targeting to cells based on UMI [30,31]. In fact, the aptamer selection targeting CD38 in this study also required only one round according to the sequencing results. Although the first round of enriched library showed no binding to CD38, sequences possibly binding CD38 (sequences of high abundance) were already present in the first round and showed a clear difference in copy number (Table S2 in Supporting information).

To identify aptamers with specific binding to CD38 from the enriched library, we performed a detailed analysis of the top sequences and ultimately selected five sequences for preliminary truncation and synthesis (Table S3 in Supporting information). The secondary structures of five aptamer candidates were predicted using the mFold web server [32], with one possible structure shown in Fig. 2a. Subsequently, we assessed the binding of five aptamer candidates to target protein CD38 and negative protein EGF using flow cytometry. All five aptamers exhibited significant binding to CD38 while no binding to EGF was observed (Fig. S2 in Supporting information). We further evaluated binding affinity of

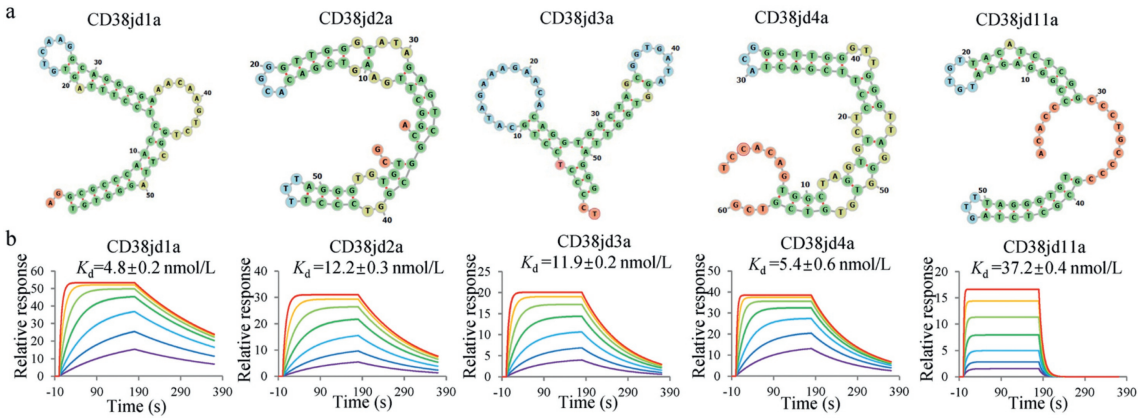


Fig. 2. Identification and characterization of aptamers. (a) Possible secondary structures of five aptamer candidates. (b) Bindings and K_d values of five aptamers to CD38 recombinant protein determined by SPR.

five aptamers to CD38 by directly measuring their equilibrium dissociation constants (K_d) using surface plasmon resonance (SPR). As shown in Fig. 2b, all five aptamers demonstrated high binding affinities to CD38, with K_d values in nanomolar range. Among them, CD38jd1a exhibited the highest binding affinity, with a K_d value of 4.8 ± 0.2 nmol/L, which was consistent with the results obtained from flow cytometry. Interestingly, CD38jd4a, despite showing the lowest binding signal in flow cytometry assay, also displayed strong affinity in the SPR analysis, with a K_d value of 5.4 ± 0.6 nmol/L. The remaining three aptamers showed K_d values of 12.2 ± 0.3, 11.9 ± 0.2, and 37.2 ± 0.4 nmol/L, respectively. Given their superior binding affinities, CD38jd1a and CD38jd4a were selected for further investigation.

Subsequently, we attempted to truncate and mutate aptamers CD38jd1a and CD38jd4a to improve their binding affinity. Based on predicted secondary structures, we designed a series of truncated and mutant sequences (Fig. S3a and Table S2 in Supporting information). We then evaluated the binding ability of all sequences to CD38 by flow cytometry. However, compared to the parent aptamer CD38jd1a, the binding ability of CD38jd1b decreased, while CD38jd1c and CD38jd1d almost completely lost their binding ability (Fig. S3b in Supporting information). Similarly, compared to the parent aptamer CD38jd4a, CD38jd4b exhibited a complete loss of binding, and CD38jd4c showed a significant reduction in binding ability (Fig. S3c in Supporting information). Their K_d values were all significantly larger, also indicating a weaker binding compared to parent aptamers (Fig. S4 in Supporting information). These results indicated that all altered nucleotides of truncated and mutant sequences appeared to play critical roles in maintaining the high-affinity structures of parent aptamers. Consequently, CD38jd1a and CD38jd4a were continued to be selected for subsequent further investigation.

Currently, CD38-targeting monoclonal antibody drugs, such as Daratumumab [6] and Isatuximab [7], have shown promising therapeutic efficacy in the treatment of multiple myeloma (MM). However, both also cause new challenges in clinical diagnostics, as both interfere with the detection of CD38 by masking the epitopes recognized by antibody-based detection kits [9]. We next explored whether the binding epitopes of aptamers CD38jd4a and CD38jd1a binding CD38 are the same as two CD8-targeted monoclonal antibody drugs. As shown in Fig. 3a, CD38 was first immobilized using either Daratumumab or Isatuximab, and the ability of CD38jd4a and CD38jd1a to bind CD38 was subsequently assessed by flow cytometry. The results, presented in Figs. 3b and c, revealed that both CD38jd4a and CD38jd1a exhibited significant binding to CD38 immobilized by both monoclonal antibodies. These findings indicated that CD38jd4a and CD38jd1a all recognize distinct epitopes on CD38, separate from those targeted by Daratumumab and Isatuximab. Owing to small molecular weight (<19 kDa), aptamer-based detection of CD38 would not be hindered by the presence of monoclonal antibody drugs, thereby avoiding false-negative results in clinical assays. The property highlights the potential of CD38-specific aptamers as reliable tools for CD38 detection in patients undergoing therapy of monoclonal antibody drugs.

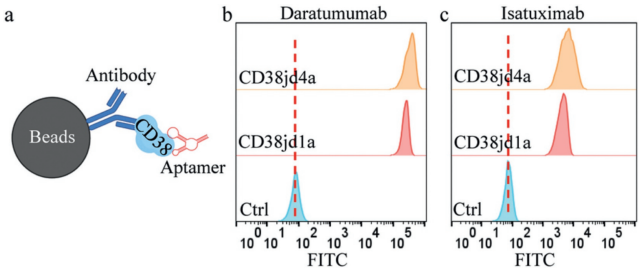


Fig. 3. Binding epitopes of aptamers against CD38. (a) Schematic diagram of aptamer binding to CD38 immobilized by antibodies. (b) Binding of aptamers to CD38 immobilized with Daratumumab by flow cytometry. (c) Binding of aptamers to CD38 immobilized with Isatuximab by flow cytometry.

Next, we evaluated bindings of CD38-specific aptamers to natural CD38 expressed on cell surfaces, as the structure of purified recombinant human CD38 protein may differ from its natural conformation. CD38 is highly expressed in cancer cell lines associated with lymphoma, myeloma, and leukemia, as previously reported and summarized on website of ProteinAtlas (Fig. S5 in Supporting information) [33]. Based on these findings, we selected three CD38-positive cell lines (CCRF-CEM, RPMI8226, and Ramos) and one CD38-negative cell line (K562) to assess the binding of aptamers CD38jd1a and CD38jd4a by flow cytometry. As shown in Fig. 4a, both aptamers exhibited significant binding to all three CD38-positive cell lines but showed no binding to CD38-negative cell K562, consistent with the binding patterns observed for the validated monoclonal antibodies Daratumumab and Isatuximab (Fig. S6 in Supporting information). Unexpectedly, despite demonstrating the highest fluorescence intensity in protein-binding assays, aptamer CD38jd1a exhibited lower fluorescence intensity in cell-binding assays compared to CD38jd4a. This discrepancy may result from differences in protein's conformation or microenvironment on the cell surface compared to the purified protein, which can affect epitope accessibility and aptamer binding [34]. These findings highlight the importance of assessing aptamer performance in more physiologically relevant settings and suggest a di-

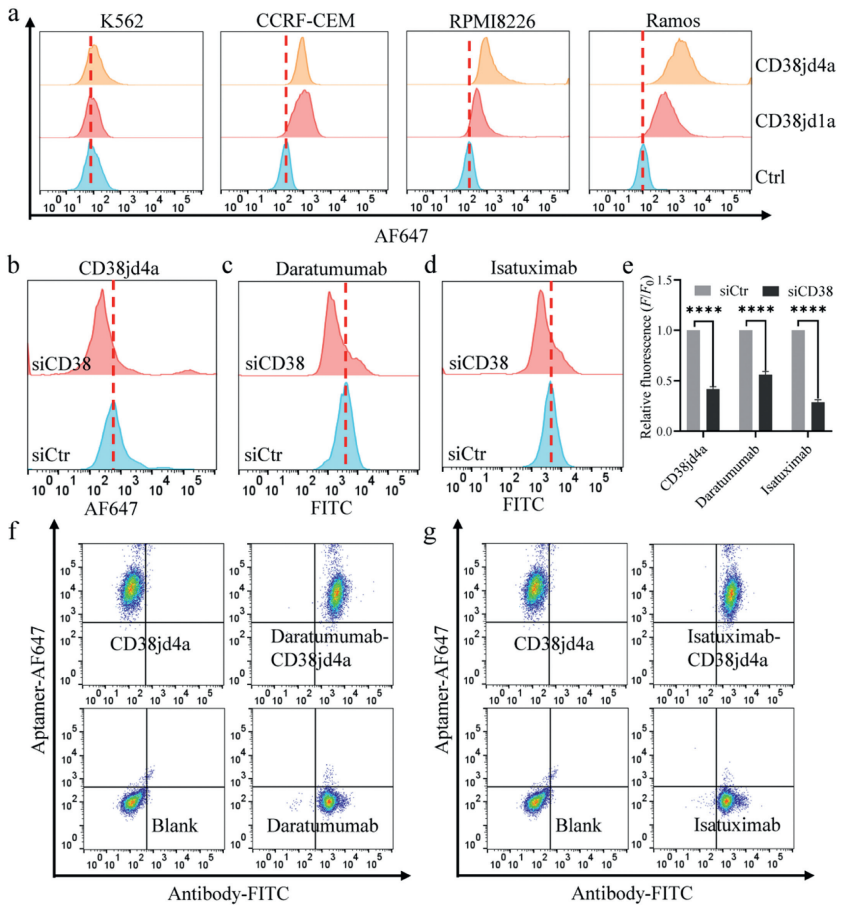


Fig. 4. Binding profiles of aptamer CD38jd4a to CD38 on cell surface. (a) Binding of aptamers with K562, CCRF-CEM, RPMI8226, and Ramos cell lines characterized by flow cytometry. Binding of CD38jd4a (b), Daratumumab (c) and Isatuximab (d) to Ramos cells treated with siCD38 or siControl (siCtr) RNA by flow cytometry. (e) Histogram with statistical analysis of (b, c and d). Co-staining of AF647-labbled CD38jd4a with FITC-labeled Daratumumab (f) and Isatuximab (g) respectively by flow cytometry on Ramos cells.

rection for further optimization. Therefore, CD38jd4a was selected for our further studies.

To confirm that the cellular target of CD38jd4a binding was indeed CD38, we next performed siRNA knockdown experiments and antibody co-staining analysis. CD38 expression on the surface of Ramos cells was knocked down using small interfering RNA (siRNA), followed by staining with AF647-labeled CD38jd4a and FITC-labeled CD38 antibodies. As shown in Figs. 4b-e, the fluorescence intensities of both CD38jd4a and CD38 antibodies were significantly reduced in Ramos cells treated with siCD38 compared to cells treated with the control siRNA (siCtr), indicating that the target protein bound by CD38jd4a on cells was indeed CD38. Additionally, antibody co-staining analysis revealed that CD38jd4a could still bind CD38 on Ramos cells without competing with Daratumumab or Isatuximab (Figs. 4f and g). These results demonstrate that the selected aptamers, particularly CD38jd4a, are capable of recognizing CD38 independently of monoclonal antibodies and would be more suitable as a superior detection tool for CD38.

Subsequently, we evaluated the ability of CD38jd4a to detect CD38-positive cells of cell mixtures to investigate its potential for clinical applications. Prior to incubation of cell mixtures with CD38jd4a, Ramos cells were labeled with CFSE dye so that the different cell populations could be clearly distinguished after mixing with K562 cells. As shown in Fig. 5a, CD38jd4a was capable of specifically recognizing and binding to Ramos cells, even in cell mixtures containing only 10 % Ramos cells, while not binding at all to CD38-negative cells. To further investigate the clinical diagnostic potential of CD38jd4a, we assessed its ability to detect CD38-positive cells in clinical blood samples by flow cytometry. CD38jd4a with two monoclonal antibody drugs (Daratumumab and Isatuximab) were added directly to the blood samples individually or jointly to bind CD38-positive cells. As shown in Figs. 5b and c, CD38jd4a was still capable of efficiently recognizing and detecting CD38-positive cells in the complex environment of blood samples, performing comparably to Daratumumab and Isatuximab. Notably, even in the presence of Daratumumab and Isatuximab, CD38jd4a maintained its ability to specifically recognize CD38, successfully co-labeling CD38-positive cells alongside Daratumumab (Fig. 5b) or Isatuximab (Fig. 5c) without interference. These findings highlight CD38jd4a as a novel molecular probe with significant potential for clinical diagnostics and therapeutics, particularly in detecting and monitoring CD38-related diseases.

In summary, we successfully identified a series of high-affinity aptamers targeting CD38 through oligo rounds of selection against CD38 protein. SPR analysis revealed that aptamers CD38jd1a and CD38jd4a exhibited the highest binding affinities, with K_d values as low as 4.8 ± 0.2 nmol/L and 5.4 ± 0.6 nmol/L, respectively. Moreover, binding analysis using antibody-immobilized CD38 confirmed that the binding epitopes of both aptamers were distinct from both monoclonal antibody drugs of CD38. At cellular level, CD38jd4a still exhibited strong and specific binding to CD38 positive cells. siRNA knockdown experiments further validated that protein CD38jd4a binds was indeed CD38 naturally expressed on the cell surface. Additionally, CD38jd4a was capable of co-staining CD38-positive cells alongside both monoclonal antibody drugs without mutual interference. CD38jd4a also showed robust

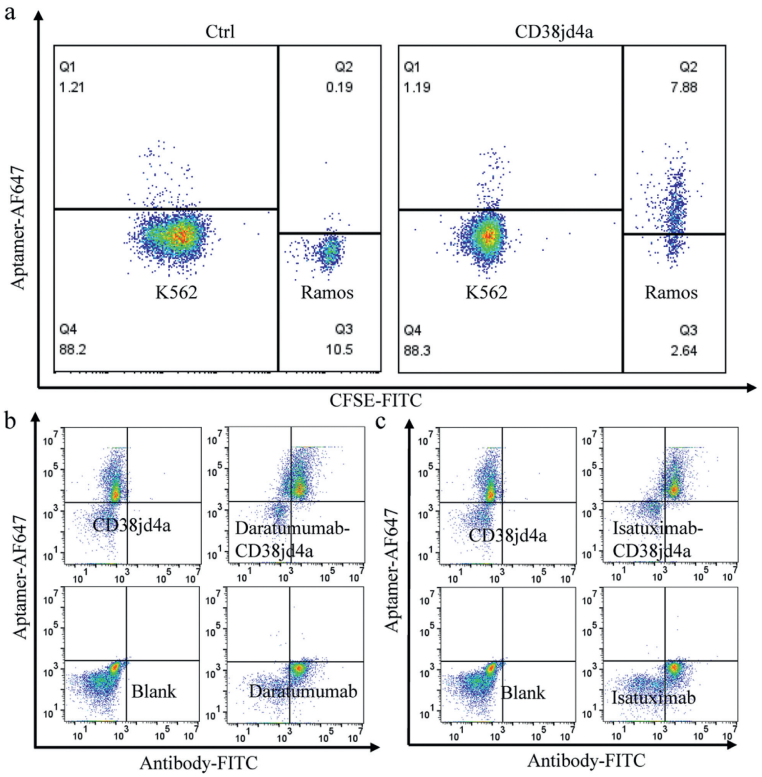


Fig. 5. Detection of CD38 positive samples by aptamer CD38jd4a. (a) CD38jd4a-based detection of CD38 positive cell populations in a mixture of 90 % K562 and 10 % Ramos. Co-staining of CD38jd4a with Daratumumab (b) or Isatuximab (c) to CD38-positive cells in clinical blood samples.

performance in distinguishing CD38-positive cells in mixed populations of positive and negative cells. Importantly, CD38jd4a efficiently detected CD38 in clinical blood samples, even in the presence of daratumumab or isatuximab, avoiding interference caused by these therapeutic antibodies. Due to the relatively limited number of clinical samples used in this study, further expansion of sample size is needed in the future to validate the stability and broad applicability of CD38jd4a in different clinical settings. Nevertheless, given its excellent specificity and high affinity, CD38jd4a holds great promise as a molecular probe for precision diagnosis and treatment of multiple myeloma, as well as other diseases related to CD38 [35]. Moreover, with the advent of the era of tumor targeted therapy [36], the aptamer selection and detection strategy will provide new recognition molecules and detection methods for monitoring targeted therapy.

Ethical statement

The clinical plasma sample used in this study was obtained from Zhejiang Cancer Hospital with the explicit consent of the subject. The study protocol was approved by Ethics Committee of Zhejiang Cancer Hospital (Hangzhou, China) (No. IRB-2023–1182(IIT)), and complied with all relevant laws and regulations of China.

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.

CRediT authorship contribution statement

Di Jiang: Writing – original draft, Methodology, Data curation. **Ling Wang:** Formal analysis, Data curation. **Hengyi Lin:** Methodology, Formal analysis, Data curation. **Xiaoqiu Wu:** Methodology, Formal analysis. **Mingxin Zhang:** Formal analysis, Data curation. **Songxiao Xu:** Resources, Methodology. **Zhenhao Long:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Tao Bing:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Acknowledgments

The authors gratefully acknowledge financial support from the National Natural Science Foundation of China (Nos. 22274139, 22293030, 22293031), Pioneer R&D Program of Zhejiang (Nos. 2023SDYXS0001, 2023SDYXS0002, 2024SDYXS0003), Zhejiang Provincial Natural Science Foundation of China (No. YXD24B0401), National Health Commission Science Research Fund-Zhejiang Provincial Health Key Science and Technology Plan Project (No. WKJ-ZJ-2424).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2025.111502.

References

[1] E.Z. Liu, P. Sudha, N. Becker, et al., Blood Cancer J. 13 (2023) 144.
[2] J.P. Laubach, P.G. Richardson, Clin. Cancer Res. 21 (2015) 2660–2662.
[3] F. Morandi, A.L. Horenstein, F. Costa, et al., Front. Immunol. 9 (2018) 2722.
[4] X.W. Xue, W.J. Zhu, L.G. Zhang, et al., J. Chin. Pharm. Sci. 24 (2015) 572–580.
[5] D. Atanackovic, M. Steinbach, S.V. Radhakrishnan, et al., Oncoimmunology 5 (2016) e1217374.
[6] H.M. Lokhorst, T. Plesner, J.P. Laubach, et al., N. Engl. J. Med. 373 (2015) 1207–1219.
[7] M. Attal, P.G. Richardson, S.V. Rajkumar, et al., Lancet 394 (2019) 2096–2107.
[8] N. van de Donk, P.G. Richardson, F. Malavasi, Blood 131 (2018) 13–29.
[9] S.Z. Usmani, B.M. Weiss, T. Plesner, et al., Blood 128 (2016) 37–44.
[10] E.L. Courville, S. Yohe, P. Shivers, et al., Am. J. Clin. Pathol. 153 (2020) 221–228.
[11] J. Flores-Montero, L. Sanoja-Flores, B. Paiva, et al., Leukemia 31 (2017) 2094–2103.

[12] D.P. Ng, Int. J. Lab. Hematol. 43 (2021) 71–77.
[13] L.J. Pape, J. Hambach, A.J. Gebhardt, et al., Front. Immunol. 13 (2022) 1010270.
[14] A. Broijl, A.C.M. de Jong, M. van Duin, et al., Am. J. Clin. Pathol. 157 (2022) 494–497.
[15] A. Mahmuda, F. Bande, K.J.K. Al-Zihiry, et al., Trop. J. Pharm. Res. 16 (2017) 713–722.
[16] J.K.H. Liu, Ann. Med. Surg. 3 (2014) 113–116.
[17] M. Famulok, G. Mayer, M. Blind, Acc. Chem. Res. 33 (2000) 591–599.
[18] R.B. Liu, F.Y. Zhang, Y.X. Sang, et al., Trends Food Sci. Technol. 123 (2022) 355–375.
[19] H.X. Yu, O. Alkhamis, J. Canoura, et al., Angew. Chem. Int. Ed. 60 (2021) 16800–16823.
[20] A. Ruscito, M.C. DeRosa, Front. Chem. 4 (2016) 14.
[21] Z. Li, X.K. Fu, J. Huang, et al., Front. Cell Dev. Biol 9 (2021) 662791.
[22] L.L. Wu, Y.D. Wang, X. Xu, et al., Chem. Rev. 121 (2021) 12035–12105.
[23] L. He, R.R. Huang, P.F. Xiao, et al., Chin. Chem. Lett. 32 (2021) 1593–1602.
[24] G.J. Yang, Z.Y. Li, R. Usman, et al., Chin. Chem. Lett. 36 (2025) 109930.
[25] Q. Pan, F.L. Luo, M. Liu, et al., J. Infect. 77 (2018) 83–98.
[26] Z.K. Guo, B.J. Jin, Y.L. Fang, et al., Chin. Chem. Lett. 35 (2024) 108528.
[27] S.T. Xie, W.D. Sun, T. Fu, et al., J. Am. Chem. Soc. 145 (2023) 7677–7691.
[28] G.Z. Zhu, X.Y. Chen, Adv. Drug Del. Rev. 134 (2018) 65–78.
[29] T. Bing, T.J. Chang, X.J. Yang, et al., Biorg. Med. Chem. 19 (2011) 4211–4219.
[30] X.Q. Wu, Y.Q. Liu, D.W. Zhang, et al., J. Am. Chem. Soc. 146 (2024) 26667–26675.
[31] D. Zhang, Y. Liu, H. Huang, et al., Anal. Chem. 96 (2024) 16686–16694.
[32] M. Zuker, Nucleic Acids Res. 31 (2003) 3406–3415.
[33] M. Uhlen, C. Zhang, S. Lee, et al., Science 357 (2017) eaan2507.
[34] L. Kelly, K.E. Maier, A. Yan, et al., Nat. Commun. 12 (2021) 6275.
[35] Y.F. Chen, Y.M. Xu, H.Y. Li, et al., N. Engl. J. Med. 390 (2024) 2178–2190.
[36] M. Liu, X. Wang, Innov. Med. 3 (2025) 100107.