Journal of Controlled Release 333 (2021) 418–447

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Review article

Advances in receptor modulation strategies for flexible, efficient, and enhanced antitumor efficacy

Dan-dan Wang, Xue-nong Zhang *

Department of Pharmaceutics, College of Pharmaceutical Sciences, Soochow University, Suzhou 215123, People's Republic of China

ARTICLE INFO

Keywords:
Receptors modulation
Nano drug delivery systems
Cancer therapy
Tumor-targeting
Receptor-mediated endocytosis

ABSTRACT

Tumor-sensitivity, effective transport, and precise delivery to tumor cells of nano drug delivery systems (NDDs) have been great challenges to cancer therapy in recent years. The conventional targeting approach involves actively installing the corresponding ligand on the nanocarriers, which is prone to recognize the antigen blasts overexpressed on the surface of tumor cells. However, there are some probable limitations for the active tumor-targeting systems *in vivo* as follows: a. the limited ligand amount of modifications; b. possible steric hindrance, which was likely to prevent ligand-receptor interaction during the delivery process. c. the restrained antigen saturation highly expressed on the cell membrane, will definitely decrease the specificity and often lead to "off-target" effects of NDDs; and d. water insolubility of nanocarriers due to excess of ligands modification. Obviously, any regulation of receptors on surface of tumor cells exerted an important influence on the delivery of targeting systems. Herein, receptor upregulation was mostly desired for enhancing targeted therapy from the cellular level. This technique with the amplification of receptors has the potential to enhance tumor sensitivity towards corresponding ligand-modified nanoparticles, and thereby increasing the effective therapeutic concentration as well as improving the efficacy of chemotherapy. The enhancement of positively expressed receptors on tumor cells and receptor-dependent therapeutic agents or NDDs with an assembled "self-promoting" effect contributes to increasing cell sensitivity to NPs, and will provide a basic platform for clinical therapeutic practice. In this review, we highlight the significance of modulating various receptors on different types of cancer cells for drug delivery and therapeutic benefits.

1. Introduction

1.1. Cancer therapy: targeted drug delivery systems

In view of the side effects and low therapeutic effects induced by chemotherapeutic drugs due to the weakness of specificity to tumor cells, targeted nano drug delivery systems (NDDs) based on nanotechnology have emerged as a promising strategy for cancer treatment. The NDDs studied in the past few decades have gained importance due to increases in drug stability and solubility [1], their ease of administration [2], improved pharmacokinetic profiles benefiting from prolonged blood circulation [3], modified biodistribution *in vivo* [4], and to some extent decreased drug cytotoxicity to normal tissue [5]. With or without the surface modification of NDDs, the systems are classified into two groups: passive and active targeting NDDs. Passive targeting NDDs without tumor-site specificity have the properties of targeting tumor cells *via* an enhanced tumor penetration and retention (EPR) effect [6,7], partly owing to the defective vascular architecture and devastating lymphatic return [8]. They are mainly influenced by surface charge, composition and size distribution of NDDs as well as the intrinsic tumor microenvironment, which is distinctively different from normal tissues (Fig. 1A&B). For instance, human serum albumin-bound paclitaxel (PTX, trade name: Abraxane) with a nano size of 170 nm, obtained better inhibition effects on many types of tumors than free drug, officially approved for clinical use [9]. In general, targeting particular biomarkers overexpressed on tumor cells endowed nano systems with high selectivity and enhanced therapeutic efficacy (Fig. 1C&D). In the past few decades, a vast majority of receptors have been implicated as detectable biomarkers in various tumor cell types; thus, receptor-guided delivery systems actively have attracted considerable attention, providing the possibility of selective, effective tumor-targeting and tumor penetration. For example, an antibody-drug conjugate for FRα specifically binding to ovarian cancer provides a targeting strategy for treatment [10]. The delivery of receptor-mediated NPs for the treatment

* Corresponding author.
E-mail address: zhangxuenong@163.com (X.-n. Zhang).

https://doi.org/10.1016/j.jconrel.2021.03.045
Received 13 October 2020; Received in revised form 29 March 2021; Accepted 30 March 2021
Available online 1 April 2021

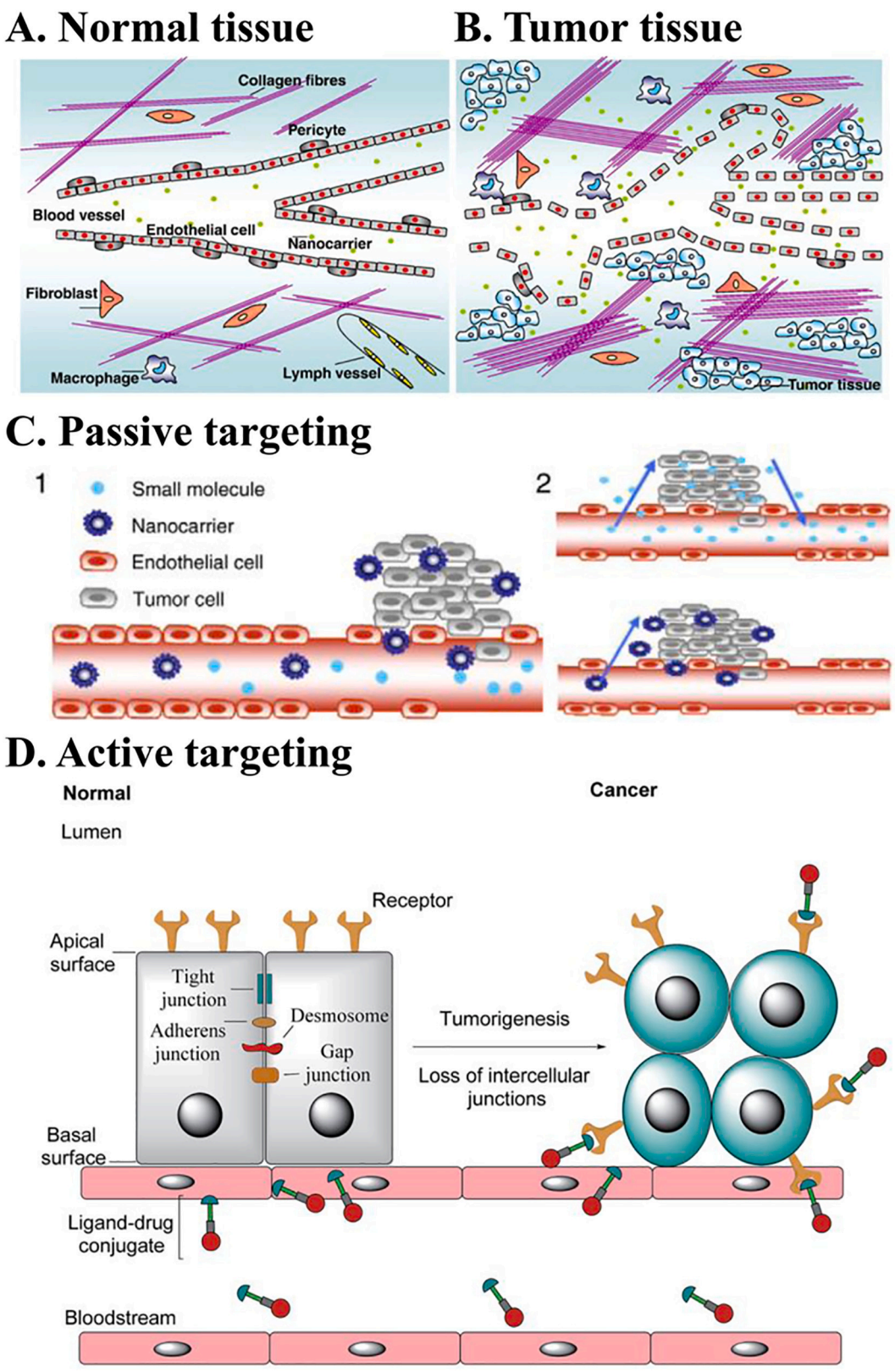


Fig. 1. The differences between normal tissues and tumor tissues; and the passive targeting and active targeting owing to tumor-environment. A. Normal tissues usually have smooth muscle veins, intracellular matrix, and tight junctions. B. Tumor tissues abnormally lack intercellular junctions and tight vasculature. C. (1) Nanocarriers can penetrate through the leaky vessels surrounding the interstitium of tumors to reach the tumor site. (2) Free drugs freely diffuse out of tumor blood vessels due to their small size and dramatically decreased effective concentration of drugs in tumor sites. In contrast, drug-loaded nanocarriers cannot diffuse back into the bloodstream benefited from their larger size, achieving subsequent accumulation *via* the EPR effect. D. The strategy of active targeting effects mediated by receptors, overexpressed on tumor cells. The figure was adopted from [6,11] [12].

Table 1
The receptor-mediated systems for the treatment of different types of tumor cells.

Targeted ligand	Receptor	Cell types	Targeted systems	Year	Ref
FA	FRα	Hepatocellular carcinoma	Nanoparticles	2019	[13]
		Breast cancer	Nanoparticles	2016	[14]
		Glioma	Nanoparticles	2016	[15]
		Ovarian carcinomas	Drug-conjugate	2003	[16]
FA	FRβ	Myeloid leukemia	Nanoparticles	2014	[17]
ApoB	LDL receptor	Glioma	Nanoparticles	2010	[18]
cRGD	αvβ3	Pancreatic cancer	Antibody-drug conjugate	2016	[19]
Biotin	Integrin	Breast cancer	Nanoparticles	2011	[20]
Her-2	Her-2 antibody	Breast cancer	Nanoparticles	2008	[21]
Transferrin	Transferrin receptor	Glioma	Liposomes;	2010	[22,23]
			Nanoparticles	2018	
Mannose	Mannose receptor	Hepatocellular carcinoma	Nanoparticles	2016	[24]
Galactose	ASGPR	Hepatocellular carcinoma	Nanoparticles	2013	[25]
Glycyrrhetinic acid	Glycyrrhetinic acid receptor	Hepatocellular carcinoma	Nanoparticles	2015	[26]
Anti-Flk-1	VEGFR	Colon cancer	Nanoparticles	2004	[27]

Table 2
The receptor-targeted chemo drugs in clinical trials or practical use.

Receptor	Ligand	Drugs	Cancer cell	Status	Year	Ref
FRα	FA	Mirvetuximab soravtansine (IMGN853)	Ovarian cancer	Phase II	2015	[10,38]
		Farletuzumab (MORab003)	Ovarian cancer	Phase I	2008	[39]
FRβ	CAR-T		AML	Preclinical	2015	[40]
	Anti-m909		Macrophages	Clinical use	2001	[41]
Transferrin receptor	Transferrin		Metastatic solid tumor	Phase I/II	2011	[42]
ASGPR		Lectins	Hepatocellular carcinoma	Phase I	2002	[43]
GAH		GAH Fab'	Metastatic stomach cancer	Phase I	2004	[44]
ANG1005	Angiopep-2	Paclitaxel	Brain metastasis	Phase II	2010	[45]

of different cancer cell types is described in the following table (Table 1).

1.2. Cancer therapy: receptor-mediated endocytosis and the necessity to upregulate receptors

Addressing the drawbacks of current cancer therapeutics, efficient specific targeted delivery nanosystems are developed as a promising therapy at the site of action. It should be noted that active tumor targeting is well-performed functionally *in vivo* [28]: a. Intercellular tight junctions are often lost upon tumorigenesis, and the interaction between receptors and ligand-modified nanoparticles (NPs) only occurs on tumor cells owing to the exposure of surface receptors. b. Receptors positioned on normal tissues are physiologically usually not available in the bloodstream, avoiding unnecessary drug uptake and decreasing the toxicity to the whole body. The combined advantages of corresponding ligand linking, receptor exposure and to targeting tumor site in the bloodstream made NPs desirable for targeted therapy. At the NPs' level, designed chemo drugs-loaded nanocarrier with the modification of activated ligand attached to the tumor cell membrane performed specific functions by receptor-ligand interactions. Clinical and pre-clinical trial investigations have shown the great potential of specific receptor-targeted monoclonal antibodies for targeted therapy (examples as are shown in Table 2). Although receptor-targeted therapy has preliminarily attained excellent outcomes, another concern has been aroused. There are some probable limitations for the active tumor-targeting systems *in vivo* as follows [29]: a. the limited ligand amount of modifications; b. the possible steric hindrance, which was likely to prevent the ligand-receptor interactions during the delivery process. c. the restrained antigen saturation highly expressed on the cell membrane, will definitely decrease the specificity and often lead to "off-target" effects of NDDs; d. water insolubility of nanocarriers due to excess ligand modification. The details presented in Table 3.

Evidently, the increase in the ligand graft ratio to NPs may not afford more efficient tumor targeting. What's more, given the receptor-mediated internalization recycling pathway: a. the ligand-modified NPs were internalized by cells with prolonged time. b. The drug was released from NPs to the cytoplasm; and c. the receptors were recycled back to the cell membrane [37], it is notable that the receptor amount should be enriched preferentially on the surface of tumor cells for specific delivery and efficient intracellular transport. Herein, from the cellular level, the methods of enhancing receptor expression on the surface of the membrane contribute to the outcomes of receptor-mediated endocytosis and increasing the sensitivity of tumor cells to active-targeting nanosystems. As the effectiveness of receptor-modified NPs was partly related to the level of receptors on cancer cells, thus we hypothesized that the upregulation of surface receptors on tumor cells could provide solutions for this dilemma. That is, when there are no abundant antigens expressed on the surface of the tumor cells, it would be unlikely to obtain sufficient tumor internalization and efficient receptor-guided therapies. This review will first discuss some advances in the upregulation of receptors specifically binding to tumor cells, and offer possible applications or potential risks, which may lay a foundation for enhancing NDDs tumor targeting and therapeutic benefits.

Table 3
Possible strategies, limitations for the active tumor-targeting systems *in vivo*.

Limitations	Explanation and the disadvantages	References
Limited ligand amount of modifications	In general, the defined functional groups (amino and carboxylic group) or reaction site in compound or biomacromolecules are limited and insufficient to covalently link to the ligand.	[30,31]
Steric hindrance and multivalency of ligand	Affected by steric hindrance closely related to the ligand size, the ligand is inaccessible to receptor expressed on tumor cells and the efficiency of receptor-ligand interactions may be undesirable. Otherwise, small molecules may not be directly linked to the surface of nanocarriers, this linkage which may negatively influence the recognition between receptor and binding site of ligand.	[32,33]
Antigen saturation	Although some research addressed the modification of ligand on targeted systems, the saturation of antigen expressed on tumor cells is evitable in the receptor-mediated endocytosis. The lack of activated receptor could not adhere to the binding site of ligand.	[34,35]
Water insolubility of nanocarriers and colloidal stability	Although increasing the graft ratio of moiety provides the possibility of receptor-ligand interactions, excess insoluble small molecules may affect water solubility of nanocarriers, colloidal stability and nanosize.	[29]
Orientations	The orientations of receptors on the surface of cells are important during the recognition, which decide whether the ligand bond to the activated site of receptor. If the receptors or ligand on targeted systems could not be exposure to each other, the failure may lead to ineffective endocytosis.	[29]
Receptor mobility	The cell-cell interactions such as cellular adhesion, the affinity of ligand to receptor, ligand density make great influence on receptor mobility. Otherwise, receptor mobility also has impact on the interaction between ligand-targeted systems and receptor by the adhesion.	[36]

2. The types of receptors for upregulation

2.1. Folate receptor (FR)

Folate receptor (FR) is a kind of glycoprotein consisting of a family of three subtypes: FRα, FRβ, and FRγ. FRα commonly binds to the surface of most cancer cells, including epithelial cells or gynecological cells, such as ovarian cancer, and triple negative breast cancer 4 T1 cells, while FRβ is often aberrantly expressed on malignant hematological linage cell lines, such as most types of activated myeloid leukemia cells [46]. Evidence shows that the expression of FRβ is also relatively increased during neutrophil maturation [46] and macrophage activation. Otherwise, FRβ was not overexpressed in normal hematological cells without the ability to bind folate acid (FA) and showed an inactive form [47,48]. Both antigens have been shown great affinity to FA, as reported. In addition, FRγ was merely reported as an intracellular secreted protein, at low levels from hematological cells. Benefitting from the tumor tissue specificity of FR expression different from normal organs, NDDs modified with FA have been widely applied in FR-targeted therapies to FR (+) cell lines [49,50]. The FR-guided endocytosis and intracellular trafficking processes are shown in Fig. 2B. As previous study, FA-modified NPs or FA-conjugated drugs have the ability to achieve active tumor-targeted delivery due to being capable of enhancing accumulation at the intended tumor sites, facilitating cellular internalization by FA-FR interactions and increasing the intracellular concentration of anticancer drugs [51,52]. Yueqing Gu's group constructed a prodrug based on folate-conjugated BSA (FA-BSA-CAD). The *in vitro* and *in vivo* results consistently demonstrated that the prodrug selectively targeted to tumor cells positively expressing FR and reduced the toxicity to normal cells (Fig. 3) [53]. Shaobing Zhou et al. designed doxorubicin (DOX)-loaded micelles based on folate installation for active tumor target delivery, which promoted their targeting ability and increased the cellular uptake amount in FRα (+) HeLa cells [54]. In addition, Luan's group [55] designed bexarotene-loaded FA-modified albumin NPs (FA-BEX-BSA NPs). For FR (+) MCF-7 cells, the inhibition effect of FA-modified albumin NPs was markedly stronger than that of non-targeted group (BEX-BSA NPs), with an obvious increase in the intracellular fluorescence signal, while FR(−) A549 cells showed the equivalent intensity and cytotoxicity of FA-BEX-BSA NPs to BEX-BSA NPs (Fig. 3). Apparently, the difference in cytotoxicity of FA-BEX-BSA NPs was ascribed to the density of FR on tumor cells. These results pointed out the significance of the levels of surface FR to FR-guided endocytosis and cell viability. Of note, these studies were essentially aimed to obtain tumor control effectively as a result of abundant antigen and small molecule interactions.

2.1.1. FRβ

FRβ is often aberrantly expressed on hematological linage cell lines, such as lymphoma and leukemia. Thus, FRβ can function as an optimal target due to the narrow tissue specificity of FRβ expression [46]. For instance, FRβ on FRβ (+) KG-1 cells could be augmented by curcumin (Fig. 4), which decreased the cell viability and demonstrated significant therapeutic intervention for leukemia progression of methotrexate (MTX), using FR-mediated drug delivery systems [56]. Therefore, it was not difficult to determine that receptor augmentation plays critical roles in intracellular and extracellular transport efficiency, and extends the utility of receptor-mediated therapies.

Tan's group investigated the upregulation effect of FRβ induced by arsenic trioxide (ATO) and the therapeutic efficacy of FA-modified ATO-loaded human serum albumin NPs (FA-HSA-ATO) in a chronic myeloid leukemia (CML) xenograft tumor model. Cellular and tissue level results showed that FA-HSA-ATO could upregulate FRβ binding in FRβ (+) CML cells, and could thereby promote even more intracellular accumulation of FA-HSA-ATO, resulting in stronger inhibition of CML [57]. K562 cells (CML) highly expressing FRβ showed excellent FA-HSA-ATO uptake behavior and upregulated FRβ signaling after the induction, like a "self-promoting" effect, and attained an increased inhibitory effect to xenograft tumor, contrast to non-FA-targeted group (Fig. 5). Besides, the induction of FRβ by ATO could be blocked by pre-treatment of free FA, illuminating the FR-mediated trafficking pathway. Interestingly, to further prove that FA-HSA-ATO can improve the cytotoxicity of other FRβ-targeting drug-loaded NDDs, they evaluated the cytotoxicity of FA-HSA-PTX on K562 cells and leukemia mononuclear cells, with or without FA-HSA-ATO for 72 h. Surprisingly, FA-HSA-PTX showed stronger cytotoxicity against K562 cells pretreated with 1 mM FA-HSA-ATO, compared to K562 cells without treatment, with a 3.7-fold enhancement of IC50. The study also revealed that the intracellular

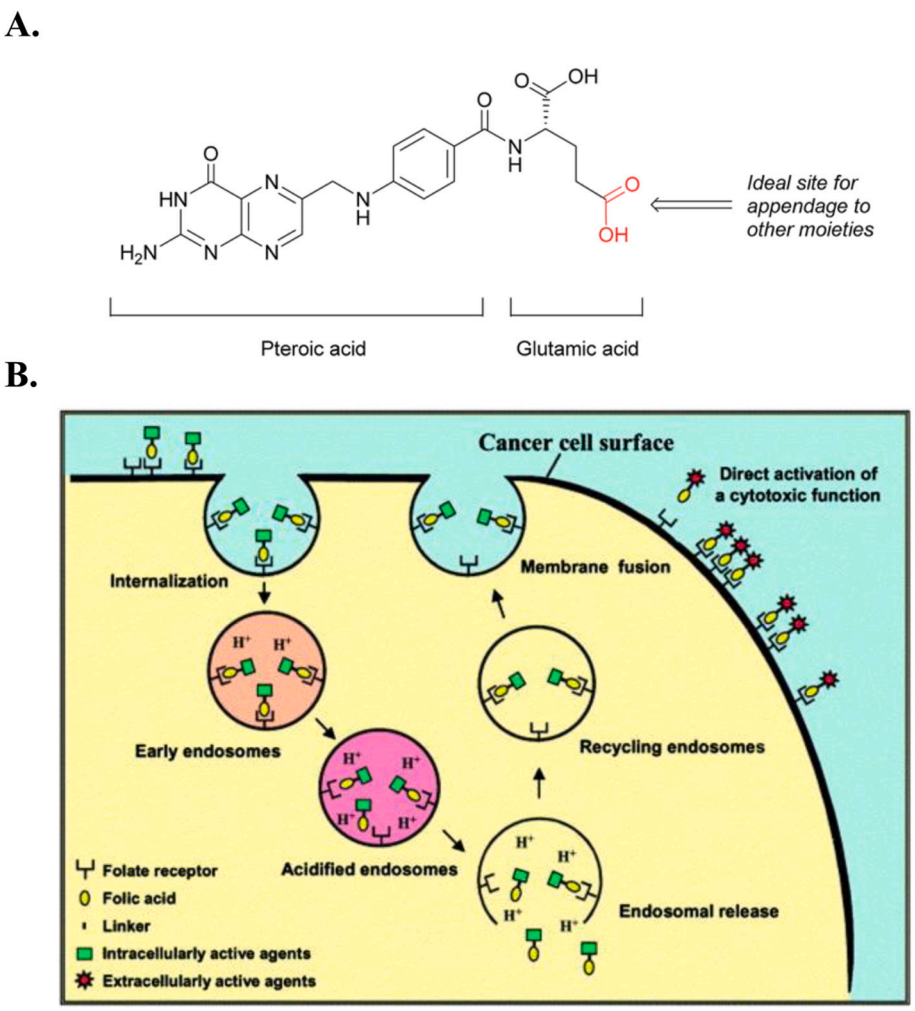


Fig. 2. A. The structure of FA and the activated site for conjugation. B. Active endocytosis mediated by the recognition of FA-FR [49].

action strongly depended on the intracellular concentration of ATO, which was closely related to the density of FRβ in K562 cells. Validated evidence confirmed that the uptake of FA-HSA-ATO increased FRβ expression in FRβ-expressing cells but had no significance in FRβ-negative cells, further enhanced tumor targeting of FA-targeted drugs, and finally, dramatically decreased the tumor volume during the treatment. Contributing to therapeutic benefits, this strategy increased the selectivity to CML and benefited to decrease damage to other organs, increasingly reduced the toxicity of ATO to the body.

Additionally, all trans retinoic acid (ATRA) has been indicated as the transcriptional regulator of the FRβ. *In vitro* studies demonstrated that the induction of ATRA for 5 d significantly increased FRβ signals on FRβ (+) acute monocytic leukemic THP-1 cell lines. And the upregulation was reversible [58]. However, increased FRβ production was observed only on the FRβ (+) cell surface but not in the FRβ (−) HL-60 cell line [59]. And it was noted that the FRβ would decrease to the primary level once the stimulation was interrupted. Based on this notion, the sequential delivery of ATRA for 5 consecutive days plus FRβ-guided m909 chimeric antigen receptor T cells (CAR-T) led to increased T-cell activation, exhibiting stimulated IFN-γ release and lytic activity (Fig. 6) [40]. In contrast, the capacity to upregulate FRβ was not observed in healthy tissues such as hematopoietic stem and progenitor cells (HSCs), suggesting reduced toxicity and potential clinical applications. Although there was no augmentation of the antitumor effects of m909 CAR-T cells, the optimal dosage and regimen of ATRA may systematically increase the safety for its specificity to upregulate FRβ on malignant FRβ (+) leukemic cells, mitigating the potential risk of "off-target" of m909 CAR-T cells. The study preliminarily determined that pre-treatment with ATRA selectively enhanced the reactivity and recognition of m909 CAR-T cells to acute monocytic leukemia. Another study, also indicates this point of view [60]. The flow cytometry results verified that the increase of FRβ expression in FRβ (+) acute myeloid leukemia (AML) KG-1 cells was positively correlated with the cellular uptake amount of FR-targeted NPs. In contrast to FRα (+) FRβ (−) L1210JF, a stronger fluorescence signal of f-L-DOX (FA-targeted group) with the pre-treatment of ATRA was clearly shown in the FRβ (+) KG-1 leukemic cell model, which increased by 5-fold. In addition, for the non-targeted group (L-DOX), the endocytosis indeed indicates no significant difference with or without pre-treatment with ATRA. Interestingly, the uptake rate of f-L-DOX pre-exposure to ATRA could be completely suppressed by the addition of FA (1 mM). These results presumably concluded that the consecutive induction by ATRA selectively increased the sensitivity of FRβ (+) KG-1 cells to f-L-DOX by upregulating FRβ. As a result, superior cytotoxicity of f-L-DOX over L-DOX was observed, with a 25-fold increase, while with the preincubation of ATRA, it increased to 63-fold. Moreover, evident from survival rate analysis, ATRA-facilitated delivery exhibited more

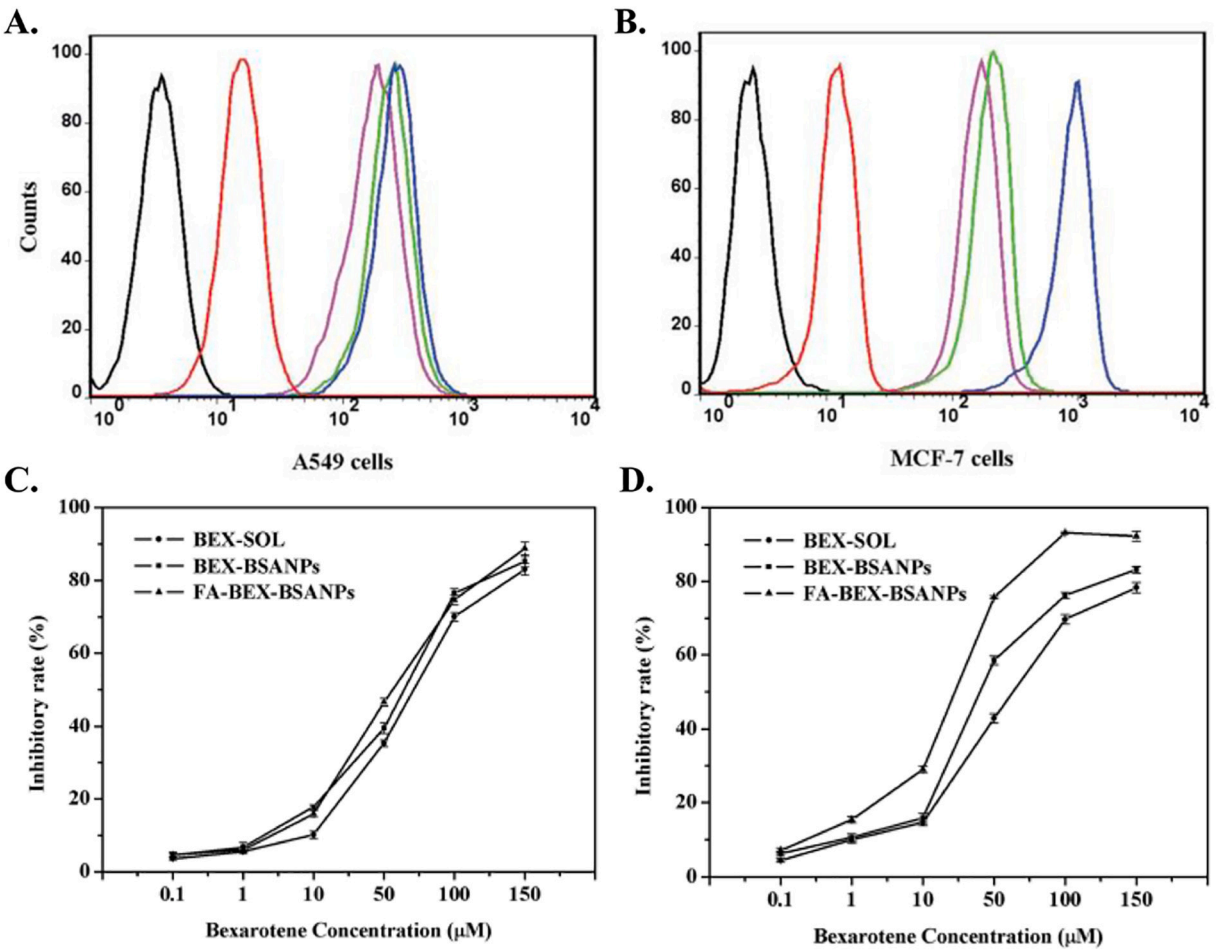


Fig. 3. A. The cellular uptake of A549 cells analyzed by flow cytometry after treatment with different agents. B. The fluorescence intensity of coumarin-loaded NPs in MCF-7 cells. Black: control, Red: free coumarin-6, Purple: coumarin-6-BSA NPs, Blue: FA-coumarin-6-BSA NPs, Green: FA-coumarin-6-BSA NPs pretreated with 2 mM free FA. C. The inhibition effect of A549 cells treated with different formulations by an MTT assay. D. The cytotoxicity of the non-targeted (BEX-BSA NPs) and targeted groups (FA-BEX-BSA NPs) against MCF-7 cells [55]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

pronounced therapeutic effects. The intraperitoneal injection of ATRA could be mostly beneficial for the therapeutic effects of f-L-DOX in FRβ (+) KG-1 ascites tumors, with the cure rate increasing from 10% to 60% (Fig. 7).

The inhibition to types of cancer of ATRA plus anticancer drugs was studied as above-mentioned report, our group evaluated whether the enhanced targeting effect of FA-modified NPs induced by ATRA *in vivo* [61]. We constructed a FA-modified ATRA NPs and measured the FRβ expression on KG-1 nude mice model. Notably, from the 100× magnification images (Fig. 8A), 3 d pre-treatment with ATRA NPs (I.V., 10 mg/kg) group showed stronger green fluorescence intensity (represented FRβ levels) considerably at internal tumor or edges of tumor sites. Similarly, in view of the 400× and 630× magnification images, the FRβ expression on tumor slices of nude mice treated with I.V. ATRA NPs at 10 mg/kg showed 10-fold times higher than I.P. (free ATRA, 10 mg/kg), and 1.8-fold times enhancement than I.V. ATRA NPs at 8 mg/kg group. Having shown an increased expression of FRβ on KG-1 subcutaneous tumor model, we further verified whether the active AML-targeting could be enhanced by ATRA (Fig. 8B). Interestingly, the significant difference of DiR intensity between II and V demonstrated the selective targeting enhancement of FA-modified NPs forced by ATRA NPs for consecutive 3 d treatment, increased by 1.4-fold. Therefore, the enhanced surface FRβ levels was desirable for increasing effective intracellular concentration of siRNA, and importantly, providing a foundation for enhancing targeting FRβ (+) cancer cells therapy.

Investigations have revealed that FRβ is implicated as a potential target for FR-targeted drug delivery. Among various types of retinoid analogous compounds, consisting of ATRA, 9-cis-retinoic acid, LG101093, LG100364, or TTNPB, ATRA alone showed stronger induction of FRβ expression in FRβ (+) KG-1 cells after 5 d of treatment compared with its counterparts (Fig. 9A) [59]. Northern blot analysis demonstrated that the treatment of ATRA did not induced changes in FRα expression in different types of FRα (+) carcinomas, while relatively high degree of FRβ levels were detected in FRβ (+) ATRA-resistant leukemic cells (Fig. 9B). Furthermore, evident from western blot analysis, FRβ levels depend on ATRA in a dose-dependent manner and time-response behavior, which was also confirmed by the above-mentioned similar research. Otherwise, the results analyzed by flow cytometry demonstrated that FRβ could not be upregulated by the following compounds: including phorbol ester, dexamethasone (Dexa), 1, 25-

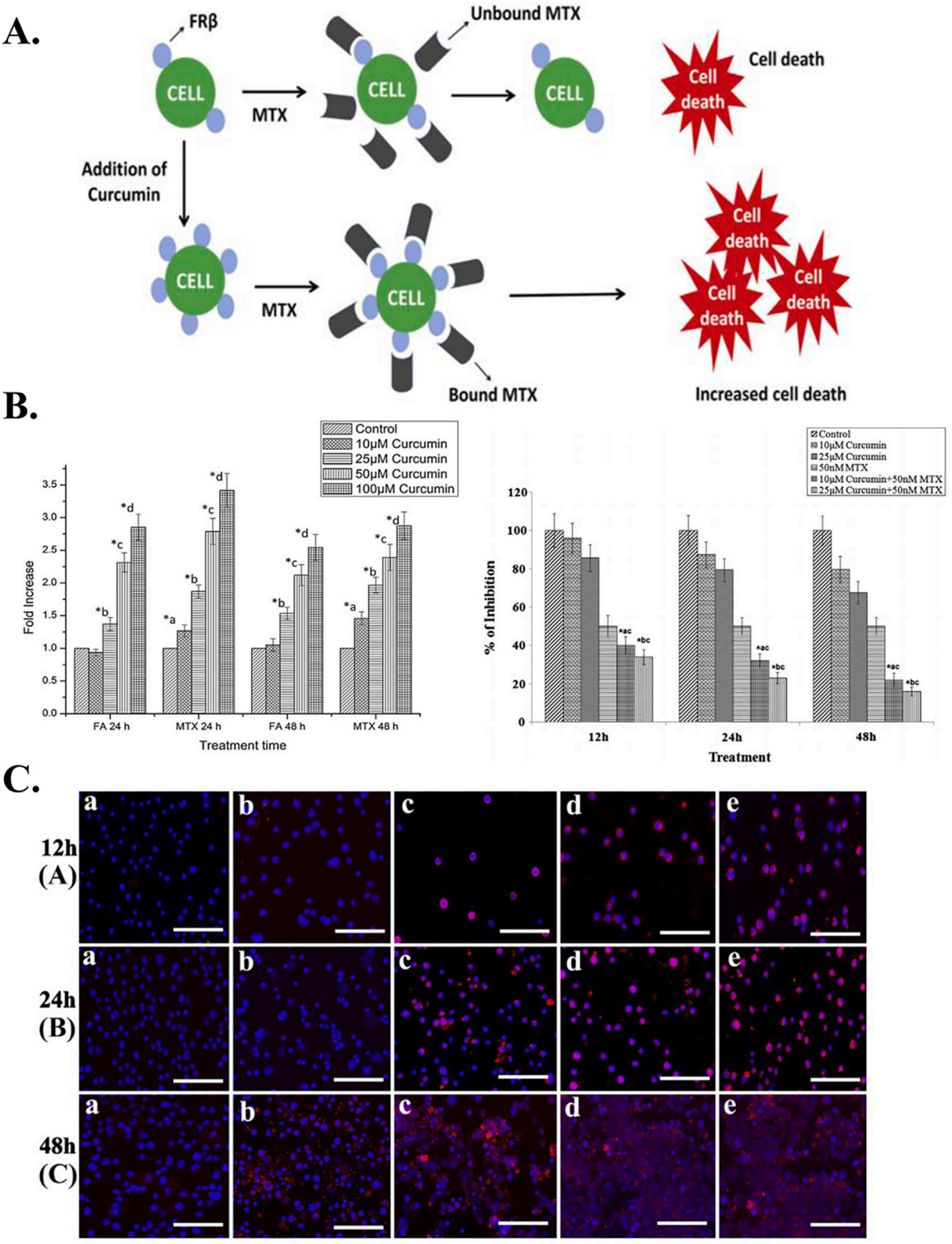


Fig. 4. A. Workflow of curcumin enhancing uptake and cytotoxicity of methotrexate to KG-1 cells by augmenting levels of FRβ. B. Uptake fold increase of ^{3}H-labeled FA and ^{3}H-labeled methotrexate with treatment of different concentrations of curcumin, under pre-designed time points, in KG-1 cells (Left). Inhibition rate of KG-1 cells induced by methotrexate with or without curcumin (Right) for 12 h, 24 h or 48 h. C. Confocal images of FRβ signals in KG-1 cells increased by curcumin. (a-e). FRβ intensity in KG-1 cells treated with various concentrations of curcumin including 0, 10, 25, 50 and 100 mM, for 12 h, 24 h or 48 h [56].

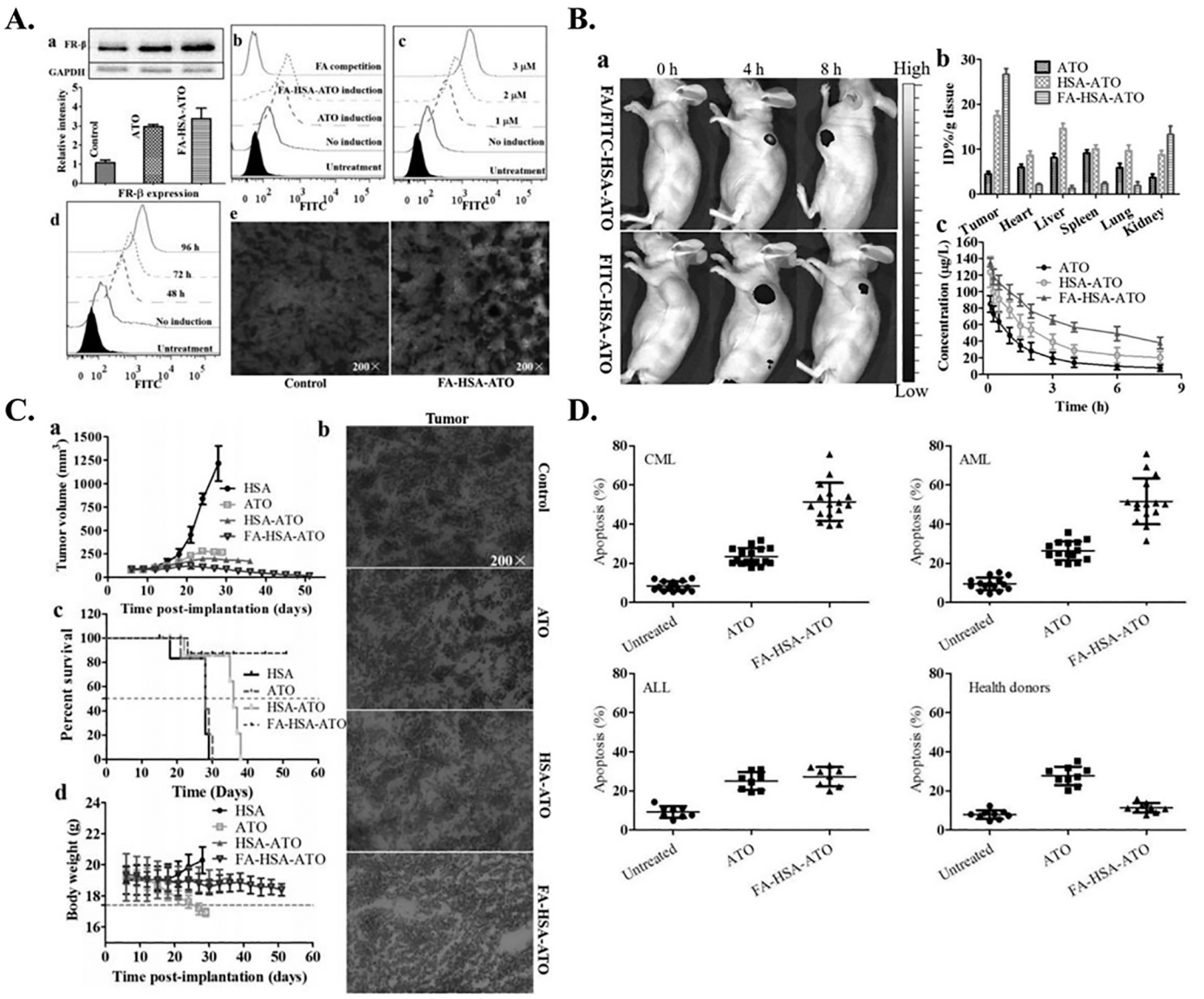


Fig. 5. A. Induction effect FRβ in K562 cells by FA-HSA-ATO *via* western blotting, flow cytometric analysis, tissue section images. The surface FRβ analysis measured *via* FITC channel. B. FRβ tumor-targeting ability and biodistribution of FA-HSA-ATO in subcutaneous K562 model. C. Evaluation of anti-tumor effect in of FA-HSA-ATO. D. The apoptosis of non-targeted group and FRβ-targeted ATO formulations to FRβ (+) CML or acute myeloid leukemia (AML) cells and FRβ (−) ALL or cells from healthy donors. ATO represent arsenic trioxide for chronic myeloid leukemia [57].

dihydroxy vitamin D3, or transforming growth factor β (TGF-β). It was highlighted that this upregulating effect would be contemporarily restored to the basal level when the stimulation of ATRA was withdrawn. And data has shown that the incubation of ATRA at the optimal concentration of 10^{-6} M for 5 d markedly increased FRβ levels up to 20-fold, compared with the control group. Moreover, ATRA did not trigger the differentiation of KG-1 cells during the FRβ induction period detected by the NBT reduction assay (an assay indicates the degree of differentiation by NBT agents). The conclusion could be made that FRβ on FRβ (+) leukemic cells was selectively upregulated reversibly following the addition of ATRA, which may be mainly due to the direct effect on the activity of the FRβ promotor *via* its receptor RARα, RARβ or RARγ, but not on RARX. An ATRA modulation effect was observed in FRβ mRNA transcription accompanied by FRβ protein levels according to the experiment.

Another study investigated the FRβ levels in MV-411 leukemic cells treated with ATRA combined with histone deacetylase inhibitors (HDACi) [62]. A preliminary study showed that exposure to 0.1 μM ATRA in MV-411ATRA-sensitive (MV-411S) cells induced more cytotoxicity than MV-411 ATRA-resistant (MV-411R) cells by an apoptosis assay. Nonobese diabetic-severe combined immunodeficient mice (NOD-SCID) mice, are an appropriate optimal animal model for reconstructing AML. The hFRβ signals were relatively undetectable in the NOD-SCID mice model engrafted with MV-411S cells with the induction of ATRA. Importantly, observed in the MV-411R subline group, the hFRβ levels obviously increased by approximately 10-fold compared with the vehicle group after 5 consecutive days of ATRA treatment (Fig. 10A). To further verify the effect of the combination of ATRA and HDACi on hFRβ

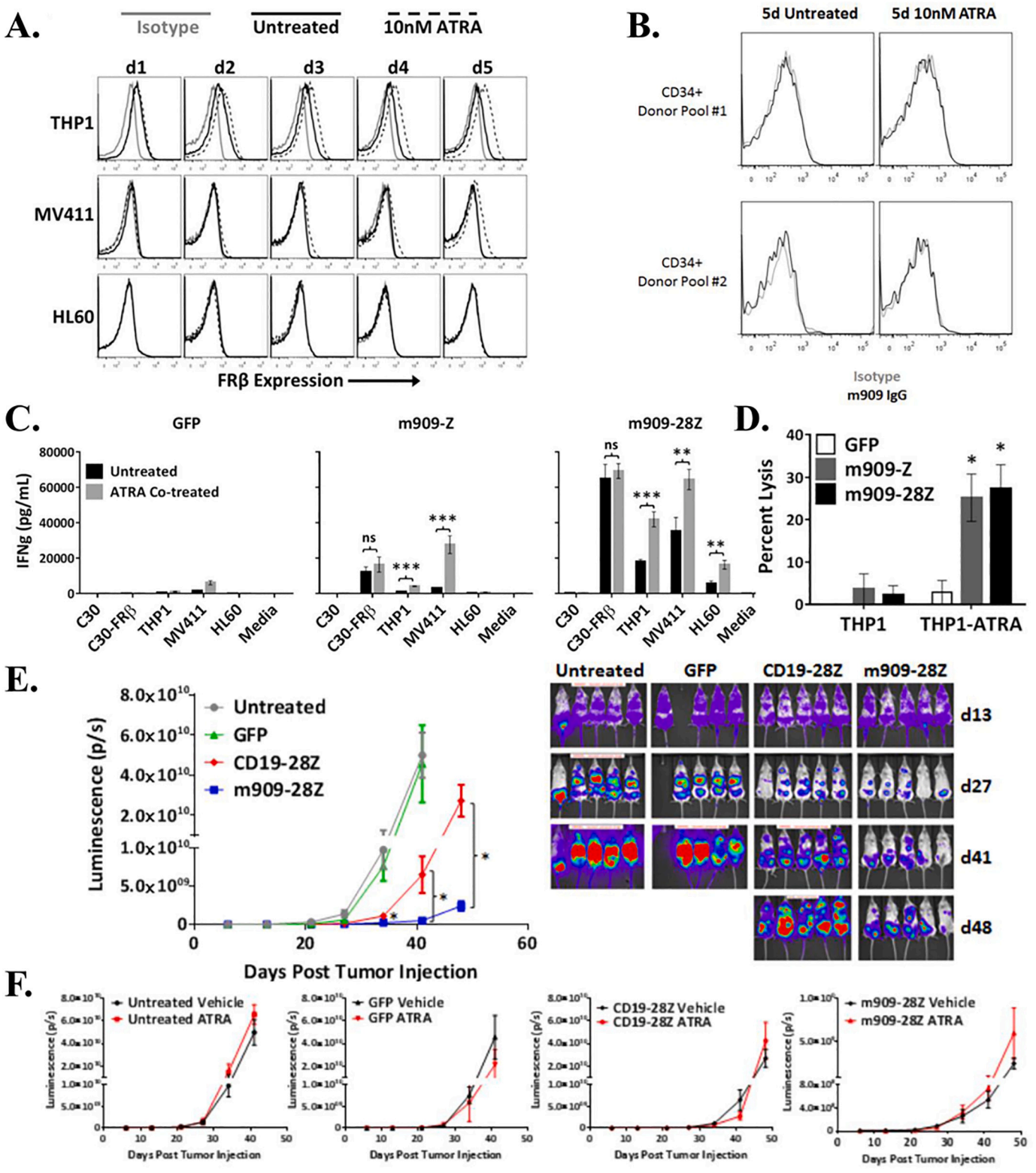
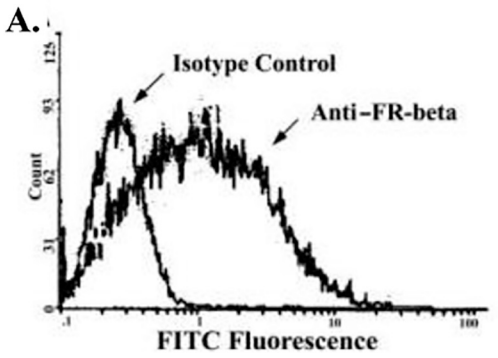
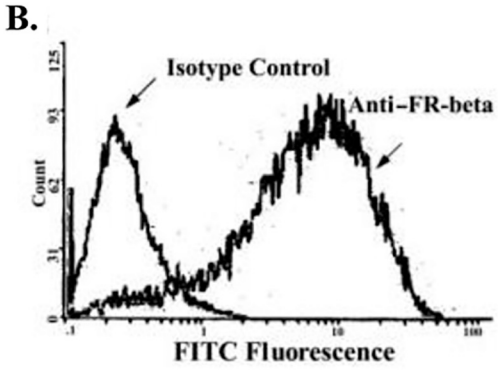
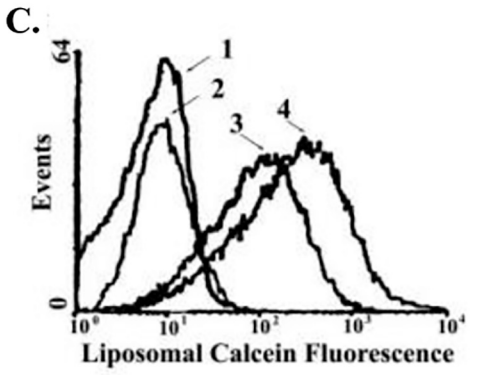


Fig. 6. A. FRβ expression measured by flow cytometry in THP-1 cells, MV-411 cells, and HL-60 cells after incubation of 10 nM ATRA. B. ATRA does not induce FRβ in normal HSCs. Healthy cells isolated from normal donors' bone marrow independently were cultured with or without 10 nM ATRA. FRβ expression was assessed by flow cytometry using m909 IgG (m909 indicates human FRβ, black lines) and human IgG isotype (gray lines). Live, CD34+ gates were used for FRβ analysis. The FRβ expression was undetectable on HSCs following ATRA treatment. C. IFN-γ release of FRβ (+) or FRβ (−) cells with or without co-treatment of ATRA. D. Percent lysis using m909 CAR-T co-cultured with ATRA. E. Tumor volume treated with the following groups: no treatment, GFP-T cells, CD19-28Z CAR-T cells, and human FRβ specific m909 CAR-T cells, monitored after THP-1 post injections detected using bioluminescence. CD19 CAR-T was used as a control for none of AML expressing CD19. F. Tumor growth of THP-1 treated with ATRA combined with CAR-T function [40].







D.

Leukemia cell line	KG-1		KG-1a		L1210JF	L1210
FR expression status	FR-β (+)		FR (−)		FR-α (+)	FR (−)
Pre-exposure to ATRA	−	+	−	+	−	−
Free DOX	0.65	0.63	0.61	0.59	0.86	0.91
f-L-DOX	0.97	0.43	19	17	1.3	27
Nontargeted L-DOX	24	27	23	22	34	29

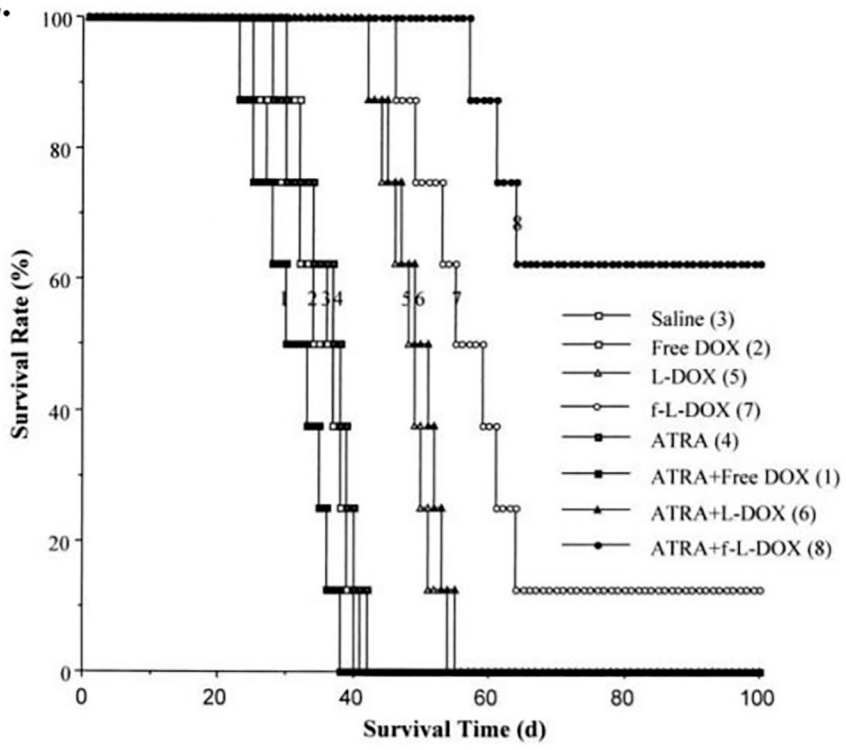


Fig. 7. A. FRβ levels in non-treated KG-1 cells. B. FRβ signals in KG-1 cells after a 5-d exposure of 1 μM ATRA. C. Uptake of f-L-calcein and L-calcein against KG-1 cells with or without ATRA. (1), L-calcein without ATRA; (2), L-calcein with ATRA pre-treatment; (3), f-L-calcein without ATRA pre-treatment; (4) f-L-calcein with ATRA pre-treatment. D. Cytotoxicity of some types of leukemic cells incubated with various formulations of free DOX, f-L-DOX (FA-targeted liposomes) and L-DOX (non-targeted group), with the pre-exposure to ATRA. E. Survival rate of non-targeted group and FA-targeted liposomes in KG-1 ascites tumor model during tumor detection period time of 100 d, including saline, groups treated with or without pre-treated ATRA [60].

levels, valproate acid (VPA, 300 mg/kg) and ATRA (10 mg/kg) were intraperitoneally administrated into the MV-411S cell engrafted mice model. Interestingly, VPA could potentiate this effect induced by ATRA, increasing hFRβ mRNA expression up to 40-fold compared with either VPA alone or a single ATRA dose (Fig. 10B), as in the above animal model. The regimen could provide an attractive method for FR-targeted ATRA-resistance therapies.

Except that, a research also validated the synergistic effect of ATRA combined with HDACi, including trichostatin A (TSA), valproic acid (VPA) and FK228, to enhance antifolate dideazatetrahydrofolate cytotoxicity by selectively inducing FRβ [63]. The molecular mechanism revealed that the upregulation effect of FRβ by ATRA was associated with the direct modulation of the FRβ gene promotor and FRβ mRNA expression (Fig. 11), consistent with previous reports. More valuable reference to clinical practices may be found if the mechanism of action is clearly elucidated. These studies probably provide a potential targeted therapy to enhance trafficking transport and FRβ (+) AML treatment. There is no doubt that receptor upregulation mostly contributes to sensitizing tumor cells to positively express this type of receptor and its mediated antifolates delivery.

2.1.2. FRα

For FRα, it has been reported that the addition of dexamethasone (Dexa) and valproic acid (VPA) may synergistically induce its expression on gynecologic cancer cells. Dexa, as an induction agent of VPA, which is the FOLR1 promoter (for FRα transcriptional gene) stimulator intracellularly. The combination of the two agents increased FOLR1 expression in HeLa cells and A2780 cells by 2.9- and 4.9-fold respectively [64].

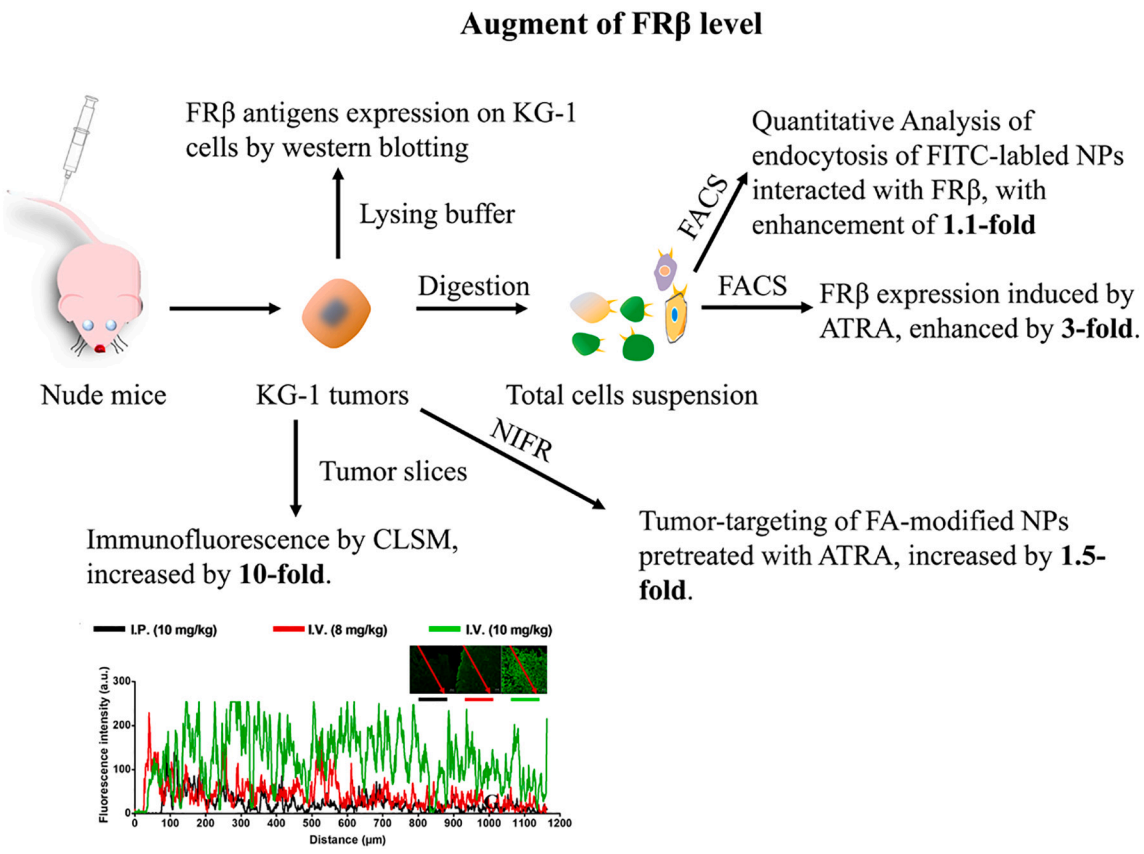
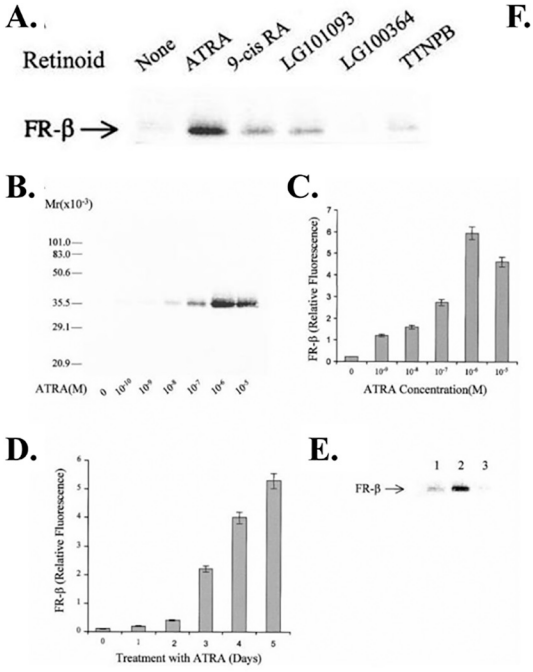


Fig. 8. FRβ expression measured by various methods in KG-1 cellular level and tissue level. FRβ expression treated with ATRA NPs dosages, including I.P. injection of free ATRA at 8 mg/kg and I.V. administration at 8 mg/kg or 10 mg/kg for consecutive 3 days. CLSM: Mean fluorescence intensity of different groups ranges from tumor edges to intertumoral sites. NIFR: Tumor-targeting of different DiR-loaded NPs including non-targeted group Lip-DiR@BSA alone, non-targeted group Lip-DiR@BSA + pre-treated ATRA NPs (10 mg/kg, for consecutive 3 d), FA-targeted group Lip-DiR@FBH alone, FA-targeted group Lip-DiR@FBH + ATRA NPs (for one-time administration simultaneously), and FA-targeted group Lip-DiR@FBH + pre-treated ATRA NPs (10 mg/kg, for consecutive 3 d) [61].



F.

Cell line	Cell type*	FR expression†		
		Before treatment		After treatment
		FR-α	FR-β	
KG-1	Acute myelogenous leukemia	–	0.02 ± 0.01	0.5 ± 0.1
KG-1a	Acute myelogenous leukemia	–	–	–
NB4	Acute promyelocytic leukemia	–	–	–
HL60	Acute promyelocytic leukemia	–	–	–
KCL22	Myeloblastic leukemia	–	–	–
K562	Erythroleukemia	–	–	–
CCFR-CEM	Acute lymphoblastic leukemia	–	–	–
L1210	Mouse lymphoblastic leukemia	–	–	–
SVG	Transformed fibroblast	–	–	–
MG-63	Osteosarcoma	–	–	–
293	Transformed primary embryonal kidney epithelial cell	–	–	–
SKOV3	Ovarian adenocarcinoma	0.25 ± 0.02	–	0.26 ± 0.03
JAR	Placental choriocarcinoma	1.50 ± 0.20	–	1.10 ± 0.10
HeLa	Cervical carcinoma	1.70 ± 0.20	–	1.20 ± 0.20
Caki-1	Kidney carcinoma	–	–	–

Fig. 9. A. FRβ mRNA induction in MV-411 cell lines by ATRA. Cells were treated with ATRA (0.1 μM) or vehicle for 48 h. The hFRβ mRNA levels were determined by RT-PCR, normalized to GAPDH (as internal control) expression values. B. hFRβ mRNA expression levels in bone marrow cells obtained from NOD-SCID mice engrafted with MV4-11R cells following treatment with vehicle (as control), ATRA alone, VPA alone or ATRA and VPA co-treatment [59].

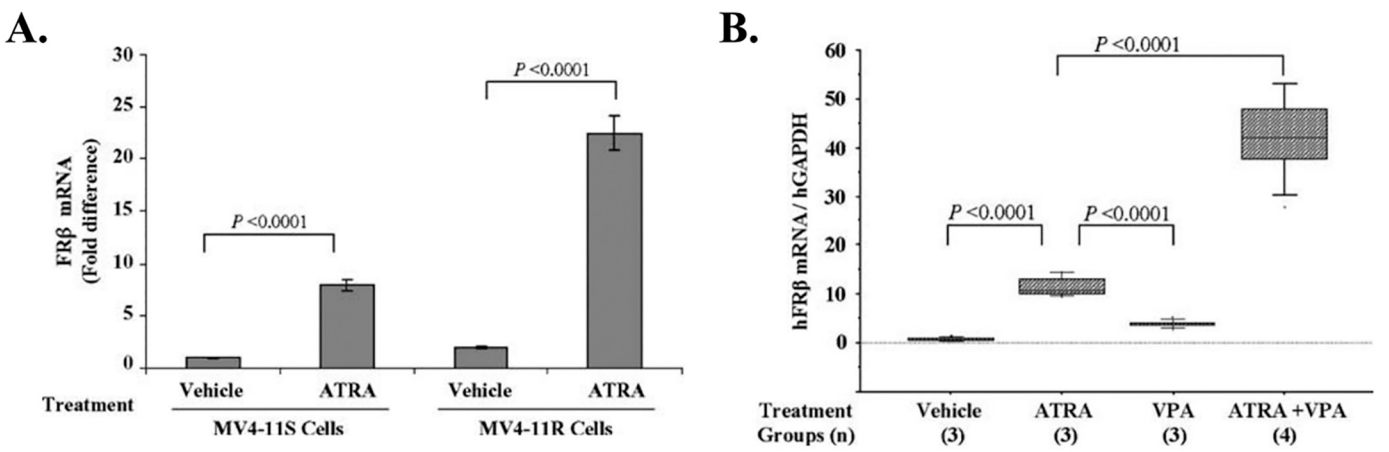


Fig. 10. A. FRβ band amount induced by ATRA measured by western blot. B. Relative FITC labeled FRβ fluorescence intensity on KG-1 cells stimulated by different concentrations of ATRA, examined by flow cytometry. C. FRβ levels measurement treated with 10^{-6} M ATRA for pre-arranged time points. D. FRβ proteins expression under different conditions analyzed by western blot. Lane1, absence of ATRA for 5 d, lane 2, presence of ATRA for 5 d, lane 3, pre-incubated ATRA cells were washed and cultured in ATRA-free medium for further 7 days [62].

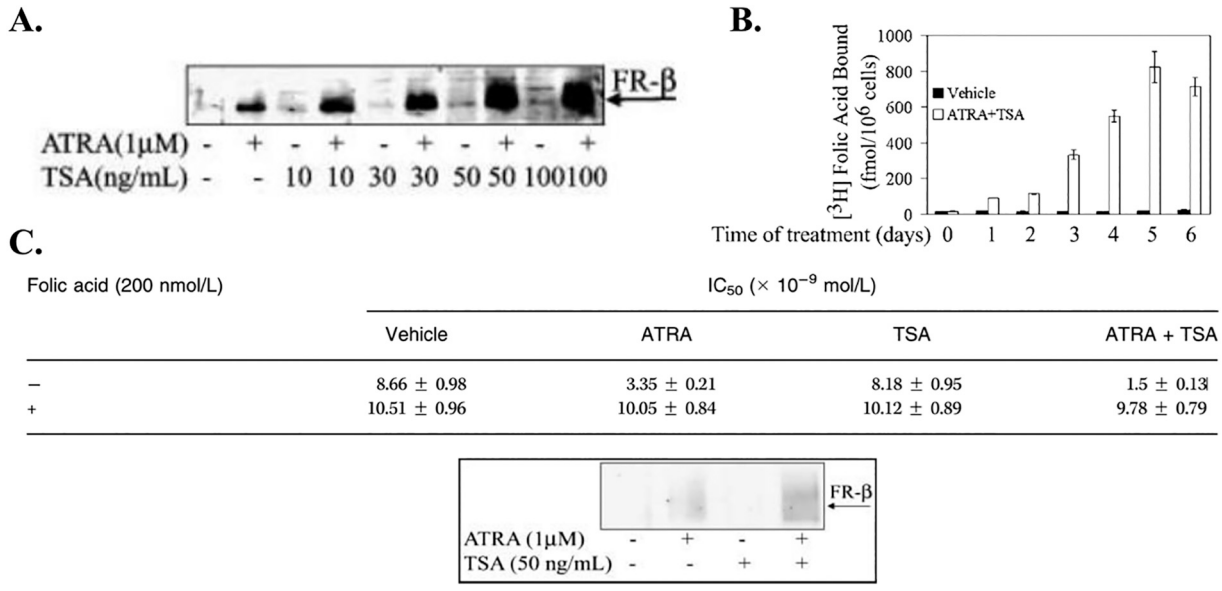


Fig. 11. A. FRβ expression induced by ATRA or in combination with TSA as detected by western blotting. B. ^{3}H-labeled FA binding ability when treated with ATRA and TSA for different predetermined times. C. IC50 values following the exposure to ATRA or TSA or both [63].

Importantly, after the stimulation of Dexa and VPA, FA-conjugated drugs displayed high inhibition rate of up to 81% during the therapeutic period, which outperformed other groups, including the single use of anticancer drugs (non-targeted group) and the Dexa plus VPA-treated group (Fig. 12). A similar strategy of using a combination of Dexa and HDACi selectively increased FRα levels in FRα-positive HeLa cancer cells and FR-guided therapy [65].

As mentioned above, curcumin increases the density of FRβ on AML cells and enhances the therapeutic efficacy of antifolate MTX. Similarly, they found the curcumin could also augment the FRα levels expressed on HeLa cells in a time- and a dose-dependent manner, and then the modulation was beneficial for the cytotoxic effect of paclitaxel subsequently [66]. Cellular results demonstrated that the uptake of paclitaxel presented concentration-dependent on curcumin and pre-treatment with curcumin at a maximum concentration of 100 μM for 48 h significantly increased the uptake of paclitaxel by 4.8-fold. Furthermore, curcumin (10 μM and 25 μM) followed by incubation with paclitaxel showed 77% and 88% decreases in cell viability, respectively. Northern blotting revealed that the effect of curcumin on FRα was dependent on the efficacy of promoting FRα mRNA production (Fig. 13). Thus, the study reported that curcumin enhanced FRα in HeLa cells resulting in higher uptake, and stronger inhibition in combination with paclitaxel.

Some findings indicate the limitations of the antifolate methotrexate (MTX) used for cancer therapy, such as resistance or weak specificity [67]. Furthermore, the lack of an FA transporter or the influx of MTX in the presence of excess FA can provide adverse conditions for the delivery of antifolates. To increase the sensitivity of MTX to cancer cells, researchers performed the transfection of stable functional human FR

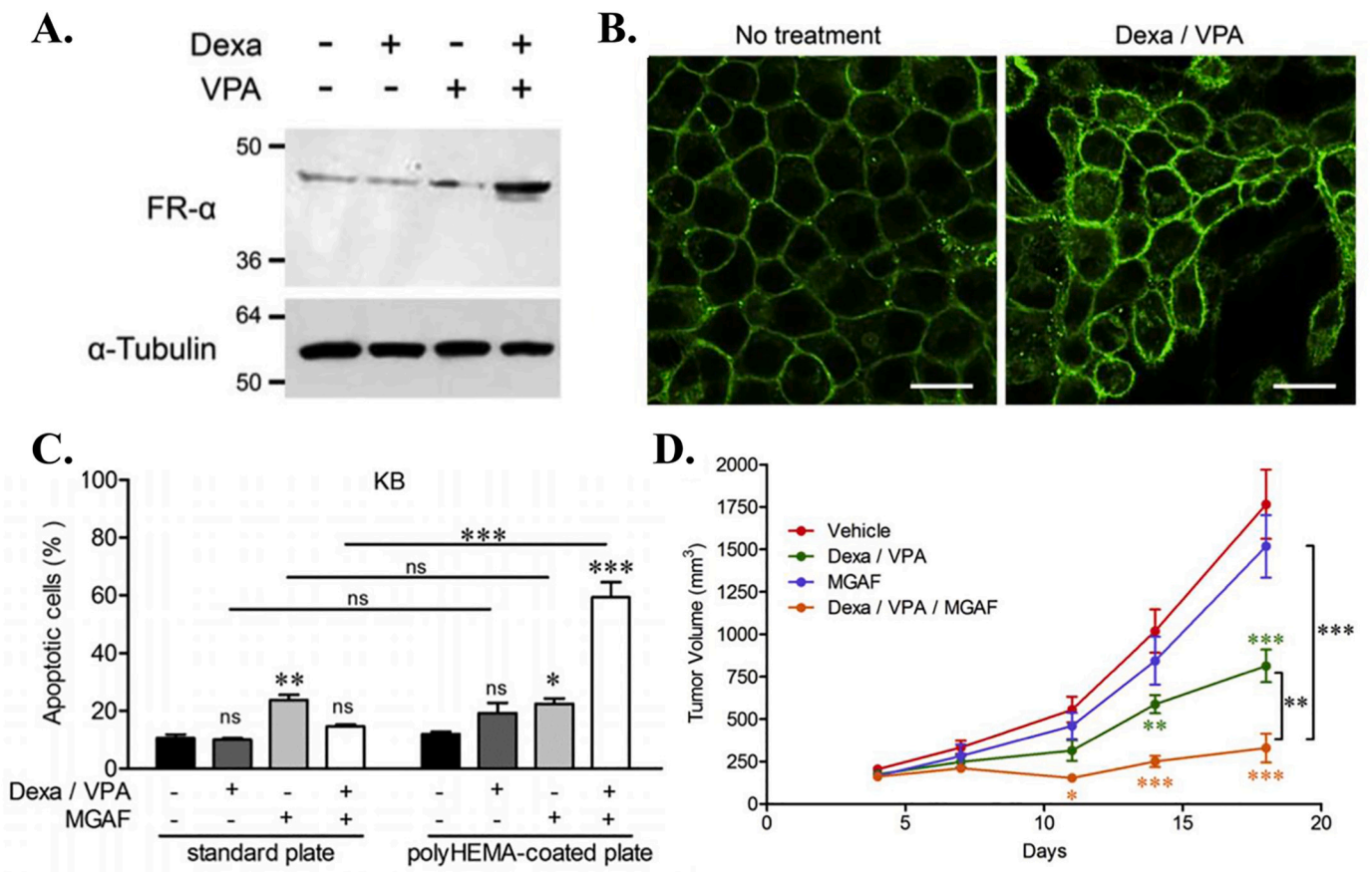


Fig. 12. A. FRα expression induced by Dex and VPA measured by western blotting. B. Confocal images of FRα location in KB cells with the treatment of Dex and VPA. C. Apoptosis against KB cells induced by MGAF, with co-treatment of Dex and VPA. D. Tumor volume detection in KB xenografts under the treatment of MGAF (0.5 mg/kg) with or without Dex (2 mg/kg) and VPA (300 mg/kg). MGAF presented folate-monomethyl auristatin E (MMAE) conjugate [64].

(hFR) into tumor cells in a promising way [68]. Briefly, recombinant KB cell cDNA encoding the hFR was constructed *in vitro*, and subsequently transfected into the FR (+) human mammary carcinoma (MCF-7, FRα overexpression) cells and FR (−) Chinese hamster ovary cells (CHO) cells. The results in Fig. 14A showed the increased capacity for cell surface binding to FA. Fig. 14B demonstrates the markedly raised intracellular MTX concentration in A6 or A4 clones after the transfection of hFR, by 3.2- and 2.4-fold than vector alone (neo), which indicated the increased sensitivity of MTX. Having confirmed that the uptake ability of FA or antifolates was positively correlated with hFR blast expression, the effect on cell function merits investigation. Notably, the detectable inhibition of cell growth in either hFR transfected MCF-7 cells (A6 and A4) or CHO cells (clones 1 and 2) was observably enhanced, compared with their control counterparts. The improved ability to internalize additional MTX by expressing higher hFR levels, which is close to MTX transport efficiency and cell growth, better contributes to increasing the sensitivity of endocytosis and therapeutic efficacy. Nonetheless, the intrinsic interaction mechanism and detailed relationship between hFR level and function have not been thoroughly investigated. It is possible that the two types of clones differ in terms of hFR function and amount, although the binding to MTX or cell inhibition mediated by hFR was consistently increased.

As is known, Dexa is an antagonist to glucocorticoid receptor (GR). Treatment of Dexa alone led to a successive increase in FRα-promoter activity and FRα levels, and the ability to increase FRα could be blocked by pre-incubation with PLC and exogenous free FA. FRα mRNA levels elevated up to 7-fold after incubation of 96 h with Dexa (100 nM). Besides, the results shown in Fig. 15 illustrated the evident increases in FRα-promoter activity and FRα levels in HeLa cells treated with Dexa (100 nM) combined with either VPA (1 mM) or VSA (4 ng/mL), presented in a progressive dose- and time-dependent manner. Specially, the upregulation effect mediated by Dexa was only found in FRα (+) cells, such as SKOV-3 cells, but not in FRα (−) FRβ (+) hematological cells such as KG-1 and K-562 cells. More importantly, the effect was further validated *in vivo*, and the administration of Dexa responsible for the increased FRα levels. These results indicated that HDACi VPA or VSA potentiated the FRα induction effect of Dexa selective to FRα (+) cells, by exerting directly action on GR, at the transcriptional level [65]. As reported, FR, as a kind of glycosyl-phosphatidylinositol (GPI)-anchored receptor, express restricted to the luminal surface of normal epithelial cells and is inaccessible in the blood circulation while being activated in certain types of diagnoses such as cancer conditions. It is reasonable that FRα has the ability to bind and internalize FA only when its subtypes are activated functionally on the surface of some types of tumor cells. Researchers have shown the serum FRα levels could be further augmented by Dexa in a tumor model compared with the group not bearing tumors. Thus, the response to Dexa and HDACi could be applied to detect FRα-positive tumors by tracing FR-targeted whole-body imaging. Albeit to

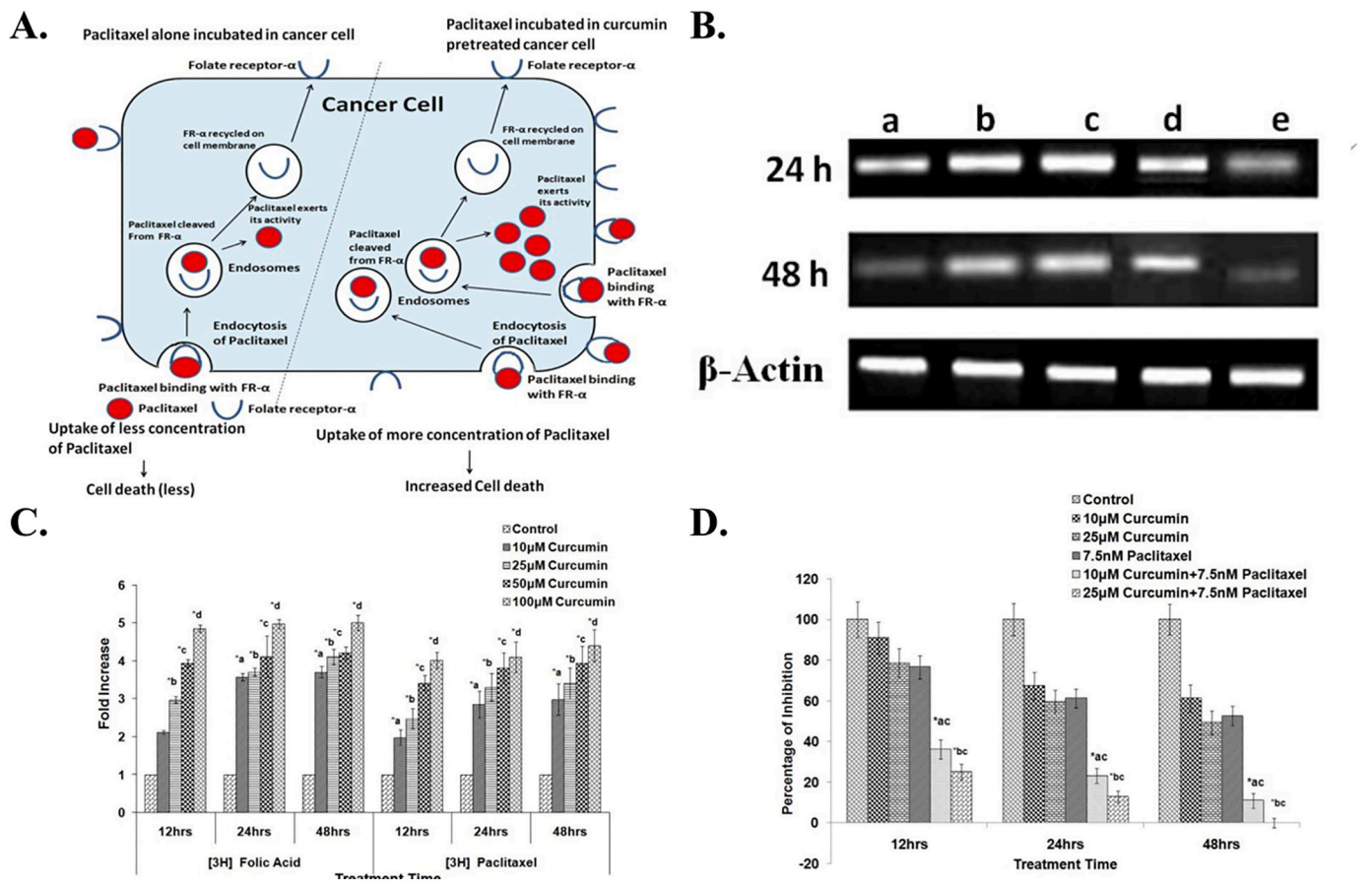


Fig. 13. A. Schematic figure of curcumin enhanced uptake and cytotoxicity of paclitaxel by upregulating FRα. B. FRα mRNA expression in HeLa cells incubated with various concentrations of curcumin including 0, 10, 25, 50,100 μM for 24, and 48 h, respectively. C. Uptake of ^{3}H-labeled FA and ^{3}H-labeled paclitaxel measured with or without treatment of curcumin (10–100 μM) for pre-designed time points. D. Inhibition effects against HeLa cells induced by curcumin combined with paclitaxel [66].

the FRα-targeted therapies are in the stage of early clinical and preclinical trials, the effect mediated by combination agents is mostly desired to enhance the FRα-targeted targeting efficiency.

These studies reported combination strategies to increase tumor cell sensitivity *via* receptor upregulation, and to subsequently enhance FR-targeted outcomes, indicating the possible application to leukemic cell targeting and the precise, flexible delivery of FA-guided NPs. Some potential perspectives may be supported by the notion that gene transcriptional regulators selectively downregulate or upregulate certain types of receptors, in particularly combined with therapeutic agents, whose functions are definitely dependent on these specific gene levels.

2.2. Low density lipoprotein related protein-1 (LRP-1)

In contrast to endothelial cells in normal vasculature, which lack low-density lipoprotein (LDL) receptors, brain capillary endothelial cells (BCECs) relatively overexpress an LDL receptor *in vivo*. Low-density lipoprotein-related protein-1 (LRP-1) functions as the delivery transporter of cholesterol across membranes, and could be up-regulated under appropriate conditions for efficient crossing of the blood brain barrier (BBB) (Fig. 16) [69].

Research has enhanced the anti-glioma effects of Angiopep-2-mediated NPs loaded DOX by up-regulating human LRP-1 on both brain microvascular endothelial cells (BMECs) and brain metastatic tumor cells (BMTCs). The LRP-1 level is induced by the transport of Angiopep-2 mediated NPs loaded simvastatin (S@A-NPs), as a transcript modulator [70]. As a result, the NPs can self-promotingly penetrate through the BBB *via* specific recognition of Angiopep-2 to LRP-1. Meanwhile, simvastatin (SIM) suppressed drug efflux from BMTCs by blunting Pgp. Thus, elevated intracellular DOX signals and enhanced apoptosis of BMTCs as well as resulting significantly improved anti-metastatic effect were achieved by the combination of SIM and DOX-loaded NPs (Fig. 17).

2.3. Transcytosis-related caveolin-1

The blood-brain tumor barrier (BTB) provides limitations for permeability and therapeutic drug concentrations, partly causing the failure of brain metastases. BTB overexpressed K_{ATP} channels compared with the normal blood-brain barrier (BBB), which was beneficial for regulating permeability [71,72]. It is possible that pharmacologically positive modulation of the K_{ATP} channel plays a key role in promoting endocytosis and therapeutic efficiency [73]. And it was reported that minoxidil sulfate (MS) could selectively activate K_{ATP} channels to cross the BTB and enter tumor cells [74]. The regulation of K_{ATP} channels mediated by MS exerted effects on both transcellular and paracellular

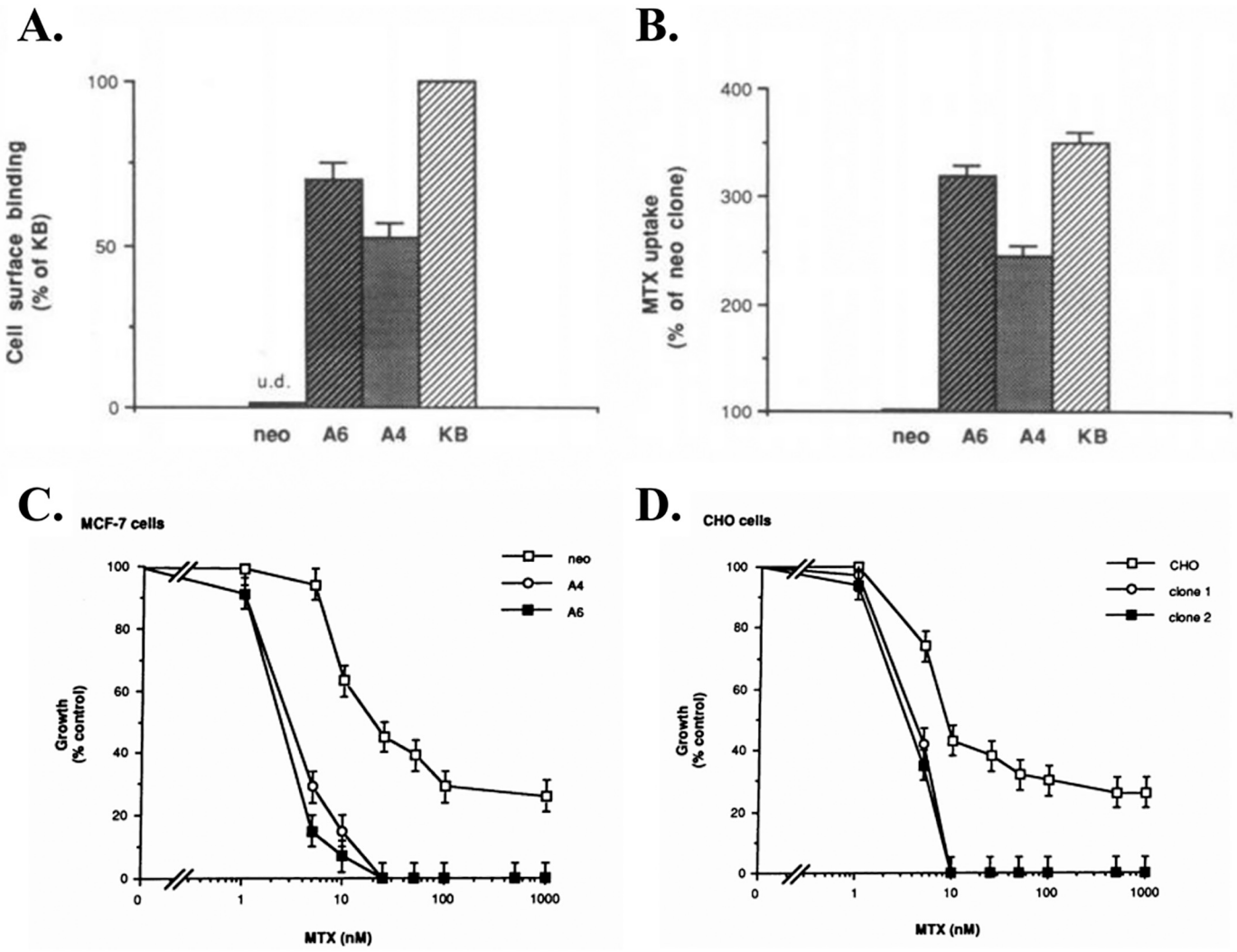


Fig. 14. A. Cell surface binding of hFR to FA in transfected MCF-7 cells and KB cells. B. Determination of the [^{3}H]-labeled MTX uptake amount after transfection. MCF-7 neo cells, A6 and A4 represent the control group, which did not express hFR, and expressed hFR at the highest levels and the next highest level, respectively. U. d. means undetectable. The data are the percentage of protein under different concentrations of MTX normalized to total protein. C. Relative cell growth conditions of different hFR transfected cells treated with MTX. MCF-7 neo cells, A6 and A4 represent the control group cells that did not expressed hFR, and expressed hFR at the highest level and the second highest level, respectively. D. CHO, clone 1 and clone 2 indicate the control group, expressing the highest level of hFR and the next highest level, respectively [68].

pathways. In one way, MS is capable of upregulating the caveolin-1 expression on BTB endothelial cells and brain metastatic (BM) tumor cells in the transcellular pathway (Fig. 18). In other words, MS downregulates tight junction proteins to promote the paracellular transport pathway. The co-delivery of MS and DOX (M@H-NPs/DOX) resulted in MS-mediated caveolin-1 upregulation and DOX-mediated cytotoxicity to BM, through CD44 + -mediated delivery, which ultimately led to enhanced transcytosis, endocytosis by BM tumor cells, and a prolonged median survival time.

2.4. CD38

CD38, as a transmembrane glycoprotein, in particular highly expressed on multiple myeloma (MM) cells and has relatively lower expression on normal hematological cells [75,76]. As is known, daratumumab has shown excellent therapeutic activity by targeting CD38 against MM cells and primary MM cell lines in preclinical investigations [77,78], presenting antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) *in vitro* [79]. Novel research has proposed that HDACi such as ricolinostat, could increase the density of CD38 on MM cells and thereby specifically enhance the anti-CD38 therapy of daratumumab [80,81]. Data have shown that the HDACi consisting of ricolinostat, ACY-241, and WT-161 enhanced CD38 antigen levels on MM cells. The measurement of cell viability in the different groups revealed that the therapy of daratumumab plus HDACi (Fig. 19) further augmented MM sensitivity and the response of CD38 to daratumumab, dramatically decreasing MM cell and primary MM cell viability. An increased lysis percentage was also observed in MM cells after treatment with daratumumab plus HDACi, compared with daratumumab alone, which provides a potential value

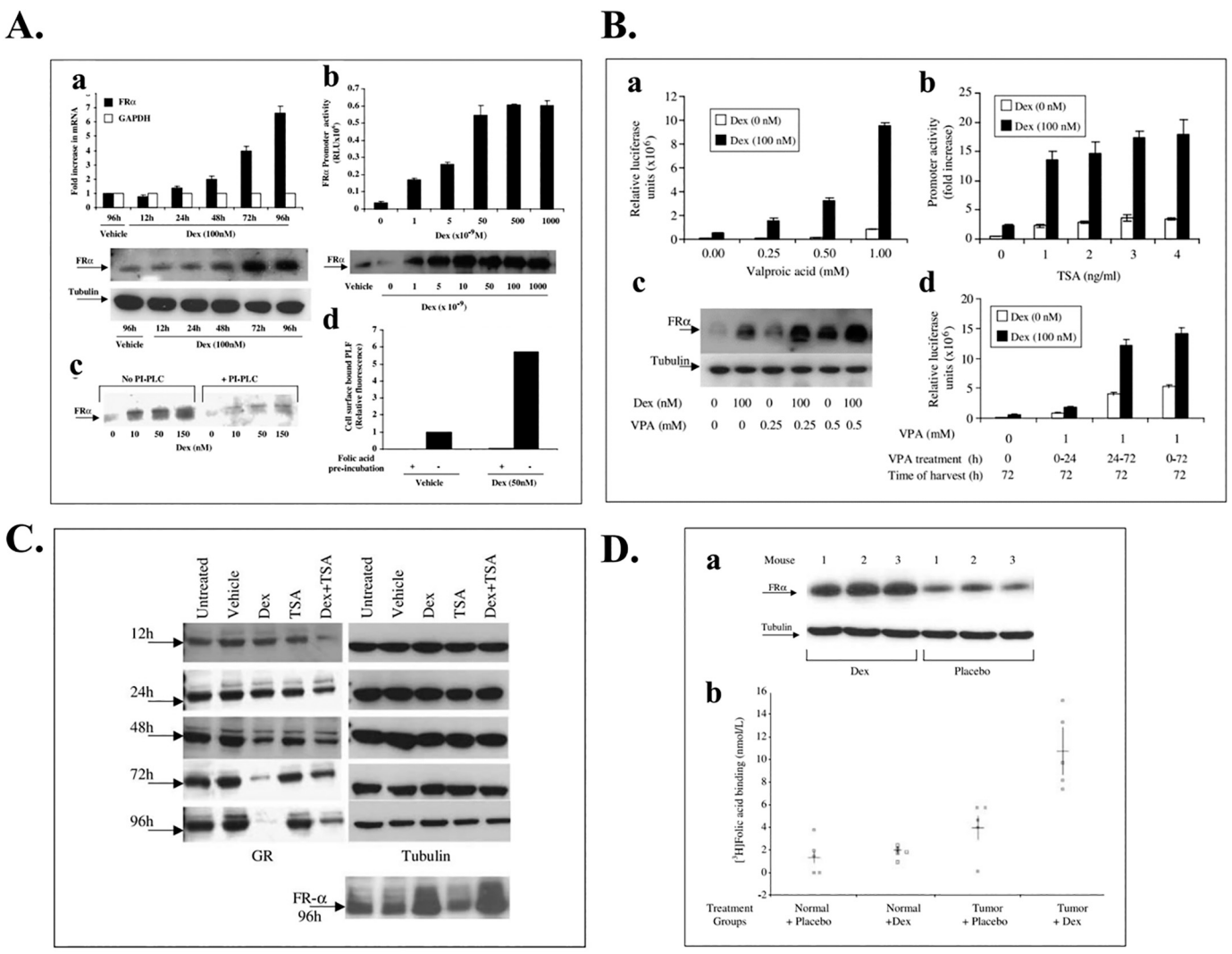


Fig. 15. A. a. Fold increase in FRα mRNA expression induced by Dexa for pre-designed times. b. FRα promotor activity induced by Dexa at various concentrations. c. FRα expression with or without treatment of PI-PLC. d. Cell surface binding ability of the vehicle group or the Dexa group with or without FA pre-incubation. B. Effect of HDACi on FRα expression induced by Dexa. a. FRα promoter-labeled luciferase HeLa cells were transfected into HeLa cells, and treated with different concentrations of VPA for 72 h with or without the addition of dexamethasone (100 nM). b. Following as the same method as in A, treated with trichostatin A, with or without the addition of Dexa (100 nM). c. FRα expression in HeLa cells, and with different concentrations of VPA combined or not combined with Dexa (100 nM) for 96 h. d. Hela cells transfected with Dexa (100 nM) and VPA for different incubation periods. C. Effect of Dexa (1 μM) or TSA (4 ng/mL) or their combination on GR expression for different time points and FRα for 96 h. D. Evaluation of the Hela xenograft model with treatment with Dexa or placebo for 5 d. a. Serum FRα levels. b. Binding amount measured by a [3H] folic acid binding assay. Normal represent mice not bearing tumors [65].

for extending the utility of daratumumab.

Another study reported that ATRA could upregulate CD38 expression on MM cells, decrease the levels of the complement-inhibitory proteins CD55 and CD59 [82] and increase ADCC and CDC levels when combined with daratumumab (Fig. 20C). An *in vitro* study demonstrated that exposure to ATRA enhanced CD38 levels in a time-response manner and a dose-dependent behavior (Fig. 20A) [80]. Additionally, incubation with 10 nM ATRA for 48 h was sufficient to induce 1.9- to 4.4-fold increase of CD38 expression in MM cell lines including RPMI8226, UM9 and XG1. The proof-of concept animal MM model showed the significant enhancement of the efficacy of daratumumab, when treated with ATRA, prolonged mice survival time (Fig. 20B). To this end, the activity of daratumumab was mostly dependent on the density of CD38 levels on the MM surface, and increased CD38 expression by ATRA enhanced the CD38-targeted antibody-mediated ADCC and CDC, resulting in more effective treatment and improved survival.

Furthermore, investigations of antibodies in combination with their enhanced targets will increase the effectiveness of antibody-mediated therapy. And a better understanding of the mechanisms of increasing sensitivity by upregulating biomarkers on tumor cells, may provide novel strategies to enhance efficacy and clinical references in future work.

2.5. *Integrins αvβ3 and αvβ5*

Adenovirus-mediated gene delivery systems are used to deliver

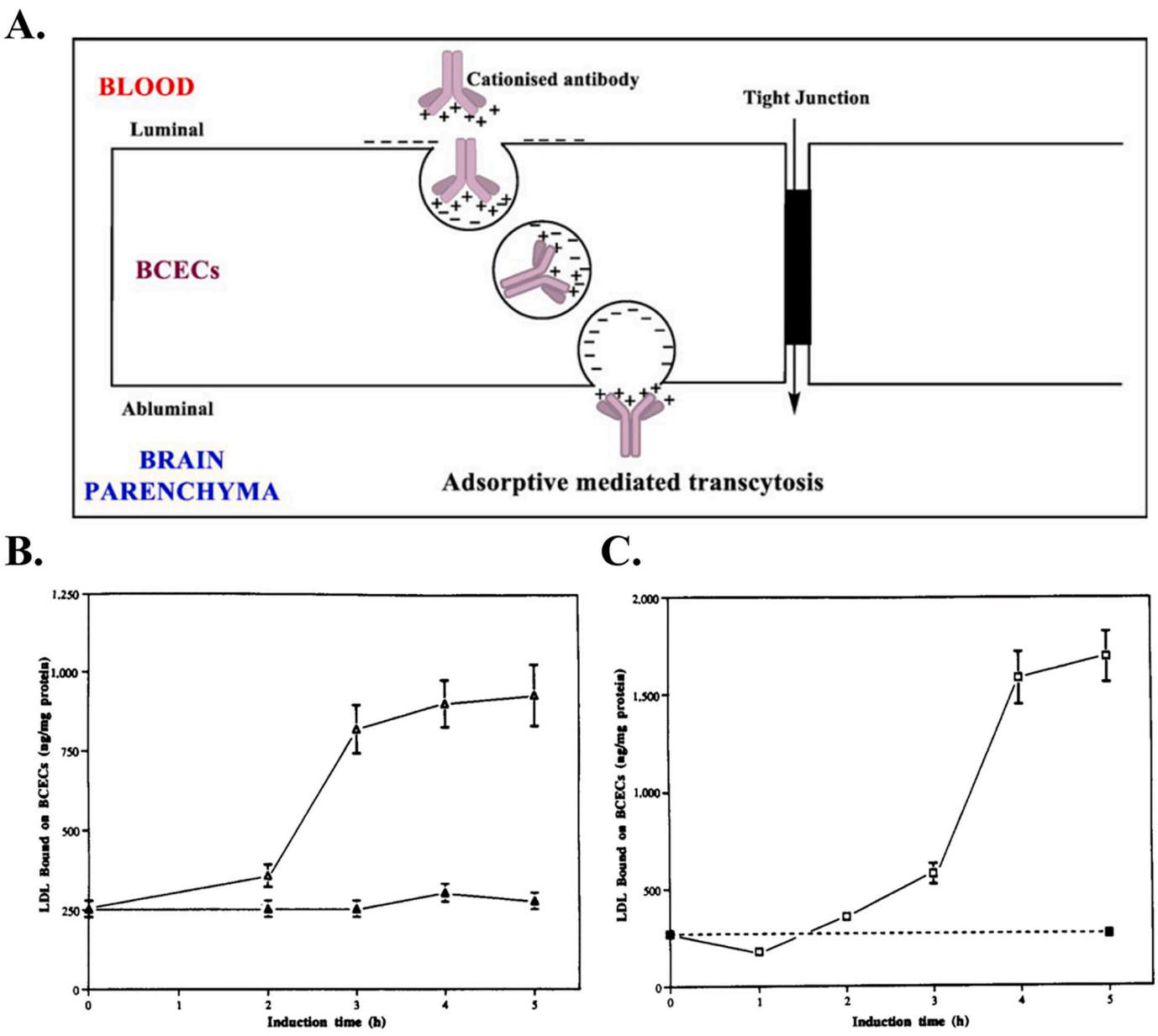


Fig. 16. A. The transport process crossing BCECs [62]. B. Upregulation of LDL receptor on BCECs. C. Upregulation of LDL receptors on BCECs by astroeyte-eonditioned medium [69].

extraneous genes fusion to the genome with high transfection efficiency, through interactions with αvβ integrins. Benefitting from human monocytes expressing, including the hematopoietic growth factors granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (MCSF), which are involved in cell-mediated immunity and also serve as host cells for viral infection, adenovirus-mediated gene infection is of considerable value [83]. However, the inability of human monocytes to internalization virus and the limited binding capacity to human lymphocytes become barriers for adenovirus delivery [84]. Previous developments have overcome this dilemma [85]. As shown in Fig. 21, the expression of integrins αvβ3 and αvβ5 can be induced on human monocytes by GM-CSF and MCSF, while phytohemagglutinin (PHA) or phorbol-12-myristate-13-acetate (PMA) function as an induction agent on that of human T-lymphocytes (Fig. 21). Exposure to recombinant adenovirus encoding the β-galactosidase gene for 3 d after PHA and PMA stimulation, endowed the ability of adenovirus-mediated entry to T-lymphocytes, as indicated by β-galactosidase activity analysis. In this case, it was confirmed that the adenovirus-mediated delivery efficiency was largely correlated with the surface integrins αvβ3 and αvβ5, providing important implications for the practical transport of genes or other immune-agents.

2.6. *Mannose receptor*

Mannose receptors are a family belongs to C-type lectins, involved in the immune response mediated by T-lymphocytes [86]. Mannose-

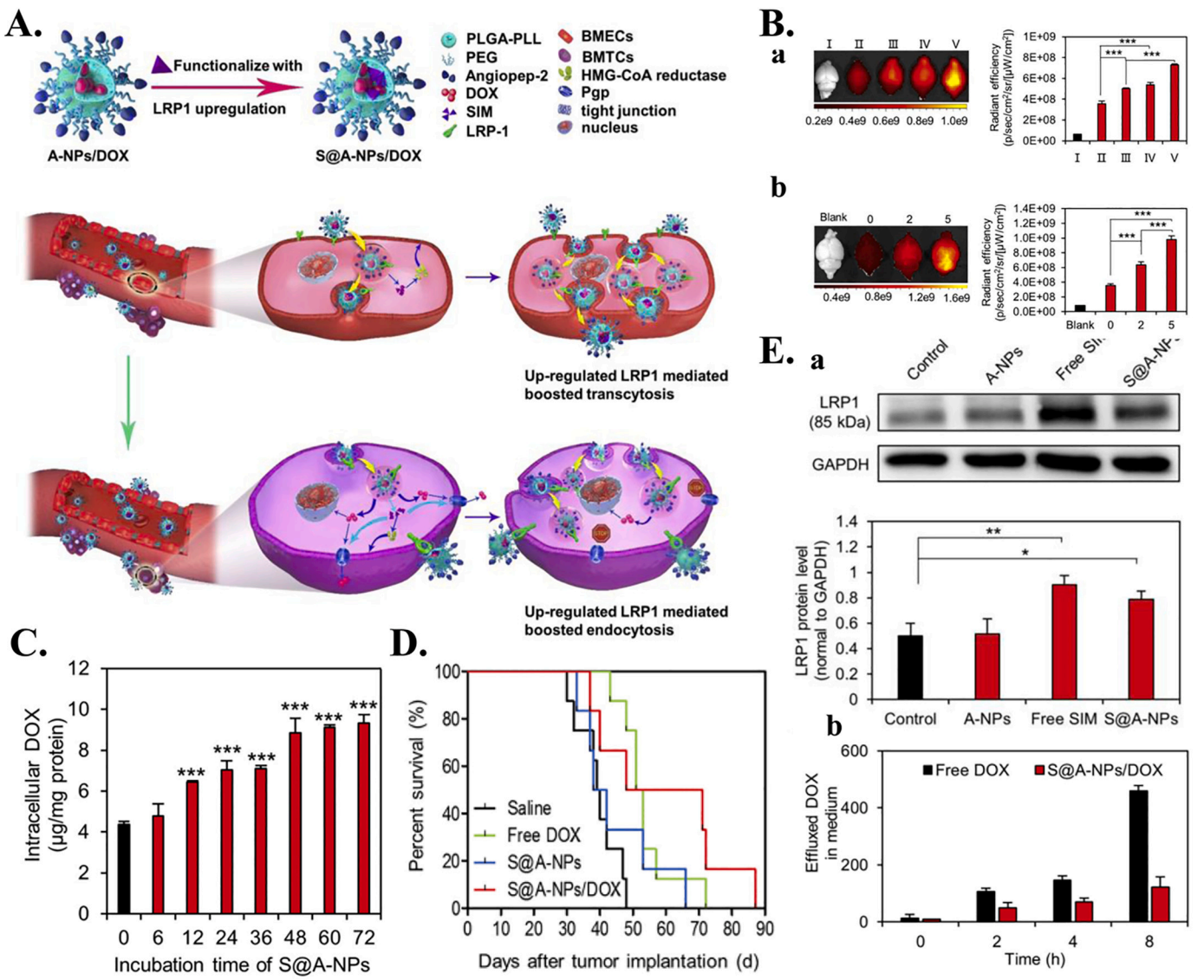


Fig. 17. A. Schematic representations of upregulating LRP-1 for BBB transcytosis and endocytosis. LRP-1 upregulated S@A-NPs/DOX to efficiently across the BBB and for the targeted suppression of multifocal and infiltrative brain metastases. a. Transport of SIM NPs upregulates LRP-1 expression in both BMTCs and BMECs, and boosts the endocytosis of Angiopep-2 functionalized NPs. b. Upregulated LRP-1 *via* a "self-promoting" effect and functional inhibition of Pgp by SIM NPs further promote the internalization of SIM NPs. Importantly, increased transport efficiency across the BBB and enhanced treatment for glioma metastatic cancer. B. a. Brain section fluorescence images of saline (I), NPs/IR780 (II), Angiopep-2-NPs/IR780 (III), NPs/IR780 with pre-treatment with I.V. free SIM twice at 48 h and 60 h, respectively (IV), or Angiopep-2-NPs/IR780 with pre-treatment with I.V. free SIM twice at 48 h and 60 h, respectively (V). b. Self-promotion of S@A-NPs at 10 mg/kg SIM for the indicated times (0 h, 2 h and 5 h) before 12 h Angiopep-2-NPs/IR780 post administration. I.V. indicates intravenous administration. C. Intracellular DOX amount with treatment of S@A-NPs/DOX over time. D. Survival curve of S@A-NPs/DOX after tumor implantation. E. a. Upregulating LRP-1 protein levels by SIM. b. Effluxed DOX in medium after the incubation with S@A-NPs [70].

targeting has wide applications in mannose receptor-expressing antigen-presenting cells (APCs) such as macrophages (MCs) and dendritic cells (DCs) [87]. The mannose receptor-mediated delivery nanocorona was intensively developed to restore the action of T cells.

In addition, enzyme replacement therapy applied in the treatment of Gaucher disease uses a recombinant glucocerebrosidase (such as Cerezyme) that mainly consists of the core of mannose residues. The effect was mediated mannose receptor-mediated endocytosis for delivering to Gaucher-affected macrophages (Fig. 22). However, the modification was not specific owing to the lack of selectivity to Gaucher-affected macrophages, for its delivery to other mannose-overexpressing cells. Researchers have found that Dexa specifically enhanced the uptake of recombinant glucocerebrosidase by MCs *in vitro* and *in vivo* [88]. Pre-treatment with Dexa enhanced the mannose receptors on Gaucher

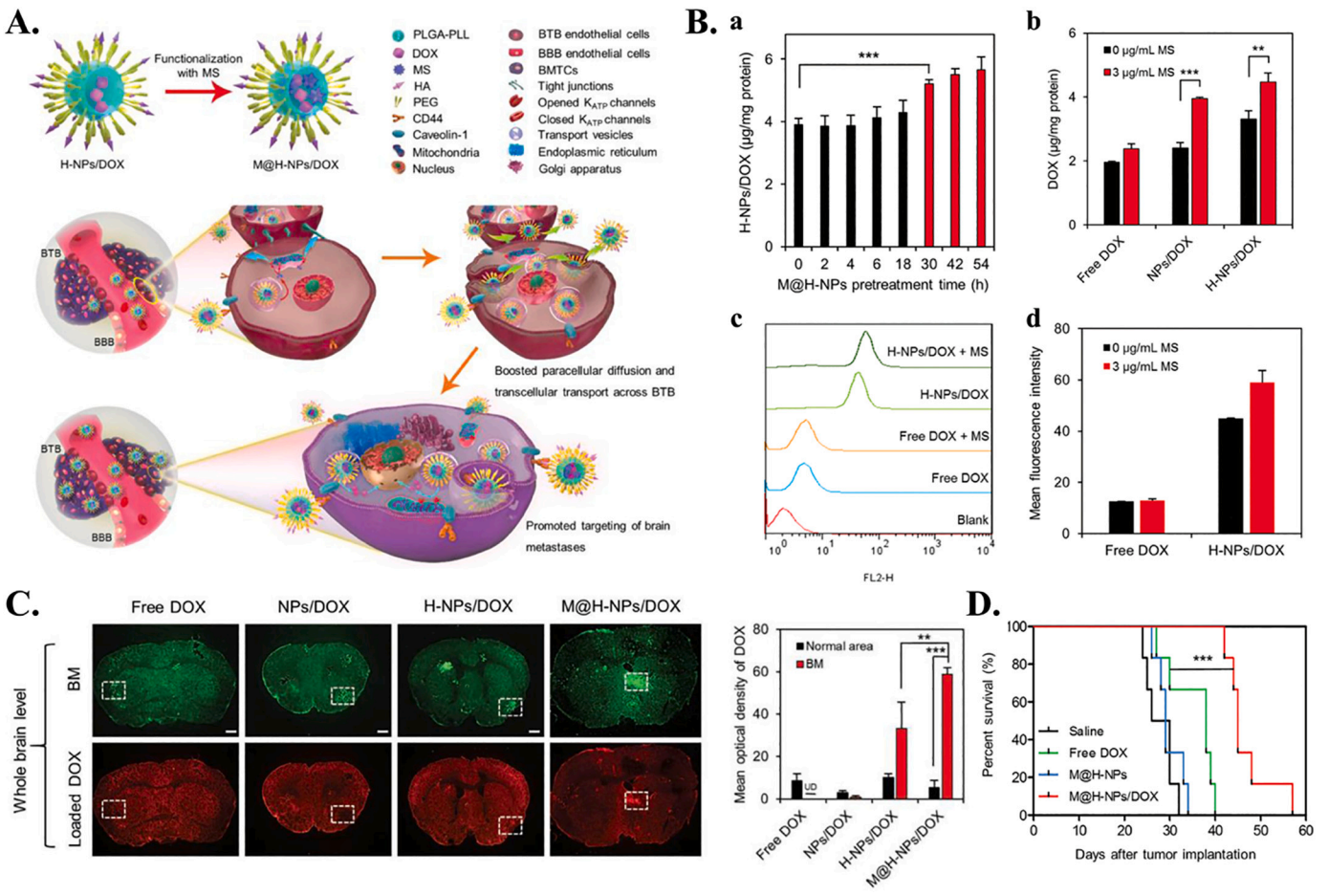


Fig. 18. A. Upregulating caveolin-1 expression on BMTCs and enhancing its targeted internalization by NPs. The released MS can induce downregulation of tight junction proteins and upregulation of caveolin-1 in BTB endothelial cells. Enhanced transcytosis increases BTB penetration and accumulation by NPs in brain metastatic tumors. After crossing the BTB, the MS can upregulate caveolin-1 expression on BMTCs and mediate the internalization into BMTCs *via* CD44 receptor–mediated endocytosis. B. a. Intracellular DOX at different M@H-NPs pre-treatment times. b. DOX uptake amount of H-NPs/DOX with or without MS co-incubation. c. Cellular uptake analyzed by flow cytometry. d. Quantification of uptake of H-NPs/DOX with or without MS co-incubation. C. Efficient brain metastasis (BM) targeting abilities of different DOX formulations at the whole brain level. D. Survival rates of various groups during the monitored time [74].

macrophages and thereby improved the accurate delivery of Cerezyme (Fig. 23). Importantly, the augmentation could not affect other cells including liver endothelial cells [86].

2.7. Downregulation of programmed death receptor (PD-L1)

The binding of PD-1 to PD-L1 expressed on malignant cancer cells could inhibit the function of T cells, leading to the immune escape, and thereby promoting the activation and evasion of tumor cells [89]. Evidence has shown that an epidermal growth factor receptor (EGFR) mutant in non-small-cell lung cancer (NSCLC) is highly associated with PD-L1 expression [90]. The EGFR-mediated signaling pathway plays a critical role in remodeling PD-L1 blasts. And the upregulation of PD-L1 mediated by EGFR activation in NSCLC contributes to the progression of NSCLC; As a result, EGFR tyrosine kinase inhibitors (TKIs) could downregulate the expression of PD-L1, which free the inhibition of T cells, reverses the immune inhibition and facilitates the production of interferon-γ on tumor sites. Furthermore, the inactivation of PD-L1 may effectively control EGFR mutations in NSCLC through this pathway (Fig. 24). The treatment strategy of PD-L1 downregulation provides the support for enhancing antitumor immunity, and for the usefulness of either anti-PD-L1 antibody or siPD-L1 which negatively regulates PD-L1 and, has great potential in NSCLC clinical practice.

3. Other receptor modulation strategies

Other than the modulation agents or combined effects, there are receptor modulation strategies induced by internal factors such as hyperthermia, irradiation, and radiotherapy. These strategies presented potential approaches for receptor-mediated transport and cancer therapy.

3.1. Hyperthermia

Researchers reported a cooperative nanosystem consisting of two nanomaterials based on photothermal gold nanorod and LyP-1 (peptide consist of nine amino acids)-modified doxorubicin-loaded liposomes, targeting p32 specifically binding on tumor cells [91]. Interestingly, this antigen could be upregulated upon thermal treatment, induced by gold nanorod. From this figure (Fig. 25), we could observe that tumor heating activated the photothermal gold nanorod to upregulate the p32 antigen, which further amplified the thermal-dependent tumor targeting of DOX-

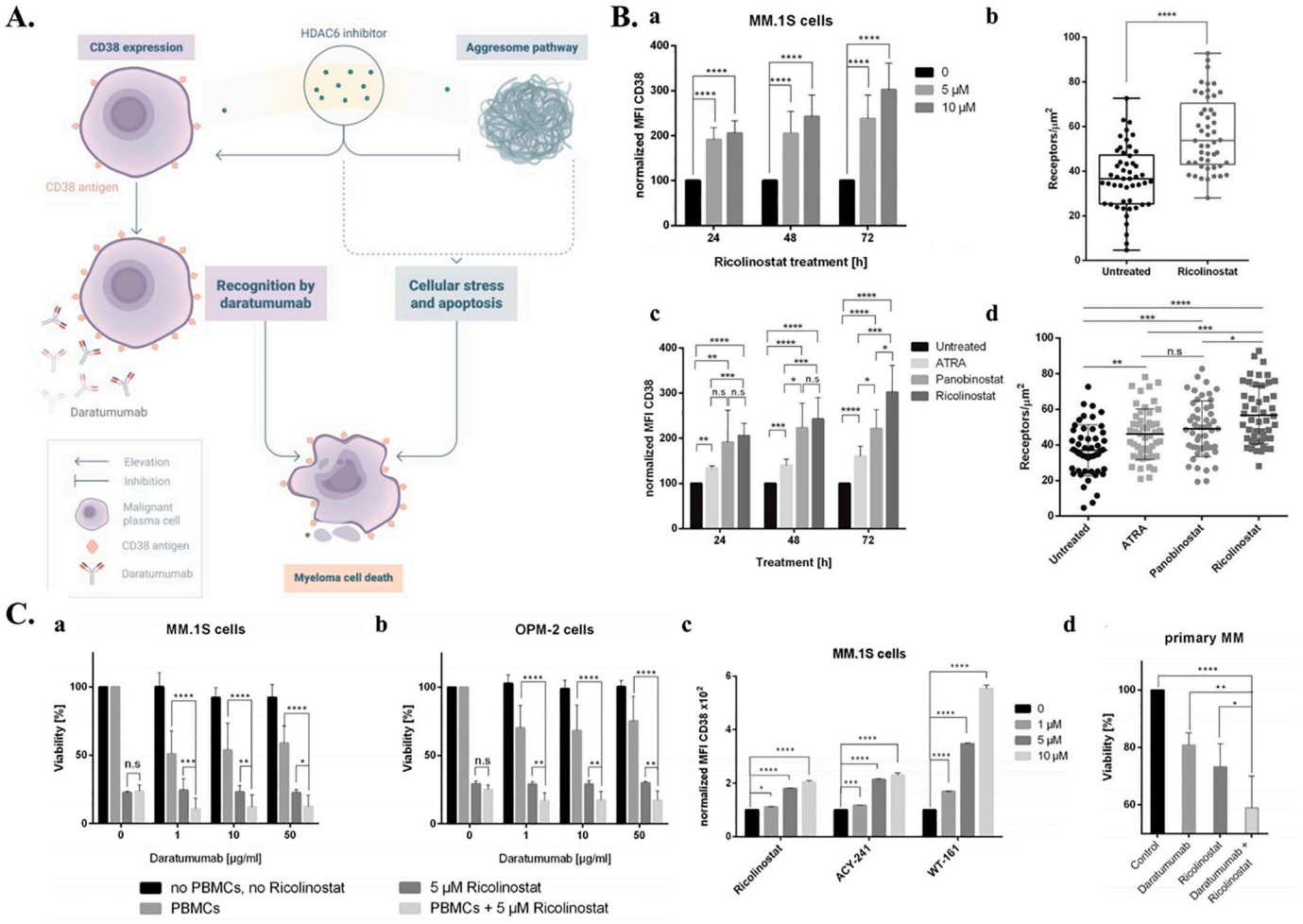


Fig. 19. A. The effect exerted by novel HDAC6 inhibitors and daratumumab. B. a. mean CD38 fluorescence intensity in MM. 1S cells co-incubated with ricolinostat for pre-designed times. b. CD38 expression measured by dSTORM with or without ricolinostat incubation. c. CD38 expression under different induction agents. d. Receptors measured by dSTORM with ATRA or HDACi. C. Cell viability treated with daratumumab under different conditions. a. MM. 1S cells. b. OPM-2 cells. PBMCs indicates peripheral blood mononuclear cells. c. CD38 expression elevated by next generation of HDACi. d. Viability against primary MM with daratumumab combined with ricolinostat [81].

loaded liposomes, and enhanced therapeutic efficacy. The combination effect to inhibit tumor volume was remarkably significant, compared with the single-used group. More importantly, the combined hyperthermal and chemotherapeutic anti-tumor effects significantly prolonged the survival rate of mice xenografted MDA-MB-435 tumors. This upregulation may also apply in phototherapy when combined the photosensitizers-loaded nanosystem, inducing reactive oxygen species (ROS) generation and tumor apoptosis.

3.2. Irradiation

An interesting work investigated the irradiation effects on membrane receptors [92]. The authors designed a recombinant peptide (GIRLRG)-modified nanoparticle delivering paclitaxel, targeting to the GRP78 receptors on gliomas (GL261) and breast cancer (MDA-MB-231) induced by irradiation. As shown in Fig. 26, GRP78 in tumors could be upregulated by irritation *in vivo* and *in vitro*. Notably, the augment of GPR78 in the irradiated tumors, specifically increased recognition of GIRLRG, cell apoptosis and obtained a better therapeutic effect in animals, compared with the no-XRT group. This regimen is well-designed and well worth considering in clinical utility.

3.3. Glycoengineering

In vivo tumor-targeting of nanosystems have many limitations because of the heterogeneity of tumor and the complexity of tumor-environment. Glycoengineering to artificially label cells with new receptors based on click chemistry has been developed as a new technology to address this problem [93]. The sequential treatment of metabolic glycoengineering to cells providing more binding site and drug-loaded nanoparticles enhanced the tumor-targeting *in situ* and cancer therapeutic efficacy. The same finding was verified in K.W's group [94], their designed systems could be applied in various tumor cells, such as lung cancer, brain cancer, and breast cancers. The tumor-targeting measured by fluorescence intensity of azide-reporter-targeted BCN-CNPs was 1.6-fold higher than that of cRGD modified-CNPs. Also, recent research reported that the based on this strategy. Artificial-DCs could covalently conjugate to dibenzocyclooctyne-bearing antigens *via* click chemistry.

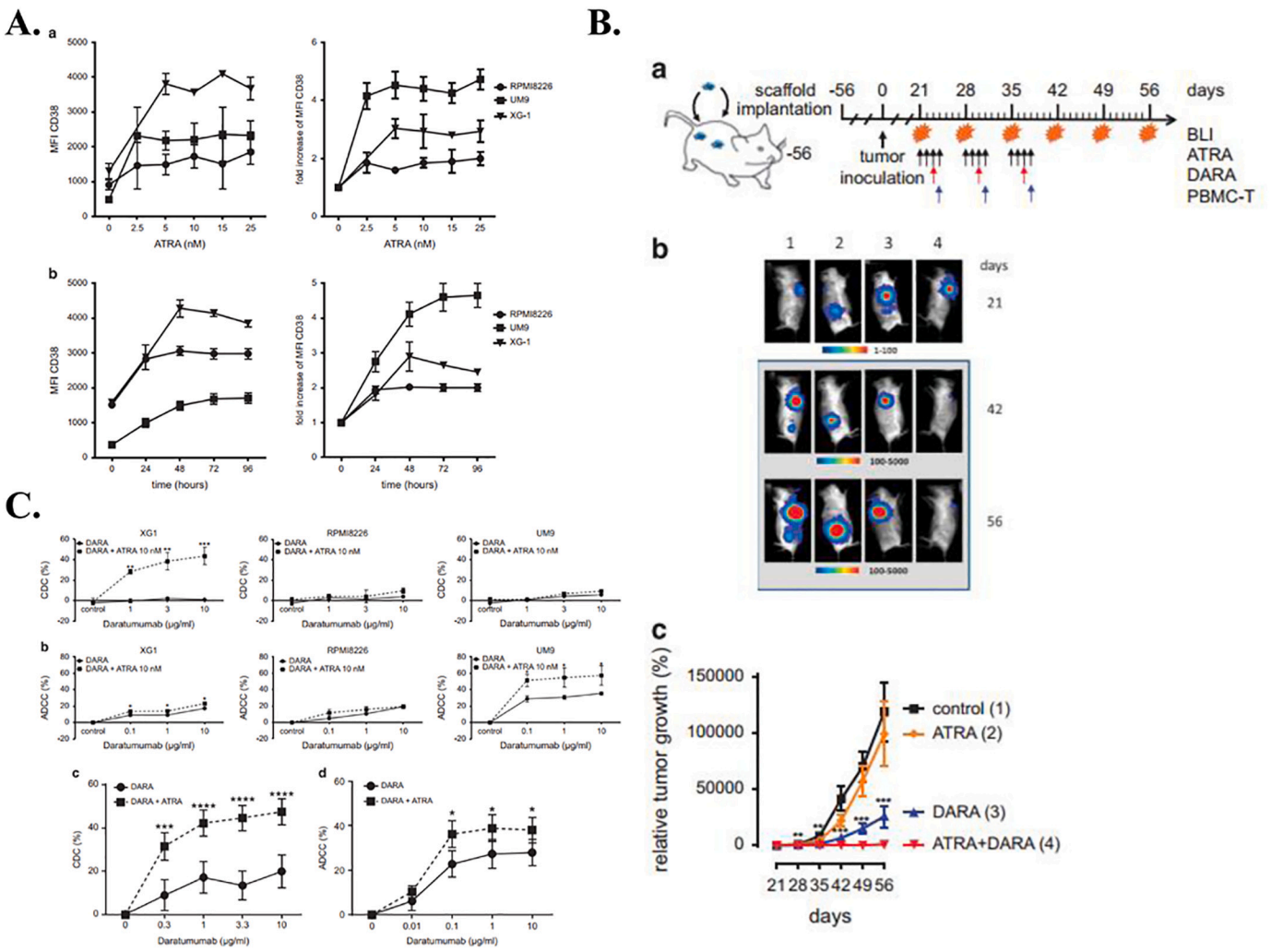


Fig. 20. A. Mean CD38 fluorescence intensity induced by ATRA. a. At different concentrations. b. For pre-arranged times. B. a. Dosage regimen. b. Biofluorescence. c. Tumor growth curve. C. Effect of daratumumab combined with ATRA in XG1, RPMI8226, and UM9 cells. a. CDC. b. ADCC. c. Evaluation of CDC and ADCC under daratumumab and ATRA as concentration of daratumumab increased [81].

The strategy has the advantages of high specificity and efficacy. And this modulation activated function of DCs, improved CD8+ T-cell responses specifically and anti-tumor efficacy. Of note, the technology of artificially labelling cells is like "receptor-generation", and the addition of click chemistry not only increased anti-tumor activity but also the immune response. These findings are encouraging in drug-induced apoptosis and immune-related killing effects; further exploration of novel techniques is significantly meaningful in the field of modulation of receptor.

3.4. Radiotherapy

Receptors binding to the surface of tumor cells has close relationship with radiotherapy [95]. It is reported that EGFR plays an important role in proliferation and metastasis of malignant tumor [96]. And the activation of EGFR is negatively correlated with cellular radiotherapy resistance. Thus, the combination of inhibition of EGFR and radiotherapy to cancer therapy was rationally proposed [97,98]. However, the authors have verified that the EGFR inhibitors could not control the tumor growth when combined with irradiation. p53 and PIK/AKT signal pathway may provide more possibility for the combined treatment with radiotherapy. Nonetheless, the intrinsic mechanism and the efficacy of the treatment still need to explore, for the complexity of interactions and micro-environmental actions. Jean Claude Reubi *et al* [99] reviewed peptide receptors in radiation therapy, which may be extended to many other tumor types. The above works are primitive and charming for receptor modulation applied in tumor therapy; Once the above key points are addressed, the clinical translation and application will be of great possibility.

The density of receptors plays a significant role in the function of drug-loaded NPs during the delivery process as described above, and the upregulated receptors are conclusively described in detail in Table. 4.

4. Upregulation of genes related to cell apoptosis

The "modulation" strategy not only may have wide applications in

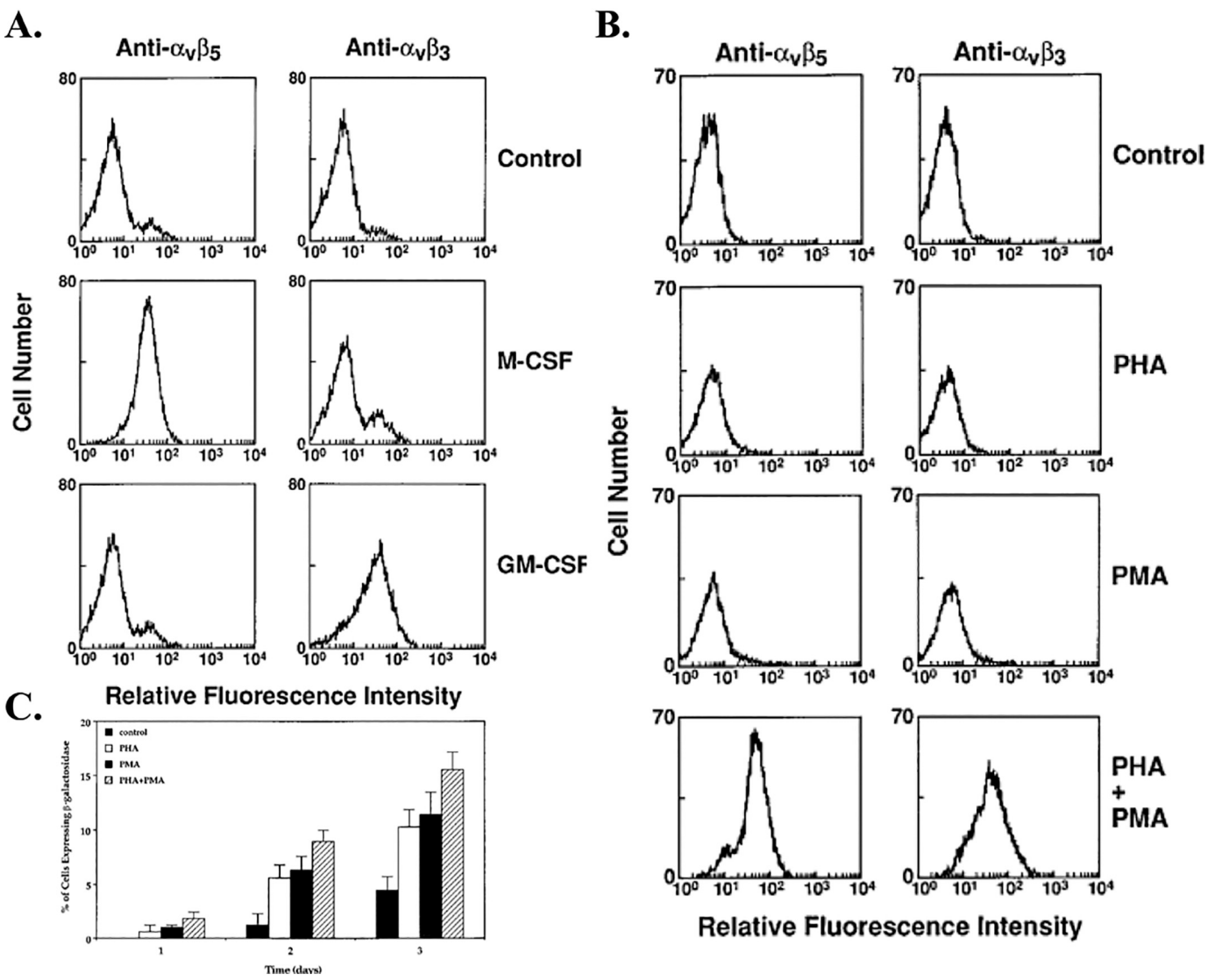


Fig. 21. A. Upregulated αvβ integrin expression on human monocytes by flow cytometric analysis. Human peripheral blood monocytes (PBMCs) were cultured in the absence (control) or presence of 10 ng of GM-CSF per ml or 50 U of M-CSF per ml for 48 h. Cells were incubated with anti-αvβ3 (LM609) or anti-αvβ5 (P3G2) MAbs. B. Upregulated αvβ integrin expression on human T lymphocytes by flow cytometric analysis. Cells treated with PHA, PMA, or a combination of these activating agents for 48 h were analyzed for expression of integrins avb3 (anti-αvβ3 MAb LM609) and avb5 (anti-avb5 MAb P3G2) by flow cytometry. C. Adenovirus-mediated gene delivery on T lymphocytes after the stimulation [84].

surface receptor upregulation, and NPs with a "self-promoting" effect, but may also be involved in the mechanism of cell growth, apoptosis and development. The modulation effect is similar to a network, through the whole homeostasis. In addition, direct or indirect upregulation or downregulation of genes inhibits cell grow or proliferation *via* signal routing, to some extent contributing to obtaining therapeutic benefits, as an exact tool of regulation for precise therapy. Once the genes contributing to apoptosis are positively regulated in intertumoral cells, the proteins production may lead to tumor shrinkage *via* specific pathways. Death receptor 5 (DR5), as a downstream gene of p53 and a receptor for TNF-related apoptosis-inducing ligand (TRAIL), causing cytotoxicity to tumor cells [100]. Obviously, any activation of DR5 may induce the interference of tumor progression. Luteolin, an anticancer agent, can induce apoptosis by stimulating DR5 expression in HeLa cell lines [101]. The molecular mechanism revealed that luteolin can upregulate DR5 expression in a dose-dependent manner and time-response manner, and show evident apoptosis against HeLa cells, but not in normal human peripheral blood mononuclear cells (PBMCs), where DR5 expression is relatively low. Additionally, luteolin induced DR5 could give rise to the cleavage of Bcl-2, and the activation of caspase-3, 9, and 10 (Fig. 27). Due to the effect could be suppressed by DR5 siRNA specifically, the proposed prediction was convincing that the cell apoptosis is induced by luteolin-mediated DR5 upregulation through necrosis-related pathway specifically to HeLa cells, not to normal human cells, providing a possibility to increase the tumor killing effects.

Bromopyruvate (3-BP), as an anticancer agent, induces cell death by interfering with glycolysis. It has been reported that 3-BP sensitizes TRAIL-induced cell apoptosis in MCF-7 breast cancer cells, by

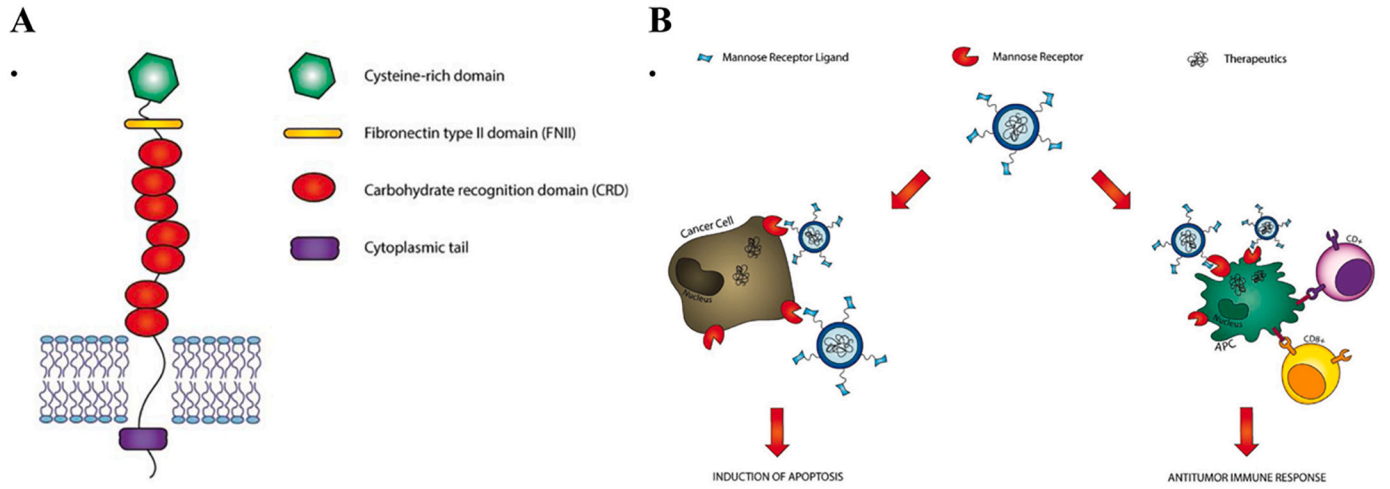


Fig. 22. A. The structure of mannose receptor [87]. B. Mannose receptor–targeted drug delivery systems in anticancer therapy, targeting malignant tumor cells-expressing mannose receptor and T cells for anti-tumor immunotherapy [88].

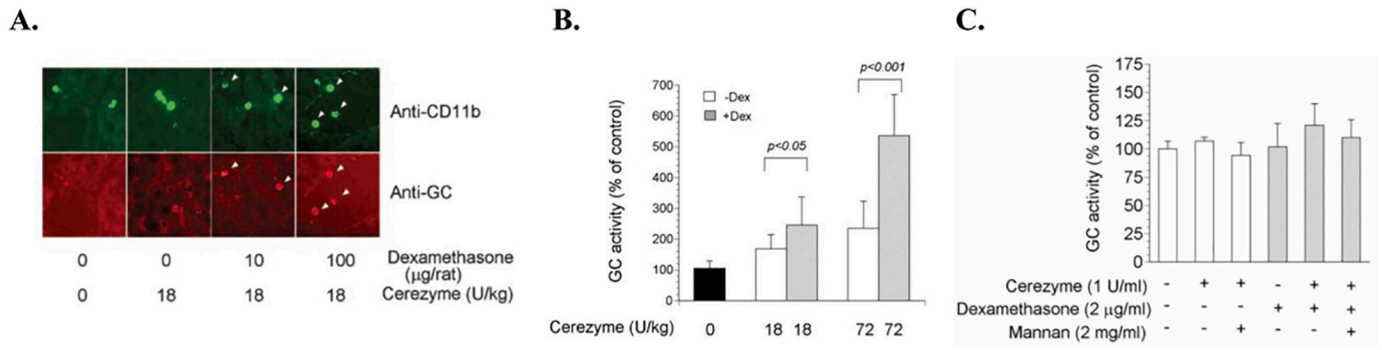


Fig. 23. A. Pre-treatment of Dexa increased the uptake of Cerezyme by liver Kupffer cells *in vivo*. B. Pre-treatment of Dexa increased the uptake of Cerezyme by splenic MCs *in vivo*. C. Uptake of Cerezyme by Hep3B (hepatocyte cell line) by the stimulation of Dexa [86].

upregulating death receptor 5 (DR5) [102]. DR5 staining shows the evidently increased expression of DR5 after stimulation with 3-BP. Following the treatment of 3-BP and TRAIL, synergistically enhanced antitumor effects can be observed in MCF-7 xenografts in nude mice, compared with a single 3-BP or TRAIL group. It was evident that 3-BP positively modulated the DR5 levels deposited in AMPK-mediated pathway to promote cell apoptosis and tumor inhibition of TRAIL.

5. Conclusions

In this regard, we reviewed upregulation strategies for enhancing the efficacy of specifically targeted-small molecules, antibodies or NDDs. It should be emphasized that weak tumor-targeting or endocytosis has been overcome by the increased sensitivity to cancer cells *via* receptor amplification. Increasing surface receptor expression is closely related to cell sensitivity, NPs binding capacity, transport, cell growth and tumor progression. Obviously, the augmented amounts of corresponding receptors on positively expressed cells possess the ability to enhance delivery or activated transport pathway efficiently, which may result in a higher tumor inhibition rate. More importantly, enhanced targeting therapy or activation of signal pathways is mostly desired to provide a foundation for specific, effective tumor treatment and its clinical transformation, while regulation of receptors primarily functions intracellularly and plays a critical role in signals transmission and cell proliferation. The former aims to increase selective delivery efficiency, further enhance the utility and targeting of receptor-mediated therapies, and the latter aims to inhibit cellular action directly (Fig. 28). Although the initial effect and action methods that are used are definitely distinct, both give priority to cancer therapies and therapeutic benefits.

6. Perspectives and future challenges

6.1. Possible benefits

These upregulation strategies are aimed at efficient antitumor effects for humans in the future. For the specific upregulation of receptors, elevated sensitivity at the cellular level and effective delivery of drug/gene-loaded nanosystems are desired for chemotherapy. Up-regulating antigen on cell surface specifically mitigated saturation of receptors. For intracellular genes, which have close relevance to cell death pathways or negative development regulatory factors, any positive modulation would certainly indicate the potential for tumor inhibition. The above aspects are highly conducive to further enhanced specific targeting and the control of tumor progression. Another benefit is

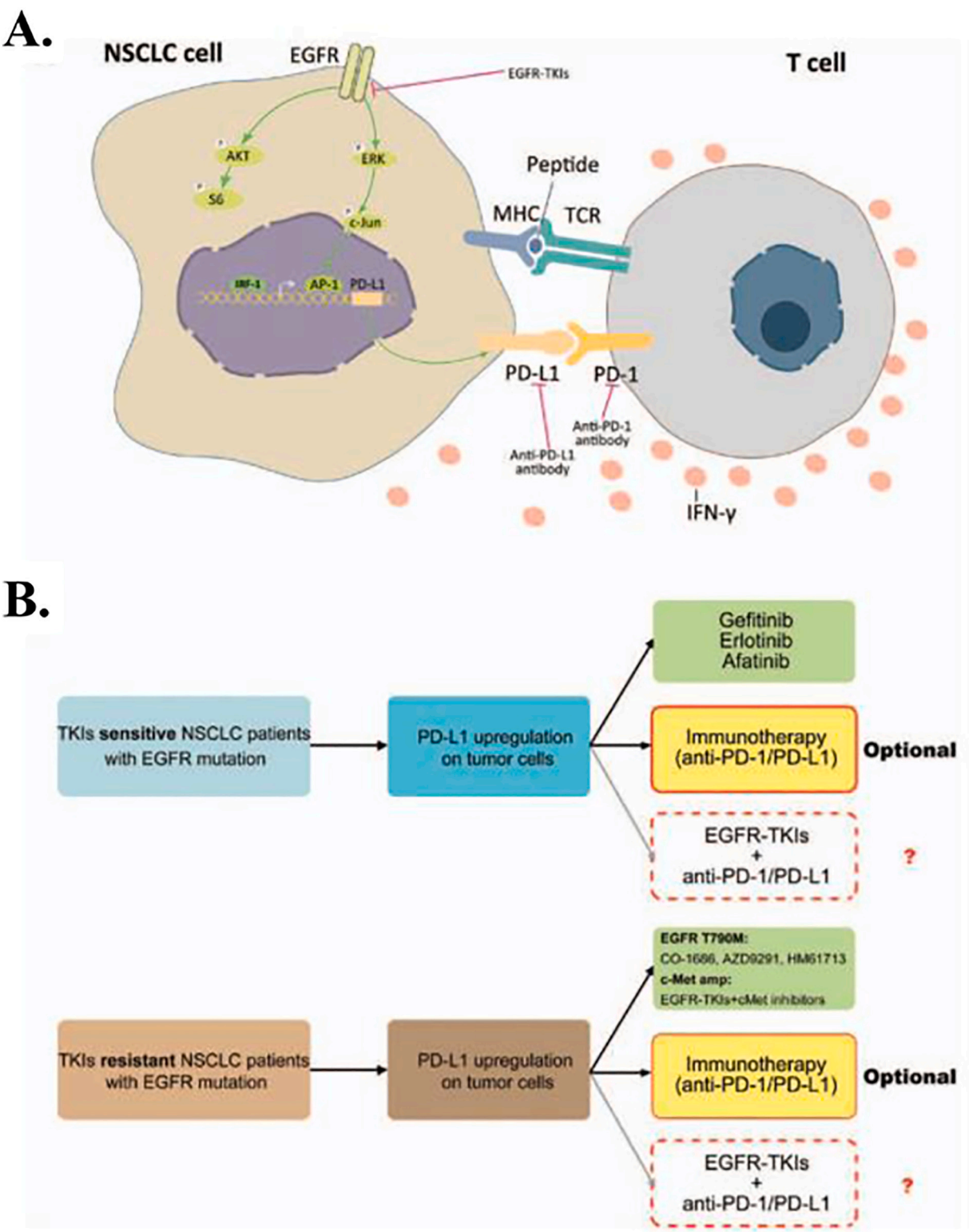


Fig. 24. (A) Molecular regulatory mechanism of PD-L1 by activated EGFR-mutant in NSCLC; EGFR TKIs could induce the downregulation of PD-L1. (B) Optional regime in NSCLC treatment [90].

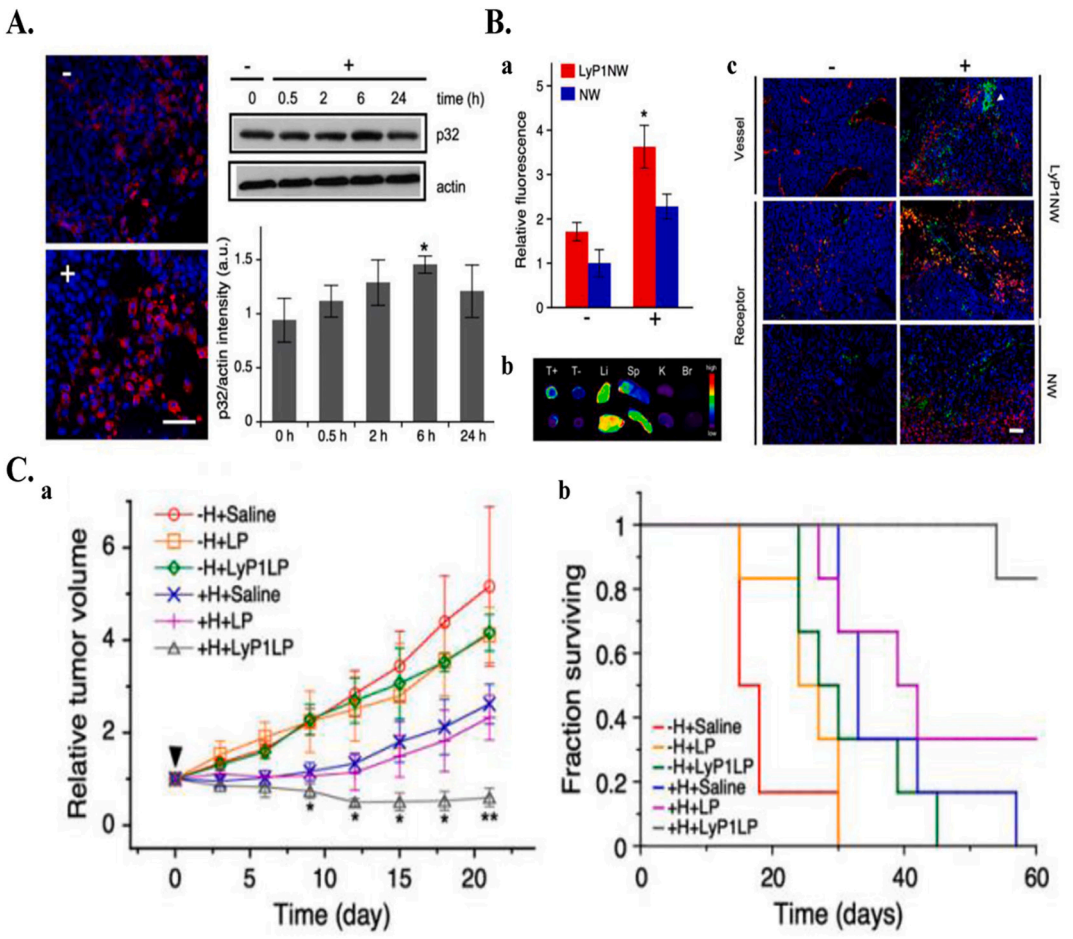


Fig. 25. A cooperative nanosystem consisting of two nanomaterials based on photothermal gold nanorod and LyP-1-modified doxorubicin-loaded liposomes. A. Temperature-induced upregulation of receptors. B. Amplification of *in vivo* tumor targeting. a. Quantitative analysis of gold nanorod or blank nanomaterials in heated tumor tissues. b. Images of major organs. c. Immunofluorescence of tumor vessels in heated or not heated sites. C. Enhancement of therapeutic effects. a. The change of tumor growth delay curve. b. The survival profile of six groups. In this figure, (−) indicates without any treatment while (+) was tumor-heated [91]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

associated with the anti-tumor or anti-inflammatory activity of receptor up-regulating agents [103,104]. The dual-effects of up-regulating agents on enhancing the targeting of NDDs and therapeutic effects [105,106] may outweigh the single regimen, and also reduce the side effects. Of note, this strategy is deserved to make an attempt in many types of malignant diseases, if appropriate.

6.2. Potential risks need to be resolved

Nonetheless, issues remain throughout the process of regulation. It remains to be investigated whether the interrupt of external factors would trigger "self-protecting" effects or "negative feedback" *in vivo*, which may lead to more powerful tumor proliferation after treatment. More importantly, although the combined anti-tumor effects may be induced by receptor upregulating agents and encapsulated drug in NDDs, the affected immune system could not be ignored. The systemic injection of two formulations may also induce serious immune response. Selective delivery of the upregulation agents may decrease the adverse effects on other major organs, reducing the potential of receptors inductions. Furthermore, tailoring the combination strategy based on tumor types and heterogeneity (with different target receptors) are required desirably to applied in therapeutic efficiency. In general, poor specificity due to the difference of receptor expressed on tumor cells such as density, motility or orientations and antigenic mutations may led to "off-targets". The influencing factors from ligand-targeted nanosystems, receptors binding to cell membrane, the heterogeneity of various tumor [107,108] and the tumor micro-environment could result in inefficient targeting and therapeutic effects.

In addition, the complexity of this approach still needs to be resolved. Given the possible anti-tumor effects of NDDs enhanced by receptor upregulating agents, optimal dosage, appropriate time and frequency of administration of NDDs may need further consideration. It is possible that the increase of receptor mediated by these agents may allow for a lowering in dosage. Inappropriate dosage may induce more adverse effects and decrease survival rate during the treatment. And constructing safe and useful NDDs to achieve targeted delivery may

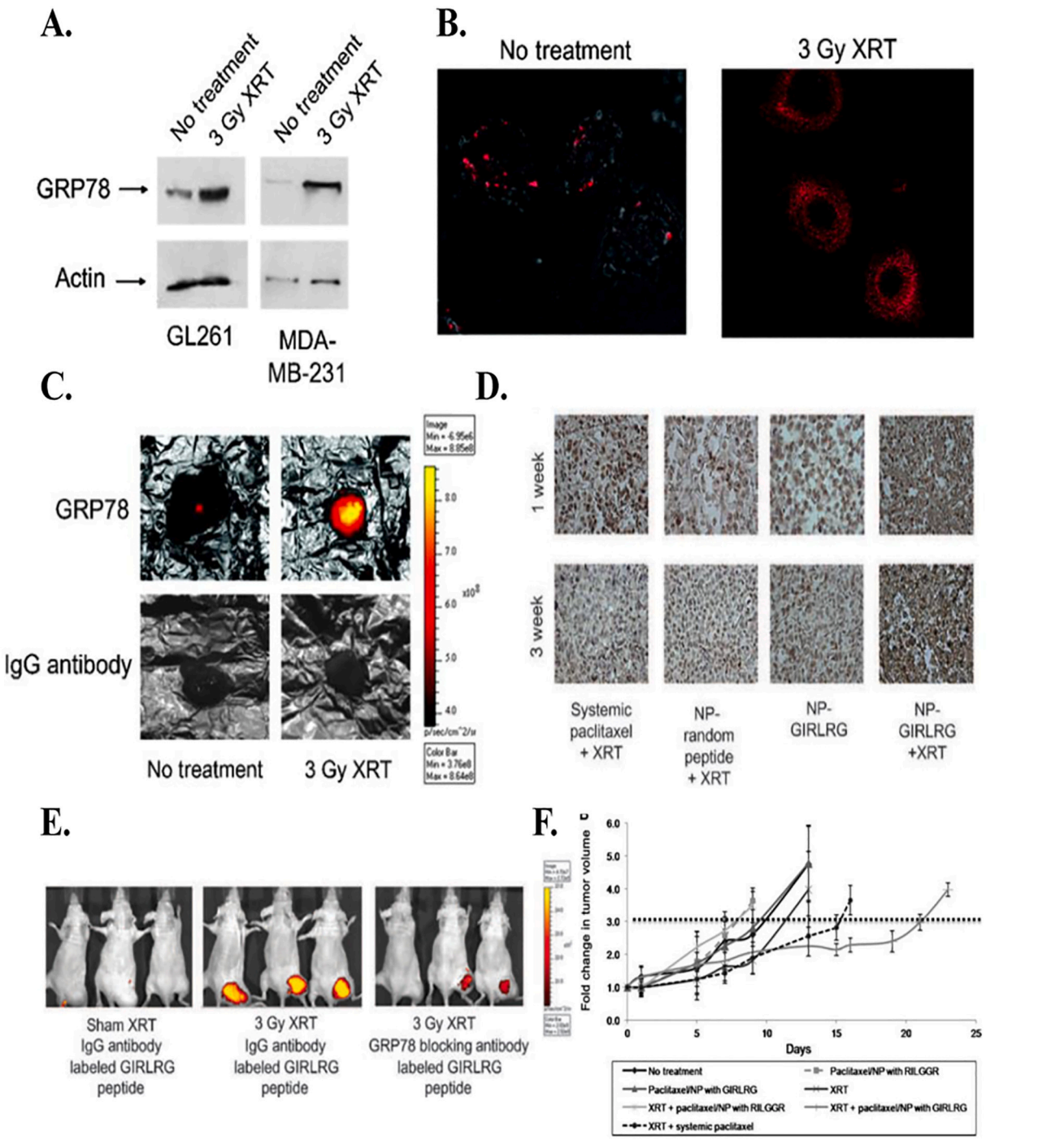


Fig. 26. A peptide with paclitaxel-encapsulating nanoparticle targeting irradiated tumors. A. Upregulation of GRP78 in glioma and breast cancer cells induced by XRT. B. Induction of GRP78 in HUVECs cocultured with gliomas, with treatment of XRT. C. Captured fluorescence images of antibody to GRP78 in nude mice xenografted glioma tumor, pre-treated with 3Gy XRT. D. Cell apoptosis of paclitaxel-loaded nanoparticles in pre-irradiated breast tumors by a Tunel assay. E. The peptide binding to GRP78 induced by irritation *in vivo*. F. Glioma tumor volume monitoring during the treatment. XRT: ionizing radiation. RILGGR: scrambled peptide [92].

Table 4
Upregulation of receptors specifically bind to the surface of tumor cells by various types of agents for enhancing therapeutic drug delivery.

Receptor	Cancer types	Upregulation agents or factors	Therapeutic agents	Formulation	Year	Ref
FRβ	CML	ATO	ATO	Nanoparticle	2017	[57]
	AML	Curcumin	Methotrexate	Anti-folates	2103	[56]
	AML	ATRA	DOX	Liposomes	2010	[60]
	AML	ATRA; HDACi	Antifolates	NR	2007	[63]
	Acute monocytic leukemic	ATRA	m909 CAR-T	CAR-T cells	2015	[40]
FRα	Ovarian	Curcumin	Paclitaxel	Paclitaxel	2019	[66]
	Ovarian	Dexa; HDACi	NR	NR	2005	[64]
	Mammary carcinoma	Recombinant cDNA	Methotrexate	Anti-folates	1993	[67]
LRP-1	BM	SIM	DOX	Nanoparticle	2019	[70]
Caveolin-1	BM	MS	DOX	Nanoparticle	2019	[74]
CD38	MM	ATRA	daratumumab	Antibody	2020	[80]
	MM	Ricolinostat	daratumumab	Antibody	2020	[80,81]
Mannose receptor	Gaucher	Dexamethasone	Cerezyme	Cerezyme	2004	[86]
$\alpha v\beta_3$ and $\alpha v\beta_5$	NR	PHA, PMA, CSF, MCSF	Adenovirus-mediated gene delivery	Recombinantdenovirus	1995	[85]
p32	Metastatic breast cancer	Hyperthermia	DOX	Liposomes	2010	[91]
GRP78	Glioma tumors and breast carcinomas	Irradiation	Paclitaxel	Nanoparticles	2010	[92]
Dibenzocyclooctyne-bearing antigens	Non-small cell lung cancer	Glycoengineering	Photosensitizer ce6	Nanoparticles	2014	[93]
EGFR	NR	Radiotherapy	EGFR inhibitors	Oral medication	2004	[97]

NR indicates not reported.

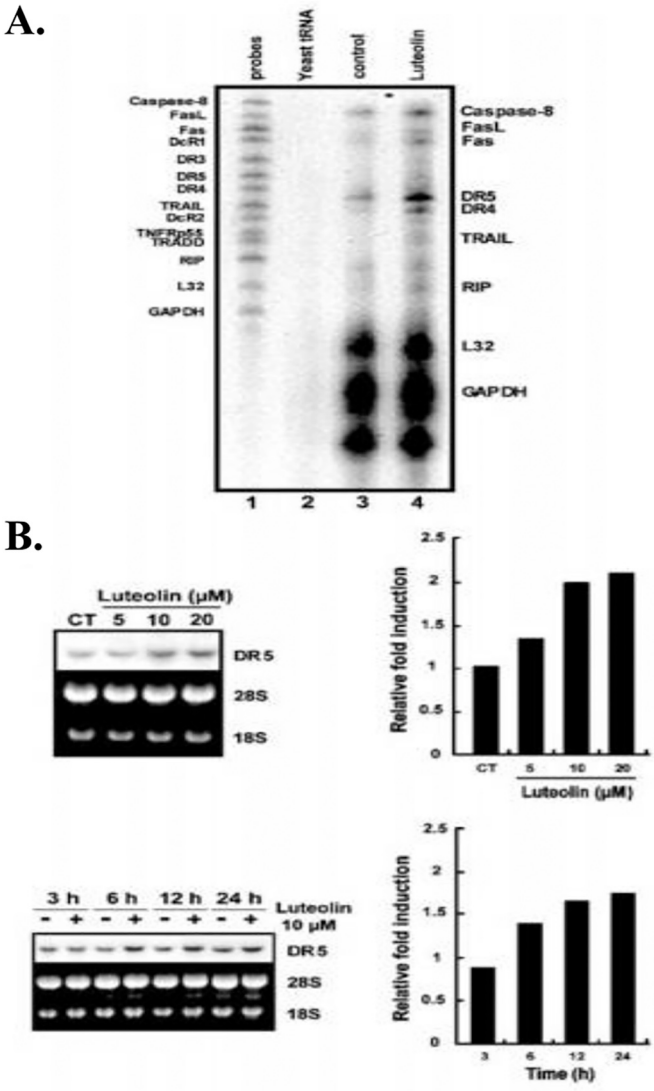


Fig. 27. Luteolin induce the expression of DR5 (a) RNase protection assay, lane 4 represents DR5 mRNA expression with the pre-treatment of luteolin in Hela cells. (b) Induction rate of DR5 mRNA by various concentration of luteolin or in the presence of 10 μM luteolin at pre-designed time points [101].

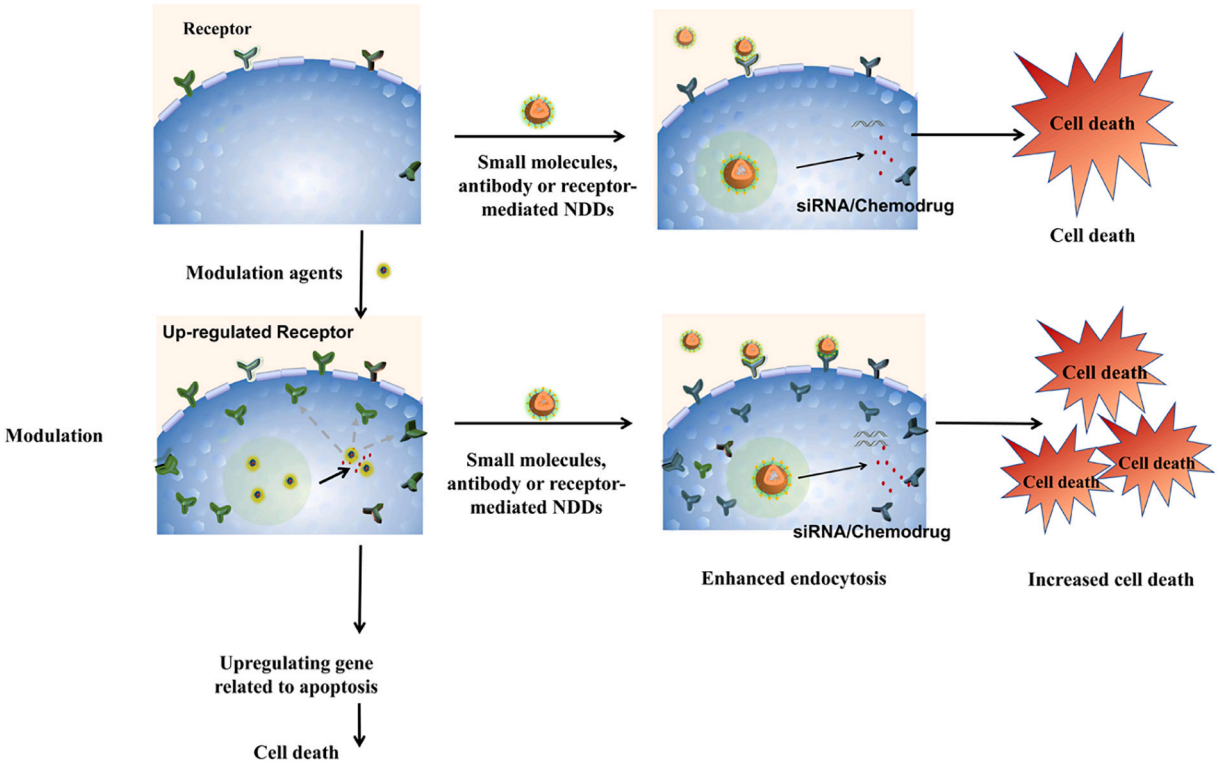


Fig. 28. Schematic presentations of up-regulating receptors for efficient delivery.

undergo more barriers than the direct use of drug/gene [109]. In recent decades, few active nanoparticle systems for systematic administration have received approval for entering clinical trials. In short, a better understanding of intrinsic molecular mechanisms, exploration for functional capacity of NDDs and optimal regimen design addressing these contingent risks are under urgent consideration.

Declaration of Competing Interest

The authors declare no conflict of interests.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (NSFC 81773183, and 81571788); Postgraduate Research and Practice Innovation of Jiangsu Province (Granted, No. KYCX19_1973); and Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jconrel.2021.03.045.

References

[1] Q. Peng, S. Zhang, Q. Yang, T. Zhang, X.Q. Wei, L. Jiang, C.L. Zhang, Q.M. Chen, Z.R. Zhang, Y.F. Lin, Preformed albumin corona, a protective coating for nanoparticles based drug delivery system, Biomaterials 34 (33) (2013) 8521–8530.
[2] J. Mariam, S. Sivakami, P.M. Dongre, Albumin corona on nanoparticles – a strategic approach in drug delivery, Drug Deliv. 23 (8) (2016) 1–9.
[3] J.Z. Du, X.J. Du, C.Q. Mao, J. Wang, Tailor-made dual pH-sensitive polymer-doxorubicin nanoparticles for efficient anticancer drug delivery, J. Am. Chem. Soc. 133 (44) (2011) 17560–17563.
[4] S.S. Suri, H. Fenniri, B. Singh, Nanotechnology-based drug delivery systems, J. Occup. Med. Toxicol. 2 (2007) 16.
[5] B. Zhang, S. Wan, X. Peng, M. Zhao, S. Li, Y. Pu, B. He, Human serum albumin-based doxorubicin prodrug nanoparticles with tumor pH-responsive aggregation-enhanced retention and reduced cardiotoxicity, J. Mater. Chem. B 8 (17) (2020) 3939–3948.
[6] F. Danhier, O. Feron, V. Preat, To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery, J. Control. Release 148 (2) (2010) 135–146.
[7] V. Torchilin, Tumor delivery of macromolecular drugs based on the EPR effect, Adv. Drug Deliv. Rev. 63 (3) (2011) 131–135.
[8] C.H. Heldin, K. Rubin, K. Pietras, A. Ostman, High interstitial fluid pressure - an obstacle in cancer therapy, Nat. Rev. Cancer 4 (10) (2004) 806–813.
[9] L. Liu, Y. Bi, M. Zhou, X. Chen, X. He, Y. Zhang, T. Sun, C. Ruan, Q. Chen, H. Wang, C. Jiang, Biomimetic human serum albumin nanoparticle for efficiently targeting therapy to metastatic breast cancers, ACS Appl. Mater. Interfaces 9 (8) (2017) 7424–7435.
[10] K.N. Moore, H. Borghaei, D.M. O'Malley, W. Jeong, S.M. Seward, T.M. Bauer, R. P. Perez, U.A. Matulonis, K.L. Running, X. Zhang, J.F. Ponte, R. Ruiz-Soto, M. J. Birrer, Phase 1 dose-escalation study of mirvetuximab soravtansine (IMGN853), a folate receptor alpha-targeting antibody-drug conjugate, in patients with solid tumors, Cancer-Am. Cancer Soc. 123 (16) (2017) 3080–3087.
[11] M. Srinivasarao, C.V. Galliford, P.S. Low, Principles in the design of ligand-targeted cancer therapeutics and imaging agents, Nat. Rev. Drug Discov. 14 (3) (2015) 203–219.
[12] M. Fernandez, F. Javaid, V. Chudasama, Advances in targeting the folate receptor in the treatment/imaging of cancers, Chem. Sci. 9 (4) (2018) 790–810.
[13] H. Wang, S. Sun, Y. Zhang, J. Wang, S. Zhang, X. Yao, L. Chen, Z. Gao, B. Xie, Improved drug targeting to liver tumor by sorafenib-loaded folate-decorated bovine serum albumin nanoparticles, Drug Deliv. 26 (1) (2019) 89–97.
[14] N. Nateghian, N. Goodarzi, M. Amini, F. Atyabi, M.R. Khorramizadeh, R. Dinarvand, Biotin/folate-decorated human serum albumin nanoparticles of docetaxel: comparison of chemically conjugated nanostructures and physically loaded nanoparticles for targeting of breast Cancer, Chem. Biol. Drug Des. 87 (1) (2016) 69–82.
[15] X. Wang, M. Tu, B. Tian, Y. Yi, Z. Wei, F. Wei, Synthesis of tumor-targeted folate conjugated fluorescent magnetic albumin nanoparticles for enhanced intracellular dual-modal imaging into human brain tumor cells, Anal. Biochem. 512 (2016) 8–17.
[16] D.S. Theti, V. Bavetsias, L.A. Skelton, J. Titley, D. Gibbs, G. Jansen, A.L. Jackman, Selective delivery of CB300638, a cyclopenta[g]quinazoline-based thymidylate synthase inhibitor into human tumor cell lines overexpressing the alpha-isoform of the folate receptor, Cancer Res. 63 (13) (2003) 3612–3618.
[17] Y. Shi, C. Su, W. Cui, H. Li, L. Liu, B. Feng, M. Liu, R. Su, L. Zhao, Gefitinib loaded folate decorated bovine serum albumin conjugated carboxymethyl-beta-cyclodextrin nanoparticles enhance drug delivery and attenuate autophagy in folate receptor-positive cancer cells, J. Nanobiotechnol. 12 (2014) 43.

[18] A. Zensi, D. Begley, C. Pontikis, C. Legros, L. Mihoreanu, C. Buchel, J. Kreuter, Human serum albumin nanoparticles modified with apolipoprotein A-I cross the blood-brain barrier and enter the rodent brain, J. Drug Target. 18 (10) (2010) 842–848.
[19] X. Yu, Y. Song, Y. Di, H. He, D. Fu, C. Jin, Enhanced tumor targeting of cRGD peptide-conjugated albumin nanoparticles in the BxPC-3 cell line, Sci. Rep. 6 (2016) 31539.
[20] A. Taheri, R. Dinarvand, F.S. Nouri, M.R. Khorramizadeh, A.T. Borougeni, P. Mansoori, F. Atyabi, Use of biotin targeted methotrexate-human serum albumin conjugated nanoparticles to enhance methotrexate antitumor efficacy, Int. J. Nanomedicine 6 (2011) 1863–1874.
[21] M.G. Anhorn, S. Wagner, J. Kreuter, K. Langer, H. von Briesen, Specific targeting of HER2 overexpressing breast cancer cells with doxorubicin-loaded trastuzumab-modified human serum albumin nanoparticles, Bioconjug. Chem. 19 (12) (2008) 2321–2331.
[22] X. Ying, H. Wen, W.L. Lu, J. Du, J. Guo, W. Tian, Y. Men, Y. Zhang, R.J. Li, T. Y. Yang, D.W. Shang, J.N. Lou, L.R. Zhang, Q. Zhang, Dual-targeting daunorubicin liposomes improve the therapeutic efficacy of brain glioma in animals, J. Control. Release 141 (2) (2010) 183–192.
[23] J. Liang, C. Gao, Y. Zhu, C. Ling, Q. Wang, Y. Huang, J. Qin, J. Wang, W. Lu, J. Wang, Natural brain penetration enhancer-modified albumin nanoparticles for glioma targeting delivery, ACS Appl. Mater. Interfaces 10 (36) (2018) 30201–30213.
[24] H.J. Byeon, L.Q. Thao, S. Lee, S.Y. Min, E.S. Lee, B.S. Shin, H. Choi, Y.S. Youn, Doxorubicin-loaded nanoparticles consisted of cationic- and mannose-modified-albumins for dual-targeting in brain tumors, J. Control. Release 225 (2016) 301–313.
[25] C. Li, D. Zhang, H. Guo, L. Hao, D. Zheng, G. Liu, J. Shen, X. Tian, Q. Zhang, Preparation and characterization of galactosylated bovine serum albumin nanoparticles for liver-targeted delivery of oridonin, Int. J. Pharm. 448 (1) (2013) 79–86.
[26] W.W. Qi, H.Y. Yu, H. Guo, J. Lou, Z.M. Wang, P. Liu, A. Sapin-Minet, P. Maincent, X.C. Hong, X.M. Hu, Y.L. Xiao, Doxorubicin-loaded glycyrrhetinic acid modified recombinant human serum albumin nanoparticles for targeting liver tumor chemotherapy, Mol. Pharm. 12 (3) (2015) 675–683.
[27] L. Li, C.A. Wartchow, S.N. Danthi, Z. Shen, N. Dechene, J. Pease, H.S. Choi, T. Doede, P. Chu, S. Ning, D.Y. Lee, M.D. Bednarski, S.J. Knox, A novel antiangiogenesis therapy using an integrin antagonist or anti-Flk-1 antibody coated 90Y-labeled nanoparticles, Int. J. Radiat. Oncol. Biol. Phys. 58 (4) (2004) 1215–1227.
[28] D.M. O'Malley, U.A. Matulonis, M.J. Birrer, C.M. Castro, L. Gilbert, I. Vergote, L. P. Martin, G.M. Mantia-Smaldone, A.G. Martin, R. Bratos, R.T. Penson, K. Malek, K.N. Moore, Phase Ib study of mirvetuximab soravtansine, a folate receptor alpha (FRalpha)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer, Gynecol. Oncol. 157 (2) (2020) 379–385.
[29] L. Li, Q. Yang, Z. Zhou, J. Zhong, Y. Huang, Doxorubicin-loaded, charge reversible, folate modified HPMA copolymer conjugates for active cancer cell targeting, Biomaterials 35 (19) (2014) 5171–5187.
[30] J. Cao, Y. Zhang, Y. Wu, J. Wu, W. Wang, Q. Wu, Z. Yuan, The effects of ligand valency and density on the targeting ability of multivalent nanoparticles based on negatively charged chitosan nanoparticles, Colloids Surf. B: Biointerfaces 161 (2018) 508–518.
[31] Y. Yang, Z. Zhou, S. He, T. Fan, Y. Jin, X. Zhu, C. Chen, Z.R. Zhang, Y. Huang, Treatment of prostate carcinoma with (galectin-3)-targeted HPMA copolymer-(G3-C12)-5-fluorouracil conjugates, Biomaterials 33 (7) (2012) 2260–2271.
[32] S.S. Mahshid, A. Vallee-Belisle, S.O. Kelley, Biomolecular steric hindrance effects are enhanced on nanostructured microelectrodes, Anal. Chem. 89 (18) (2017) 9751–9757.
[33] W.S. Hlavacek, R.G. Posner, A.S. Perelson, Steric effects on multivalent ligand-receptor binding: exclusion of ligand sites by bound cell surface receptors, Biophys. J. 76 (6) (1999) 3031–3043.
[34] M.G. Steffens, J.C. Oosterwijk-Wakka, N.E. Zegwaart-Hagemeier, O.C. Boerman, F.M. Debruyne, F.H. Corstens, E. Oosterwijk, Immunohistochemical analysis of tumor antigen saturation following injection of monoclonal antibody G250, Anticancer Res. 19 (2A) (1999) 1197–1200.
[35] A.M. Wollacott, L.N. Robinson, B. Ramakrishnan, H. Tissire, K. Viswanathan, Z. Shriver, G.J. Babcock, Structural prediction of antibody-APRIL complexes by computational docking constrained by antigen saturation mutagenesis library data, J. Mol. Recognit. 32 (7) (2019), e2778.
[36] H. Witt, M. Vache, A. Cordes, A. Janshoff, Detachment of giant liposomes-coupling of receptor mobility and membrane shape, Soft Matter 16 (27) (2020) 6424–6433.
[37] Y. Lu, P.S. Low, Folate-mediated delivery of macromolecular anticancer therapeutic agents, Adv. Drug Deliv. Rev. 54 (5) (2002) 675–693.
[38] O. Ab, K.R. Whiteman, L.M. Bartle, X. Sun, R. Singh, D. Tavares, A. LaBelle, G. Payne, R.J. Lutz, J. Pinkas, V.S. Goldmacher, T. Chittenden, J.M. Lambert, IMGN853, a folate receptor-alpha (FRalpha)-targeting antibody-drug conjugate, exhibits potent targeted antitumor activity against fralpha-expressing tumors, Mol. Cancer Ther. 14 (7) (2015) 1605–1613.
[39] J.A. Ledermann, S. Canevari, T. Thigpen, Targeting the folate receptor: diagnostic and therapeutic approaches to personalize cancer treatments, Ann. Oncol. 26 (10) (2015) 2034–2043.
[40] R.C. Lynn, M. Poussin, A. Kalota, Y. Feng, P.S. Low, D.S. Dimitrov, D.J. Powell, Targeting of folate receptor beta on acute myeloid leukemia blasts with chimeric antigen receptor-expressing T cells, Blood 125 (22) (2015) 3466–3476.
[41] Y. Feng, J. Shen, E.D. Streaker, M. Lockwood, Z. Zhu, P.S. Low, D.S. Dimitrov, A folate receptor beta-specific human monoclonal antibody recognizes activated macrophage of rheumatoid patients and mediates antibody-dependent cell-mediated cytotoxicity, Arthritis Ther. 13 (2) (2011) R59.
[42] R. Suzuki, T. Takizawa, Y. Kuwata, M. Mutoh, N. Ishiguro, N. Utoguchi, A. Shinohara, M. Eriguchi, H. Yanagie, K. Maruyama, Effective anti-tumor activity of oxaliplatin encapsulated in transferrin-PEG-liposome, Int. J. Pharm. 346 (1–2) (2008) 143–150.
[43] L.W. Seymour, D.R. Ferry, D. Anderson, S. Hesslewood, P.J. Julyan, R. Poyner, J. Doran, A.M. Young, S. Burtles, D.J. Kerr, Hepatic drug targeting: phase I evaluation of polymer-bound doxorubicin, J. Clin. Oncol. 20 (6) (2002) 1668–1676.
[44] Y. Matsumura, M. Gotoh, K. Muro, Y. Yamada, K. Shirao, Y. Shimada, M. Okuwa, S. Matsumoto, Y. Miyata, H. Ohkura, K. Chin, S. Baba, T. Yamao, A. Kannami, Y. Takamatsu, K. Ito, K. Takahashi, Phase I and pharmacokinetic study of MCC-465, a doxorubicin (DXR) encapsulated in PEG immunoliposome, in patients with metastatic stomach cancer, Ann. Oncol. 15 (3) (2004) 517–525.
[45] R. Gabathuler, Development of new peptide vectors for the transport of therapeutic across the blood-brain barrier, Ther. Deliv. 1 (4) (2010) 571–586.
[46] J.F. Ross, H. Wang, F.G. Behm, P. Mathew, M. Wu, R. Booth, M. Ratnam, Folate receptor type beta is a neutrophilic lineage marker and is differentially expressed in myeloid leukemia, Cancer-Am. Cancer Soc. 85 (2) (1999) 348–357.
[47] J.A. Reddy, P.S. Low, Folate-mediated targeting of therapeutic and imaging agents to cancers, Crit. Rev. Ther. Drug Carrier Syst. 15 (6) (1998) 587–627.
[48] J.A. Reddy, L.S. Haneline, E.F. Srour, A.C. Antony, D.W. Clapp, P.S. Low, Expression and functional characterization of the beta-isoform of the folate receptor on CD34(+) cells, Blood 93 (11) (1999) 3940–3948.
[49] B. Bahrami, M. Mohammadnia-Afrouzi, P. Bakhshaei, Y. Yazdani, G. Ghalamfarsa, M. Yousefi, S. Sadreddini, F. Jadidi-Niaragh, M. Hojjat-Farsangi, Folate-conjugated nanoparticles as a potent therapeutic approach in targeted cancer therapy, Tumour Biol. 36 (8) (2015) 5727–5742.
[50] Y. Zhang, X. Tan, T. Ren, C. Jia, Z. Yang, H. Sun, Folate-modified carboxymethyl-chitosan/polyethylenimine/bovine serum albumin based complexes for tumor site-specific drug delivery, Carbohydr. Polym. 198 (2018) 76–85.
[51] J.J. Turek, C.P. Leamon, P.S. Low, Endocytosis of folate-protein conjugates: ultrastructural localization in KB cells, J. Cell Sci. 106 (Pt 1) (1993) 423–430.
[52] D. Wang, W. Chen, H. Li, G. Huang, Y. Zhou, Y. Wang, W. Wan, B. You, Y. Liu, X. Zhang, Folate-receptor mediated pH/reduction-responsive biomimetic nanoparticles for dually activated multi-stage anticancer drug delivery, Int. J. Pharm. 585 (2020) 119456.
[53] C. Du, D. Deng, L. Shan, S. Wan, J. Cao, J. Tian, S. Achilefu, Y. Gu, A pH-sensitive doxorubicin prodrug based on folate-conjugated BSA for tumor-targeted drug delivery, Biomaterials 34 (12) (2013) 3087–3097.
[54] X. Guo, D. Li, G. Yang, C. Shi, Z. Tang, J. Wang, S. Zhou, Thermo-triggered drug release from actively targeting polymer micelles, ACS Appl. Mater. Interfaces 6 (11) (2014) 8549–8559.
[55] L. Qi, Y. Guo, J. Luan, D. Zhang, Z. Zhao, Y. Luan, Folate-modified bexarotene-loaded bovine serum albumin nanoparticles as a promising tumor-targeting delivery system, J. Mater. Chem. B 2 (47) (2014) 8361–8371.
[56] S. Dhanasekaran, B.K. Biswal, V.N. Sumantran, R.S. Verma, Augmented sensitivity to methotrexate by curcumin induced overexpression of folate receptor in KG-1 cells, Biochimi 95 (8) (2013) 1567–1573.
[57] Y. Peng, Z. Zhao, T. Liu, X. Li, X. Hu, X. Wei, X. Zhang, W. Tan, Smart human-serum-albumin-As2 O3 Nanodrug with self-amplified folate receptor-targeting ability for chronic myeloid leukemia treatment, Angew. Chem. Int. Ed. Eng. 56 (36) (2017) 10845–10849.
[58] Y. Xu, T. Wang, R. Tang, S. Tang, All-trans retinoic acid is capable of inducing folate receptor beta expression in KG-1 cells, Tumour Biol. 31 (6) (2010) 589–595.
[59] H. Wang, X. Zheng, F.G. Behm, M. Ratnam, Differentiation-independent retinoid induction of folate receptor type beta, a potential tumor target in myeloid leukemia, Blood 96 (10) (2000) 3529–3536.
[60] X.Q. Pan, X. Zheng, G. Shi, H. Wang, M. Ratnam, R.J. Lee, Strategy for the treatment of acute myelogenous leukemia based on folate receptor beta-targeted liposomal doxorubicin combined with receptor induction using all-trans retinoic acid, Blood 100 (2) (2002) 594–602.
[61] D.D. Wang, H. Li, W.L. Chen, H. Yang, Y. Liu, B.G. You, X.N. Zhang, Efficient tumor-targeting delivery of siRNA *via* folate-receptor mediated biomimetic albumin nanoparticles enhanced by all trans retinoid acid, Mater. Sci. Eng. C 119 (2021), 111583, https://doi.org/10.1016/j.msec.2020.111583.
[62] B.W. Blaser, M. Gonit, H. Qi, A. Shatnawi, M. Guimond, R.J. Lee, M. Ratnam, Induction of folate receptor type beta in a bone marrow engraftment model of acute myelogenous leukemia, Leukemia 21 (10) (2007) 2233–2235.
[63] H. Qi, M. Ratnam, Synergistic induction of folate receptor beta by all-trans retinoic acid and histone deacetylase inhibitors in acute myelogenous leukemia cells: mechanism and utility in enhancing selective growth inhibition by antifolates, Cancer Res. 66 (11) (2006) 5875–5882.
[64] E. Peraudeau, L. Cronier, A. Monvoisin, P. Poinot, C. Mergault, F. Guilhot, I. Tranoy-Opalinski, B. Renoux, S. Papot, J. Clarhaut, Enhancing tumor response to targeted chemotherapy through up-regulation of folate receptor alpha expression induced by dexamethasone and valproic acid, J. Control. Release 269 (2018) 36–44.
[65] T. Tran, A. Shatnawi, X. Zheng, K.M. Kelley, M. Ratnam, Enhancement of folate receptor alpha expression in tumor cells through the glucocorticoid receptor: a promising means to improved tumor detection and targeting, Cancer Res. 65 (10) (2005) 4431–4441.

[66] S. Dhanasekaran, Augmented cytotoxic effects of paclitaxel by curcumin induced overexpression of folate receptor-alpha for enhanced targeted drug delivery in HeLa cells, Phytomedicine 56 (2019) 279–285.
[67] J.D. Schuetz, L.H. Matherly, E.H. Westin, I.D. Goldman, Evidence for a functional defect in the translocation of the methotrexate transport carrier in a methotrexate-resistant murine L1210 leukemia cell line, J. Biol. Chem. 263 (20) (1988) 9840–9847.
[68] K.N. Chung, Y. Saikawa, T.H. Paik, K.H. Dixon, T. Mulligan, K.H. Cowan, P. C. Elwood, Stable transfectants of human MCF-7 breast cancer cells with increased levels of the human folate receptor exhibit an increased sensitivity to antifolates, J. Clin. Invest. 91 (4) (1993) 1289–1294.
[69] M. Zandl-Lang, E. Fanaee-Danesh, Y. Sun, N.M. Albrecher, C.C. Gali, I. Cancar, A. Kober, C. Tam-Amersdorfer, A. Stracke, S.M. Storck, A. Saeed, J. Stefulj, C. U. Pietrzik, M.R. Wilson, I. Bjorkhem, U. Panzenboeck, Regulatory effects of simvastatin and apoJ on APP processing and amyloid-beta clearance in blood-brain barrier endothelial cells, Biochim. Biophys. Acta Mol. Cell Biol. Lipids 1863 (1) (2018) 40–60.
[70] Q. Guo, Q. Zhu, T. Miao, J. Tao, X. Ju, Z. Sun, H. Li, G. Xu, H. Chen, L. Han, LRP1-upregulated nanoparticles for efficiently conquering the blood-brain barrier and targetedly suppressing multifocal and infiltrative brain metastases, J. Control. Release 303 (2019) 117–129.
[71] S. Dissanayake, W.A. Denny, S. Gamage, V. Sarojini, Recent developments in anticancer drug delivery using cell penetrating and tumor targeting peptides, J. Control. Release 250 (2017) 62–76.
[72] N.S. Ningaraj, M. Rao, K. Hashizume, K. Asotra, K.L. Black, Regulation of blood-brain tumor barrier permeability by calcium-activated potassium channels, J. Pharmacol. Exp. Ther. 301 (3) (2002) 838–851.
[73] N.S. Ningaraj, M.K. Rao, K.L. Black, Adenosine 5′-triphosphate-sensitive potassium channel-mediated blood-brain tumor barrier permeability increase in a rat brain tumor model, Cancer Res. 63 (24) (2003) 8899–8911.
[74] T. Miao, X. Ju, Q. Zhu, Y. Wang, Q. Guo, T. Sun, C. Lu, L. Han, Nanoparticles surmounting blood–brain tumor barrier through both transcellular and Paracellular pathways to target brain metastases, Adv. Funct. Mater. 29 (27) (2019), https://doi.org/10.1002/adfm.201900259.
[75] N.W. van de Donk, P. Moreau, T. Plesner, A. Palumbo, F. Gay, J.P. Laubach, F. Malavasi, H. Avet-Loiseau, M.V. Mateos, P. Sonneveld, H.M. Lokhorst, P. G. Richardson, Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma, Blood 127 (6) (2016) 681–695.
[76] S. Lonial, B.M. Weiss, S.Z. Usmani, S. Singhal, A. Chari, N.J. Bahlis, A. Belch, A. Krishnan, R.A. Vescio, M.V. Mateos, A. Mazumder, R.Z. Orlowski, H. J. Sutherland, J. Blade, E.C. Scott, A. Oriol, J. Berdeja, M. Gharibo, D.A. Stevens, R. LeBlanc, M. Sebag, N. Callander, A. Jakubowiak, D. White, J. de la Rubia, P. G. Richardson, S. Lisby, H. Feng, C.M. Uhlar, I. Khan, T. Ahmadi, P.M. Voorhees, Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial, Lancet 387 (10027) (2016) 1551–1560.
[77] H.M. Lokhorst, T. Plesner, J.P. Laubach, H. Nahi, P. Gimsing, M. Hansson, M. C. Minnema, U. Lassen, J. Krejcik, A. Palumbo, N.W. van de Donk, T. Ahmadi, I. Khan, C.M. Uhlar, J. Wang, A.K. Sasser, N. Losic, S. Lisby, L. Basse, N. Brun, P. G. Richardson, Targeting CD38 with Daratumumab monotherapy in multiple myeloma, N. Engl. J. Med. 373 (13) (2015) 1207–1219.
[78] M.S. van der Veer, M. de Weers, B. van Kessel, J.M. Bakker, S. Wittebol, P. W. Parren, H.M. Lokhorst, T. Mutis, The therapeutic human CD38 antibody daratumumab improves the anti-myeloma effect of newly emerging multi-drug therapies, Blood Cancer J. 1 (10) (2011), e41.
[79] M. de Weers, Y.T. Tai, M.S. van der Veer, J.M. Bakker, T. Vink, D.C. Jacobs, L. A. Oomen, M. Peipp, T. Valerius, J.W. Slootstra, T. Mutis, W.K. Bleeker, K. C. Anderson, H.M. Lokhorst, J.G. van de Winkel, P.W. Parren, Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors, J. Immunol. 186 (3) (2011) 1840–1848.
[80] I.S. Nijhof, R.W. Groen, H.M. Lokhorst, B. van Kessel, A.C. Bloem, J. van Velzen, R. de Jong-Korlaar, H. Yuan, W.A. Noort, S.K. Klein, A.C. Martens, P. Doshi, K. Sasser, T. Mutis, N.W. van de Donk, Upregulation of CD38 expression on multiple myeloma cells by all-trans retinoic acid improves the efficacy of daratumumab, Leukemia 29 (10) (2015) 2039–2049.
[81] E. Garcia-Guerrero, R. Gotz, S. Doose, M. Sauer, A. Rodriguez-Gil, T. Nerreter, K. M. Kortum, J.A. Perez-Simon, H. Einsele, M. Hudecek, S. Danhof, Upregulation of CD38 expression on multiple myeloma cells by novel HDAC6 inhibitors is a class effect and augments the efficacy of daratumumab, Leukemia 35 (1) (2020) 201–214.
[82] I.S. Nijhof, T. Casneuf, J. van Velzen, B. van Kessel, A.E. Axel, K. Syed, R. W. Groen, M. van Duin, P. Sonneveld, M.C. Minnema, S. Zweegman, C. Chiu, A. C. Bloem, T. Mutis, H.M. Lokhorst, A.K. Sasser, N.W. van de Donk, CD38 expression and complement inhibitors affect response and resistance to daratumumab therapy in myeloma, Blood 128 (7) (2016) 959–970.
[83] J. Horvath, J.M. Weber, Nonpermissivity of human peripheral blood lymphocytes to adenovirus type 2 infection, J. Virol. 62 (1) (1988) 341–345.
[84] Y. Chu, K. Sperber, L. Mayer, M.T. Hsu, Persistent infection of human adenovirus type 5 in human monocyte cell lines, Virology 188 (2) (1992) 793–800.
[85] S. Huang, R.I. Endo, G.R. Nemerow, Upregulation of integrins alpha v beta 3 and alpha v beta 5 on human monocytes and T lymphocytes facilitates adenovirus-mediated gene delivery, J. Virol. 69 (4) (1995) 2257–2263.
[86] Y. Zhu, X. Li, E.H. Schuchman, R.J. Desnick, S.H. Cheng, Dexamethasone-mediated up-regulation of the mannose receptor improves the delivery of recombinant glucocerebrosidase to Gaucher macrophages, J. Pharmacol. Exp. Ther. 308 (2) (2004) 705–711.
[87] V.E. Dalle, G. Costabile, O.M. Merkel, Mannose and Mannose-6-phosphate receptor-targeted drug delivery systems and their application in Cancer therapy, Adv. Healthc. Mater. 7 (14) (2018), e1701398.
[88] T. Keler, V. Ramakrishna, M.W. Fanger, Mannose receptor-targeted vaccines, Expert. Opin. Biol. Ther. 4 (12) (2004) 1953–1962.
[89] E.A. Akbay, S. Koyama, J. Carretero, A. Altabef, J.H. Tchaicha, C.L. Christensen, O.R. Mikse, A.D. Cherniack, E.M. Beauchamp, T.J. Pugh, M.D. Wilkerson, P. E. Fecci, M. Butaney, J.B. Reibel, M. Soucheray, T.J. Cohoon, P.A. Janne, M. Meyerson, D.N. Hayes, G.I. Shapiro, T. Shimamura, L.M. Sholl, S.J. Rodig, G. J. Freeman, P.S. Hammerman, G. Dranoff, K.K. Wong, Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors, Cancer Discov. 3 (12) (2013) 1355–1363.
[90] N. Chen, W. Fang, J. Zhan, S. Hong, Y. Tang, S. Kang, Y. Zhang, X. He, T. Zhou, T. Qin, Y. Huang, X. Yi, L. Zhang, Upregulation of PD-L1 by EGFR activation mediates the immune escape in EGFR-driven NSCLC: implication for optional immune targeted therapy for NSCLC patients with EGFR mutation, J. Thorac. Oncol. 10 (6) (2015) 910–923.
[91] J.H. Park, G. von Maltzahn, M.J. Xu, V. Fogal, V.R. Kotamraju, E. Ruoslahti, S. N. Bhatia, M.J. Sailor, Cooperative nanomaterial system to sensitize, target, and treat tumors, Proc. Natl. Acad. Sci. U. S. A. 107 (3) (2010) 981–986.
[92] R.J. Passarella, D.E. Spratt, A.E. van der Ende, J.G. Phillips, H. Wu, V. Sathiyakumar, L. Zhou, D.E. Hallahan, E. Harth, R. Diaz, Targeted nanoparticles that deliver a sustained, specific release of paclitaxel to irradiated tumors, Cancer Res. 70 (11) (2010) 4550–4559.
[93] S. Lee, H. Koo, J.H. Na, S.J. Han, H.S. Min, S.J. Lee, S.H. Kim, S.H. Yun, S. Y. Jeong, I.C. Kwon, K. Choi, K. Kim, Chemical tumor-targeting of nanoparticles based on metabolic glycoengineering and click chemistry, ACS Nano 8 (3) (2014) 2048–2063.
[94] H. Wang, M.C. Sobral, D. Zhang, A.N. Cartwright, A.W. Li, M.O. Dellacherie, C. M. Tringides, S.T. Koshy, K.W. Wucherpfennig, D.J. Mooney, Metabolic labeling and targeted modulation of dendritic cells, Nat. Mater. 19 (11) (2020) 1244–1252.
[95] G. Paganelli, S. Zoboli, M. Cremonesi, L. Bodei, M. Ferrari, C. Grana, M. Bartolomei, F. Orsi, C. De Cicco, H.R. Macke, M. Chinol, F. de Braud, Receptor-mediated radiotherapy with 90Y-DOTA-D-Phe1-Tyr3-octreotide, Eur. J. Nucl. Med. 28 (4) (2001) 426–434.
[96] A.F. Hussain, H.R. Kruger, F. Kampmeier, T. Weissbach, K. Licha, F. Kratz, R. Haag, M. Calderon, S. Barth, Targeted delivery of dendritic polyglycerol-doxorubicin conjugates by scFv-SNAP fusion protein suppresses EGFR+ cancer cell growth, Biomacromolecules 14 (8) (2013) 2510–2520.
[97] M. Baumann, M. Krause, D. Zips, F. Hessel, C. Petersen, 76 EGF-receptor inhibition and radiotherapy, Eur. J. Cancer Suppl. 1 (5) (2003) S27.
[98] J. Bussink, J.H. Kaanders, A.J. van der Kogel, Microenvironmental transformations by VEGF- and EGF-receptor inhibition and potential implications for responsiveness to radiotherapy, Radiother. Oncol. 82 (1) (2007) 10–17.
[99] J.C. Reubi, H.R. Macke, E.P. Krenning, Candidates for peptide receptor radiotherapy today and in the future, J. Nucl. Med. 46 (Suppl. 1) (2005) 67S–75S.
[100] S.R. Wiley, K. Schooley, P.J. Smolak, W.S. Din, C.P. Huang, J.K. Nicholl, G. R. Sutherland, T.D. Smith, C. Rauch, C.A. Smith, A. Et, Identification and characterization of a new member of the TNF family that induces apoptosis, Immunity 3 (6) (1995) 673–682.
[101] M. Horinaka, T. Yoshida, T. Shiraishi, S. Nakata, M. Wakada, R. Nakanishi, H. Nishino, H. Matsui, T. Sakai, Luteolin induces apoptosis *via* death receptor 5 upregulation in human malignant tumor cells, Oncogene 24 (48) (2005) 7180–7189.
[102] Y. Chen, L. Wei, X. Zhang, X. Liu, Y. Chen, S. Zhang, L. Zhou, Q. Li, Q. Pan, S. Zhao, H. Liu, 3Bromopyruvate sensitizes human breast cancer cells to TRAIL induced apoptosis *via* the phosphorylated AMPK mediated upregulation of DR5, Oncol. Rep. 40 (5) (2018) 2435–2444.
[103] V.L. Shepherd, M.G. Konish, P. Stahl, Dexamethasone increases expression of mannose receptors and decreases extracellular lysosomal enzyme accumulation in macrophages, J. Biol. Chem. 260 (1) (1985) 160–164.
[104] W. Wang, Z. Jiang, L. Wang, A. Wang, J. Liu, C. Chen, K. Yu, F. Zou, W. Wang, J. Liu, Q. Liu, All-trans retinoic acid exerts selective anti-FLT3-ITD acute myeloid leukemia efficacy through downregulating Chk1 kinase, Cancer Lett. 473 (2020) 130–138.
[105] N. Steinauer, C. Guo, J. Zhang, The transcriptional corepressor CBFA2T3 inhibits all-trans-retinoic acid-induced myeloid gene expression and differentiation in acute myeloid leukemia, J. Biol. Chem. 295 (27) (2020) 8887–8900.
[106] X. Hao, X. Zhong, X. Sun, The effects of all-trans retinoic acid on immune cells and its formulation design for vaccines, AAPS J. 23 (2) (2021) 32.
[107] I. Vitale, E. Shema, S. Loi, L. Galluzzi, Intratumoral heterogeneity in cancer progression and response to immunotherapy, Nat. Med. 27 (2) (2021) 212–224.
[108] N. Maishi, D.A. Annan, H. Kikuchi, Y. Hida, K. Hida, Tumor endothelial heterogeneity in cancer progression, Cancers (Basel) 11 (2019) 10.
[109] J. Wang, Q. Ni, Y. Wang, Y. Zhang, H. He, D. Gao, X. Ma, X.J. Liang, Nanoscale drug delivery systems for controllable drug behaviors by multi-stage barrier penetration, J. Control. Release 331 (2021) 282–295.